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A solution to the stereochemical problems posed by amaryllidaceae constituents using a highly *syn*-selective arylcuprate conjugate addition to γ-amino and γ-carbamato-α,β-enoates

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Abstract

Various substituted arylcuprates undergo stereocontrolled additions to L-serine-derived γamino- and γ-carbamato-α,β-enoates with high *syn*-selectivities. The stereochemical outcome of these reactions is fully consistent with the reductive elimination-based model proposed previously. This method is well suited for the preparation of a broad range of biologically active amaryllidaceae constituents and their aromatic analogues.

1. Introduction

Numerous natural products found in the plants of the amaryllidaceae family have been the focus of intense research effort. Their diverse biological activities and, therefore, medicinal utility attract the attention of biochemists and pharmacologists.[1] Meanwhile, the complex structures and limited natural abundance of many of these plant metabolites continue to fuel the interest of synthetic chemists.[2]

According to a recent comprehensive review, over 100 small molecule amaryllidaceae constituents that belong to pancratistatin, lycorine or lycorenine structural types have been isolated (Figure 1).[3] Many of these exhibit anticancer,[4] antiviral,[5] antiparasitic,[6] and anti-inflammatory[7] activities amongst others. Pancratistatin has been in preclinical evaluation as an anticancer agent for many years, with limited availability being a major hurdle for its advancement to clinical trials. Significantly, a number of recent reports revealed that this agent displays much better activity/toxicity ratios than the currently used anticancer drugs etoposide and paclitaxel.[8] This discovery is expected to further stimulate the development of efficient synthetic pathways to this class of structurally complex natural products.

The major synthetic challenge stems from the dense stereochemistry of the cyclitol ring, in which the creation of the benzylic stereocenter C10b can be particularly arduous due to the necessity of stereoselective installation of an aromatic group.[9] A close inspection of the structures in Figure 1 reveals consistent stereochemical relationships. Thus, the aromatic moiety is nearly always cis to the adjacent hydroxyl substituent (*C*, *O*) and *trans* to the

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nitrogen-bearing stereocenter on the other side (*C*, *N*). It follows that a flexible synthetic methodology that allows the introduction of an aromatic moiety with stereocontrol exerted by either oxygen- or nitrogen-containing adjacent stereocenters would be generally applicable to the synthesis of compounds that belong to these structural types. Furthermore, if the methodology is not sensitive to the identity and positioning of the substituents on the aromatic ring, a library of analogues of these natural products could be prepared for structure-activity studies.

We have recently reported the utilization of a highly, *anti*-selective arylcuprate conjugate addition to a γ-alkoxy-α,β-enoate as one such methodology.[10] The *anti*-stereochemical relationship of the oxygen-bearing and benzylic stereocenters in the addition products corresponds to their *cis* positioning in the target cyclic structures (Figure 2). A complementary strategy would use a *syn*-selective arylcuprate conjugate addition to α,β-enoates with stereocontrol exerted by a γ-nitrogen-containing stereocenter. Since the feasibility of this stereochemical divergence had been reported previously,[11c] we explored this alternative approach and report our results herein.

2. Results and discussion

Syn-selective conjugate additions of organocuprates have been reported for both γ-amino- and γ-carbamato-α,β-enoates and they have been utilized in the syntheses of various medicinally relevant complex targets.[11] Therefore, to evaluate this methodology for the introduction of multisubstituted aromatic rings, particularly those possessing the multiple alkoxy groups required in the synthesis of amaryllidaceae constituents, we prepared γ-amino- and γ-carbamato-enoates **1** and **2** (Scheme 1). While the synthesis of enoate **2** from L-serine had previously been described in the literature,[12] the key to the successful straightforward preparation of enoate **1** was a one-pot Swern oxidation – Wittig olefination method that resulted in exclusive formation of the E-enoate.[13]

Gratifyingly, the reactions of arylcuprates derived from aromatic Grignard reagents with enoate **1** gave addition products **3a–f** as single diastereomers (Scheme 2). The NMR analyses of crude and purified reaction mixtures revealed the presence of the β-epimeric compounds in only trace quantities. However, the reactions were sluggish and provided only modest yields of **3a-f**, while the addition product **3g** could not be detected at all. The steric congestion arising from the bulky *t*-butyldiphenylsilyl protection clearly plays a role in this unsatisfactory outcome.

In contrast, the addition products **4a-g**, resulting form the reactions of enoate **2**, were formed in excellent yields. However, the rotational isomerism associated with the carbamate moiety led to NMR peak broadening and this prevented any immediate conclusions regarding the diastereomeric purity of **4a-g**. Therefore, each addition product was reacted with methanolic HCl to remove the Boc and isopropylidene protecting groups to give ammonium salts **5a-g**. These underwent facile lactam formation upon treatment with MeONa in MeOH to give **6a-g** in good overall yields. The NMR analyses of **6a-g** clearly showed the presence of a single diastereomer in each case.

To facilitate the NMR-based stereochemistry assignment, we attempted to acetylate the primary hydroxyl group in lactams **5b** and **5f** (Scheme 3). Unexpectedly, the N-acetylated products **7b** and **7f** were isolated instead of the expected esters when the starting lactams were treated with equimolar amounts of acetic anhydride. Evidently, the intramolecular oxygen to nitrogen acetyl transfer leads to the formation of the thermodynamically more stable imides. However, treatment of **5b** and **f** with excess of Ac_2O gives diacetylated

lactams **8b** and **8f**, whose ^{1}H NMR contain well-resolved lactam proton signals allowing the unequivocal assignment of the *cis* stereochemical relationship between H_c and H_d.

To confirm the *syn*-stereochemistry in addition products **3a-f** by chemical correlation, we attempted to convert **3a** to **6a** by way of *N*-debenzylation, lactamization and *O*-desilylation. To this end, **3a** was treated with hydrogen over various palladium catalysts and high pressures. Surprisingly, ester **3a** is highly resistant to hydrogenolysis, possibly due to the steric bulk of the silyl protection and, consequently, an impaired contact with the catalyst surface. Reversing the order of the deprotections by performing the desilylation first, gave lactone **9a** (Scheme 4). This compound underwent facile double debenzylation when stirred in a mixture of dioxane-water under a hydrogen balloon. Finally, lactone to lactam isomerization **10a** to **6a** was brought about with sodium methoxide in methanol. This transformation conceivably proceeds through the intermediacy of the ring-opened methyl ester.

3. Conclusions

Highly stereoselective processes with the participation of acyclic systems are not commonplace in organic synthesis. Therefore, we hope that our previously reported highly *anti*-selective arylcuprate additions to γ-alkoxy-α,β-enoates[10] and the present *syn*-selective additions to γ-amino- and γ-carbamato-α,β-enoates will find utility in the introduction of multisubstituted aromatic groups into complex acyclic structures with high stereocontrol. Work in our laboratory is currently underway to apply this chemistry to the development of practical synthetic pathways to biologically active amaryllidaceae constituents to facilitate their advancement to clinical trials. Furthermore, the independence of the stereochemical outcome of the substitution pattern on the aromatic ring makes these processes particularly promising for the synthesis of aromatic analogues of these natural products.[14]

Recently, we proposed a stereochemical model to predict the outcomes of organocuprate addition reactions to γ-alkoxy-α,β-enoates, based on reductive elimination as a rate- and stereochemistry-determining step.[10b] We suggested that the model could be of general utility encompassing reactions of other α,β-enoates containing a γ-stereocenter. The results of the present investigation with γ-amino- and γ-carbamato–α,β-enoates are fully consistent with this model that predicts *syn*-selectivities for these processes (Figure 3).

In contrast, the modified Felkin-Anh model[11c,15] leads to the prediction of anti-isomers as the favored addition products. Furthermore, the reductive elimination model explains the low reactivity of γ-amino–α,β-enoates with a sterically demanding group R. Clearly, the hypothetical transition state would be highly energetic in this case due to the 1,3-allylic strain (C_γ–R and C_α–H in the top pathway in Figure 3). The sluggish nature of reactions of enoate **1** are in agreement with this mechanistic interpretation.

4. Experimental section

4.1. General methods

Unless otherwise noted, all commercially obtained reagents were used without purification. THF was distilled from sodium benzophenone ketyl prior to use. Dichloromethane was distilled from calcium chloride. Reactions were carried out under a nitrogen atmosphere in oven-dried glassware using standard syringe, cannula and septa techniques. Reactions were monitored by TLC (Silica Gel 60 F_{254}, 250 μm) and visualized with UV light and ceric ammonium molybdate solution. Aryl bromides **f** and **g** were prepared as previously described.[16] Flash chromatography was performed on silica gel (32–63 μm, 60A° pore size).

Optical rotations were measured with an Autopol III automatic polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on JEOL 300 MHz spectrometer.

4.2. Preparation of enoate 1

4.2.1. 5-(*tert*-Butyldiphenylsilanyloxy)-4-dibenzylamino-pent-2-enoic acid methyl ester, 1—To oxalyl chloride (5.0 ml of 2M in CH_2Cl_2, 9.7 mmol) in dry CH_2Cl_2 (50 ml) at −78 °C was added DMSO (1.42 ml, 19.9 mmol) in CH_2Cl_2 (15 ml) over 10 min and the mixture was stirred for an additional 20 min. 3-(*tert*-Butyl-diphenyl-silanyloxy)-2-dibenzylamino-1-propanol[12a,b] (2.208 g, 4.3 mmol) in CH_2Cl_2 (15 ml) was added over 10 min and the mixture stirred for an additional 10 min. Triethylamine (3.37 ml, 23.9 mmol) in CH_2Cl_2 (15 ml) was added over 10 min and the white slurry was stirred for 20 min at −78 °C. To the cold reaction mixture was added methyl (triphenylphosphoranylidene) acetate (3.34 g, 9.7 mmol) in one portion and the resulting mixture was stirred for 16 h while it was allowed to warm up to rt. Water (150 ml) was added to reaction mixture, the two layers were separated and aqueous layer was extracted with CH_2Cl_2 (3 × 75 ml). The combined organic layers were dried over $MgSO_4$ and solvent evaporated under reduced pressure. The residual oil was presorbed on silica gel and the product purified using chromatography with gradients 1% and 2% EtOAc/Hexane to afford enoate **1** (2.21 g, 90.6%) as a colorless oil. R_f 0.62 (10% EtOAc/Hexane); $[\alpha]_D^{23} = -21.4$ (*c* 0.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.63–7.19 (m, 20H), 7.03 (dd, 1H, *J* = 6.8, 15.6 Hz), 6.02 (dd, 1H, *J* = 1.3, 15.9 Hz), 4.02–3.8 (m, 3H), 3.78 (s, 1H), 3.77 (s, 3H), 3.62 (s, 1H), 3.58 (s, 1H), 3.51 (m, 1H), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 166.7, 146.1, 139.7, 135.6, 133.2, 129.8, 128.7, 128.5, 128.3, 128.2, 127.8, 127.0, 123, 63.9, 60.5, 54.5, 51.6, 26.8, 19.2; HRMS m/z (ESI) calcd for $C_{36}H_{41}NO_3Si$ $(M+H)^+$ 564.2934, found 564.2921.

4.3. General procedure for the arylcuprate addition

Ca. 1 ml of a required aryl bromide (10.0 mmol) was added to crushed Mg turnings (10.0 mmol, 0.242 g) in THF (10 ml) under a nitrogen atmosphere. Once the reaction had started, the solution was warmed up and slightly darkened. The rest of the aryl bromide was added dropwise to allow a gentle reaction. The reaction mixture was allowed to cool to room temperature and was cannulated to a slurry of CuI (5 mmol, 0.952 g) in THF (10 ml) at − 78 °C. The mixture was stirred at − 78 °C for 40 min (in the synthesis of **3e** and **4e** the mixture was stirred at 0 °C for 2 h as no transmetalation occurred at − 78 °C). Me_3SiCl (10.0 mmol, 1.08 g) and enoate **1** or **2** (1 mmol, in 10 ml of THF) was added sequentially at − 78 °C. The yellow brown solution was stirred overnight while slowly warming up to rt. The reaction mixture was quenched with a mixture of concd. NH_4OH and satd. NH_4Cl (1:9, 30 ml) and extracted with EtOAc (3 × 40 ml). The combined organic layers were washed with water and brine (2 × 5 ml) and dried over anhyd. $MgSO_4$. The solution was concentrated under reduced pressure, the residue was absorbed on silica gel and purified by column chromatography (2 – 10% EtOAc/hexanes) to yield **3a-f** (49–58%) and **4a-g** (70–95%) as an oil.

4.3.1. 5-(*tert*-Butyldiphenylsilanyloxy)-4-dibenzylamino-3-phenylpentanoic acid methyl ester, 3a—58%; R_f 0.67 (10% EtOAc/Hexane); $[\alpha]_D^{23} = -12.6$ (*c* 0.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.9 – 6.91 (m, 25H), 4.18 (dd, 1H, *J* = 3.8, 11.2 Hz), 3.92 (dd, 1H, *J* = 3.8, 11.2 Hz), 3.8 (d, 2H, *J* = 13.7 Hz), 3.72 (m, 1H), 3.45 (s, 3H), 3.41 (br d, 2H), 2.99 (m, 1H), 2.7 (dd, 1H, *J* = 4.4, 15.1 Hz), 2.41 (dd, 1H, *J* = 10.2, 15.1 Hz), 1.22 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.6, 142.1, 139.9, 136.0, 135.9, 133.4, 133.2, 131.0, 130.0, 129.1, 128.0, 126.7, 126.4, 61.3, 60.3, 54.7, 51.3, 41.8, 39.1, 27.1, 19.3; HRMS m/z (ESI) calcd for $C_{42}H_{47}NO_3Si$ $(M+H)^+$ 642.3403, found 642.3383.

4.3.2. 5-(*tert*-Butyldiphenylsilanyloxy)-4-dibenzylamino-3-(4-methoxyphenyl)-pentanoic acid methyl ester, 3b—50%; R_f 0.57 (10% EtOAc/Hexane); $[\alpha]_D^{24}$ = −10.7 (*c* 0.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.82 – 6.72 (m, 24H), 4.1 (dd, 1H, *J* = 3.8, 11.0 Hz), 3.87 (br dd, 1H), 3.83 (s, 3H), 3.79 – 3.72 (d, 2H, *J* = 13.7 Hz), 3.64 (m, 1H), 3.42 (s, 3H), 3.35 (d, 2H, *J* = 13.7 Hz), 2.91 (m, 1H), 2.62 (dd, 1H, *J* = 4.1, 15.1 Hz), 2.34 (dd, 1H, *J* = 10.4, 15.1 Hz), 1.17 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.7, 158.1, 139.9, 135.9, 135.8, 134.2, 133.4, 133.1, 129.9, 129.0, 127.9, 127.8, 126.7, 113.3, 61.4, 60.4, 55.3, 54.7, 51.3, 41.2, 39.1, 27.1, 19.3; HRMS m/z (ESI) calcd for $C_{43}H_{49}NO_4Si$ $(M+H)^+$ 672.3509, found 672.3484.

4.3.3. 5-(*tert*-Butyldiphenylsilanyloxy)-4-dibenzylamino-3-(4-fluorophenyl)-pentanoic acid methyl ester, 3c—55%; R_f 0.66 (10% EtOAc/Hexane); $[\alpha]_D^{24}$ = −22.9 (*c* 0.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.79 – 6.78 (m, 24H), 4.1 (dd, 1H, *J* = 3.6, 11.2 Hz), 3.83 (dd, 1H, *J* = 3.8, 11.3 Hz), 3.73 (d, 2H, *J* = 13.2 Hz), 3.62 (m, 1H), 3.40 (s, 3H), 3.33 (d, 2H, *J* = 13.2 Hz), 2.84 (m, 1H), 2.61 (dd, 1H, *J* = 4.1, 15.1 Hz), 2.26 (dd, 1H, *J* = 10.4, 14.8 Hz); ^{13}C NMR ($CDCl_3$) δ 172.1, 139.6, 137.9, 135.9, 135.8, 135.7, 133.3, 133.1, 130.4, 130.3, 130.1, 130.0, 128.9, 128.0, 127.9, 127.8, 126.8, 114.8, 114.5, 361.2, 60.0, 54.5, 51.3, 41.4, 41.1, 27.1, 19.2; HRMS m/z (ESI) calcd for $C_{42}H_{46}FNO_3Si$ $(M + H)^+$ 660.3309, found 660.3304.

4.3.4. 5-(*tert*-Butyldiphenylsilanyloxy)-3-(4-chlorophenyl)-4-dibenzylamino-pentanoic acid methyl ester, 3d—58%; R_f 0.67 (10% EtOAc/Hexane); $[\alpha]_D^{24}$ = −11.8 (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.82 – 6.85 (m, 24H), 4.2 (br dd, 1H), 3.86 (br dd, 1H), 3.77 (d, 2H, *J* = 13.5 Hz), 3.69 (m, 1H), 3.44 (s, 3H), 3.36 (d, 2H, *J* = 13.5 Hz), 2.90 (m, 1H), 2.65 (br dd, 1H, *J* = 3.8, 15.1 Hz), 2.31 (dd, 1H, *J* = 10.7, 15.1 Hz); ^{13}C NMR ($CDCl_3$) δ 172.3, 140.8, 139.6, 135.9, 135.8, 133.2, 133.0, 131.9, 130.4, 130.1, 130.0, 129.0, 128.0, 127.9, 127.9, 126.8, 61.2, 59.9, 54.6, 51.4, 41.5, 38.9, 27.1, 19.1; HRMS m/z (ESI) calcd for $C_{42}H_{46}ClNO_3Si$ $(M+H)^+$ 676.3014, found 676.2995.

4.3.5. 5-(*tert*-Butyldiphenylsilanyloxy)-4-dibenzylamino-3-(3,4-dimethoxyphenyl)-pentanoic acid methyl ester, 3e—49%; R_f 0.52 (10% EtOAc/Hexane); $[\alpha]_D^{24}$ = −13.6 (*c* 0.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.84 – 6.5 (m, 23H), 4.08 (br dd, 1H), 3.90 (m, 1H), 3.88 (br s, 3H), 3.74 (br d, 2H, *J* = 14.1 Hz), 3.60 (br s, 3H), 3.57 (br dd, 1H), 3.46 (br dd, 1H), 3.36 (br d, 2H, *J* = 14.1 Hz), 2.90 (br m, 1H), 2.64 (br dd, 1H, *J* = 4.7, 15.4 Hz), 2.42 (br dd, 1H, *J* = 10.2, 15.4 Hz), 1.14 (br s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.7, 148.4, 147.5, 140.0, 135.9, 135.8, 134.7, 133.3, 133.1, 130.0, 129.9, 128.8, 128.0, 127.8, 126.7, 121.0, 111.7, 110.6, 61.7, 60.4, 55.9, 55.6, 54.9, 51.3, 41.6, 38.5, 27.2, 19.2; HRMS m/z (ESI) calcd for $C_{44}H_{51}NO_5Si$ $(M+H)^+$ 702.3615, found 702.3609.

4.3.6. 3-Benzo[1,3]dioxol-5-yl-5-(*tert*-butyldiphenylsilanyloxy)-4-dibenzylamino-pentanoic acid methyl ester, 3f—52%; R_f 0.56 (10% EtOAc/Hexane); $[\alpha]_D^{24}$ = −9.1 (*c* 0.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.82 – 6.21 (m, 23H), 5.90 (s, 2H), 4.09 (dd, 1H, *J* = 4.1, 11.2 Hz), 3.82 (dd, 1H, *J* = 3.8, 11.2 Hz), 3.73 (d, 2H, *J* = 13.7 Hz), 3.95 (m, 1H), 3.43 (s, 3H), 3.34 (d, 2H, *J* = 13.7 Hz), 2.84 (m, 1H), 2.57 (dd 1H, *J* = 4.1, 11.2), 2.27 (dd, 1H, *J* = 10.2, 15.4 Hz), 1.14 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.5, 147.2, 145.9, 139.8, 135.9, 135.8, 135.7, 133.3, 133.1, 130.0, 129.0, 127.9, 127.7, 126.7, 122.3, 109.0, 107.6, 100.7, 61.4, 60.2, 54.6, 51.4, 41.8, 39.0, 29.7, 27.0, 19.3; HRMS m/z (ESI) calcd for $C_{43}H_{48}NO_5Si$ $(M+H)^+$ 286.3302, found 286.3293.

4.3.7. (*R*)-*tert*-Butyl-4-((*R*)-2-(methoxycarbonyl)-1-phenylethyl)-2,2-dimethyloxazolidine-3-carboxylate, 4a—95%; R_f 0.47 (20% EtOAc/Hexane); $[\alpha]_D^{21}$ = +35.7 (*c* 0.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.45-7.1 (m, 5H), 4.21 – 3.65 (br m, 3H), 3.6

– 3.46 (br m, 4H), 2.9 – 2.68 (br d, 2H),1.55 (br s, 6H), 1.45 (br s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.0, 152.8, 140.4, 128.8, 128.5, 128.2, 127.7, 126.1, 94.5, 80.5, 63.8, 61.6, 51.7, 42.8, 32.1, 28.5, 26.5; HRMS m/z (ESI) calcd for $C_{20}H_{29}NO_5$ $(M+Na)^+$ 386.1943, found 386.1935.

4.3.8. (*R*)-*tert*-Butyl-4-((*R*)-2-(methoxycarbonyl)-1-(4-methoxyphenyl)ethyl)-2,2-dimethyloxazolidine-3-carboxylate, 4b—87%; R_f 0.43 (20% EtOAc/Hexane); $[\alpha]_D^{21}$ = +40.0 (*c* 0.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.2 (br d, 2H), 6.8 (br d, 2H), 4.14 – 3.65 (br m, 6H), 3.58 – 3.47 (br m, 4H), 2.86 – 2.68 (br d, 2H), 1.55 (br s, 6H), 1.48 (br s, 9H); ^{13}C NMR ($CDCl_3$) δ 165.0, 150.2, 144.4, 124.1, 120.9, 120.5, 106.4, 105.7, 86.5, 72.3, 55.7, 53.7, 47.1, 44.6, 33.9, 24.2, 20.4, 18.3; HRMS m/z (ESI) calcd for $C_{21}H_{31}NO_6$ $(M+Na)^+$ 416.2049, found 416.2053.

4.3.9. (*R*)-*tert*-Butyl-4-((*R*)-2-(methoxycarbonyl)-1-(4-fluorophenyl)ethyl)-2,2-dimethyloxazolidine-3-carboxylate, 4c—92%; R_f 0.5 (20% EtOAc/Hexane); $[\alpha]_D^{21}$ = +33.6 (*c* 0.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.29 – 6.93 (br m, 5H), 4.14 – 3.63 (br m, 3H), 3.6 – 3.48 (br s, m, 4H), 2.9–2.68 (br d, 2H), 1.55 (br s, 6H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.8, 163.4, 160.1, 135.9, 128.4, 115.5, 94.3, 80.4, 63.8, 61.6, 51.7, 42.4, 32.4, 28.4, 26.1; HRMS m/z (ESI) calcd for $C_{20}H_{28}FNO_5$ $(M+Na)^+$ 404.1849, found 404.1834.

4.3.10. (*R*)-*tert*-Butyl-4-((*R*)-2-(methoxycarbonyl)-1-(4-chlorophenyl)ethyl)-2,2-dimethyl-oxazolidine-3-carboxylate, 4d—83%; R_f 0.54 (20% EtOAc/Hexane); $[\alpha]_D^{21}$ = +26.0 (*c* 0.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.33 – 7.12 (br dd, 4H), 4.14 – 3.68 (br m, 3H), 3.63 – 3.48 (br m, 4H), 2.9 – 2.7 (br d, 2H), 1.54 (br s, 6H), 1.46 (br s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.8, 152.4, 138.8, 132.8, 129.7, 128.8, 94.7, 80.6, 63.9, 61.5, 51.8, 42.6, 33.0, 28.4, 26.6; HRMS m/z (ESI) calcd for $C_{20}H_{28}ClNO_5$ $(M+Na)^+$ 420.1554, found 420.1537.

4.3.11. (*R*)-*tert*-Butyl-4-((*R*)-2-(methoxycarbonyl)-1-(3,4-dimethoxyphenyl)ethyl)-2,2-dimethyl-oxazolidine-3-carboxylate, 4e—70%; R_f 0.33 (20% EtOAc/Hexane); $[\alpha]_D^{21}$ = +38.2 (*c* 0.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.90 – 6.71 (br m, 3H), 4.14 – 3.66 (br m, 9H), 3.65 – 3.48 (br m, 4H), 2.9 – 2.71 (br s, 2H), 1.56 (br s, 6H), 1.48 (br s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.2, 152.4, 149.0, 147.9, 132.8, 118.9, 111.3, 94.6, 80.5, 63.5, 61.8, 55.8, 51.7, 42.3, 32.8, 28.5, 26.6; HRMS m/z (ESI) calcd for $C_{22}H_{33}NO_7$ $(M+Na)^+$ 446.2155, found 446.2157.

4.3.12. (R)-*tert*-Butyl-4-((R)-2-(methoxycarbonyl)-1-(benzo[d][1,3]dioxol-6-yl)ethyl)-2,2-dimethyl-oxazolidine-3-carboxylate, 4f—92%; R_f 0.42 (20% EtOAc/Hexane); $[\alpha]_D^{21}$ = +29.4 (*c* 0.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.84 – 6.6 (br m, 3H), 5.95 (br s, 2H), 4.14 – 3.66 (br m, 3H), 3.65 – 3.52 (br m, 4H), 2.74 (br d, 2H), 1.54 (br s, 6H), 1.48 (br s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.0, 152.5, 147.8, 146.4, 134.2, 120.8, 108.4, 101.0, 92.6, 80.5, 63.5, 61.9, 51.7, 42.6, 32.5, 28.5, 26.4; HRMS m/z (ESI) calcd for $C_{21}H_{29}NO_7$ $(M+Na)^+$ 430.1842, found 430.1831.

4.3.13. (R)-*tert*-Butyl-4-((R)-2-(methoxycarbonyl)-1-(4-methoxybenzo[d][1,3]dioxol-6-yl)ethyl)-2,2-dimethyloxazolidine-3-carboxylate, 4g—86%; R_f 0.38 (20% EtOAc/Hexane); $[\alpha]_D^{21}$ = +73.3 (*c* 0.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.41 (br d, 2H), 5.93 (br s, 3H), 4.14 – 3.67 (br m, 6H), 3.58 (br s, 3H), 3.54 (br m, 1H), 2.74 (br d, 2H), 1.50 (br s, 15H); ^{13}C NMR ($CDCl_3$) δ 173.3, 152.9, 152.0, 149.0, 143.7, 134.8, 128.9, 107.6, 101.4, 94.2, 91.3, 80.0, 63.8, 56.5, 42.8, 33.4, 29.9, 28.5, 26.7; HRMS m/z (ESI) calcd for $C_{22}H_{31}NO_8$ $(M+Na)^+$ 460.1947, found 460.2023.

4.4. General procedure for the removal of Boc and isopropylidene protection

A solution of HCl in MeOH was prepared by the careful addition of acetyl chloride 30 μl in 3 ml methanol at 0 °C. Compounds **4a-g** (ca. 50 mg) were refluxed in this solution (3 ml) for 2 h at rt. The solvent was evaporated under reduced pressure and the residue was triturated with ethyl acetate and hexane. White to off white solids **5a-g** were obtained in 85 – 90 % yield.

4.4.1. Methyl (3*R*,4*R*)-4-amino-5-hydroxy-3-phenylpentanoate, 5a—88%; ^{1}H NMR (D_2O) δ 7.49 – 7.31 (m, 5H), 4.0 (dd, 1H, *J* = 2.2, 9.9 Hz), 3.85 (dd, 1H, *J* = 5.5, 12.4 Hz), 3.67 (m, 1H), 3.58 – 3.4 (m, 4H), 3.01 (dd, 1H, *J* = 3.8, 15.1 Hz), 2.87 (dd, 1H, *J* = 10.7, 14.6 Hz); ^{13}C NMR (D_2O) δ 174.1, 137.4, 126.5 128.6, 128.3 59.2, 56.5, 52.3, 41.2, 37.0; HRMS m/z (ESI) calcd for $C_{12}H_{17}NO_3$ $(M+H)^+$ 224.1287, found 224.1242.

4.4.2. Methyl (3*R*,4*R*)-4-amino-5-hydroxy-3-(4-methoxyphenyl)pentanoate, 5b—90%; ^{1}H NMR (D_2O) δ 7.23 (d, 2 H, *J* = 7.2 Hz), 6.93 (d, 2H, *J* = 7.2 Hz), 3.89 (dd, 1H, *J* = 3.6, 9.4 Hz), 3.84 – 3.71 (m, 4H), 3.54 (m, 1H), 3.41 (s, 3H), 3.30 (m 1H), 2.88 (dd, 1H, *J* = 3.8, 14.1 Hz), 2.73 (br dd, 1H); ^{13}C NMR (D_2O) δ 174.2, 158.9, 129.7, 129.6, 114.9, 59.3, 56.8, 55.5, 52.4, 40.6, 37.3; HRMS m/z (ESI) calcd for $C_{13}H_{20}NO_4H$ $(M+H)^+$ 254.1392, found 254.1339.

4.4.3. Methyl (3*R*,4*R*)-4-amino-3-(4-fluorophenyl)-5-hydroxypentanoate, 5c—88%; ^{1}H NMR (D_2O) δ 7.31 (m, 1H), 7.11 (m, 1H), 3.91 (dd, 1H, *J* = 3.0, 12.6 Hz), 3.78 (dd, 1H, *J* = 5.5, 12.6 Hz), 3.59 (m, 1H), 3.44 (s, 3H), 3.39 (m, 1H), 2.93 (dd, 1H, *J* = 4.4, 15.4 Hz), 2.76 (dd, 1H, *J* = 10.7, 15.4 Hz); ^{13}C NMR (D_2O) δ 174.4, 133.3, 130.3, 130.2, 116.4, 116.1, 59.2, 56.5, 52.4, 40.7, 37.2; HRMS m/z (ESI) calcd for $C_{12}H_{16}FNO_3$ $(M + H)^+$ 242.1192, found 242.1202.

4.4.4. Methyl (3*R*,4*R*)-4-amino-3-(4-chlorophenyl)-5-hydroxypentanoate, 5d—85%; ^{1}H NMR (D_2O): δ 7.36 (d, 2H, *J* = 8.5 Hz), 7.24 (d, 2H, *J* = 8.5 Hz), 3.89 (dd, 1H, *J* = 3.0, 12.6 Hz), 3.74 (dd, 1H, *J* = 5.5, 12.6 Hz), 3.72 (m, 1H), 3.41 (s, 3H), 3.34 (m, 1H), 2.89 (dd, 1H, *J* = 3.8, 15.4 Hz), 2.74 (br dd, 1H); ^{13}C NMR (D_2O) δ 174.0, 136.1, 133.8, 130.0, 129.5, 59.2, 56.4, 52.4, 40.9, 37.0; HRMS m/z (ESI) calcd for $C_{12}H_{17}ClNO_3$ $(M+H)^+$ 258.0897, found 258.0863.

4.4.5. Methyl (3*R*,4*R*)-4-amino-5-hydroxy-3-(3,4-dimethoxyphenyl)pentanoate, 5e—85%; ^{1}H NMR (D_2O): δ 6.92 (br d, 3H), 4.16 – 3.66 (br m, 8H), 3.63 – 3.25 (br m, 5H), 2.90 (br dd, 1H), 2.75 (br dd, 1H); ^{13}C NMR (D_2O) δ 174.2, 148.7, 148.1, 130.3, 121.4, 112.4, 111.6, 59.3, 55.8, 52.4, 48.9, 41.2, 37.2; HRMS m/z (ESI) calcd for $C_{14}H_{21}NO_5$ $(M+H)^+$ 284.1498, found 284.1506.

4.4.6. Methyl (3*R*,4*R*)-4-amino-3-(benzo[d][1,3]dioxol-6-yl)-5-hydroxypentanoate, 5f—90%; ^{1}H NMR (D_2O) δ 6.83 – 6.70 (m, 3H), 5.87 (s, 2H), 3.88 (dd, 1H, *J* = 2.3, 12.1 Hz), 3.71 (dd, 1H, *J* = 5.2, 12.6 Hz), 3.46 (s, 3H), 3.24 (m, 1H), 2.84 (br dd, 1H, *J* = 3.8, 14.8 Hz), 2.68 (br dd, 1H); ^{13}C NMR (D_2O) δ 174.0, 148.0, 147.2, 130.9, 122.0, 109.0, 108.1, 101.0, 59.1, 56.5, 52.3, 41.1, 37.2; HRMS m/z (ESI) calcd for $C_{13}H_{20}NO_4$ $(M+H)^+$ 268.1185, found 268.1105.

4.4.7. Methyl (3*R*,4*R*)-4-amino-5-hydroxy-3-(4-methoxybenzo[d][1,3]dioxol-6-yl)pentanoate, 5g—76%; ^{1}H NMR (D_2O): δ 6.57 (d, 2H, *J* = 8.8 Hz), 5.93 (br s, 2H), 3.95 – 3.73 (m, 5H), 2.89 (br dd, 1H), 2.76 (br dd, 1H); ^{13}C NMR (D_2O) δ 174.1, 149.2, 143.5, 134.9, 132.1, 108.2, 101.8, 59.2, 56.7, 56.6, 52.4, 41.5, 37.3; HRMS m/z (ESI) calcd for $C_{14}H_{19}NO_6$ $(M+H)^+$ 298.1291, found 298.1281.

4.5. General procedure for lactam formation

Compounds **5a-g** (ca. 30 mg) were stirred in a freshly prepared solution of sodium methoxide in methanol (2 ml; pH ~ 9) for 1h at rt. The solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (15 ml) and washed with water (3 × 3 ml), organic phase was dried with brine (3 ml) and over anhydrous $MgSO_4$. After evaporation of CH_2Cl_2 under reduced pressure, white to pale yellow solids **6a-g** were obtained in 70 – 85 % yield.

4.5.1. (4*R*,5*R*)-5-(Hydroxymethyl)-4-phenylpyrrolidin-2-one, 6a—80%; R_f 0.48 (5% MeOH/EtOAc); $[\alpha]_D^{23}$ = −63.4 (*c* 0.01, CH_3OH); ^{1}H NMR (D_2O) δ 7.31 (m, 5H), 4.04 (br m, 1H), 3.90 (dd, 1H, *J* = 9.4, 17.0 Hz), 3.27 (m, 1H), 3.16 (m, 1H), 2.82 (dd, 1H, *J* = 8.8, 17.0 Hz), 2.64 (dd, 1H, *J* = 8.9, 16.8 Hz); ^{13}C NMR (D_2O) δ 181.0, 138.1, 128.7, 128.0, 127.3, 61.7, 59.6, 41.5, 35.3; HRMS m/z (ESI) calcd for $C_{11}H_{13}NO_2$ $(M+H)^+$ 192.1025, found 192.1018.

4.5.2. (4*R*,5*R*)-5-(Hydroxymethyl)-4-(4-methoxyphenyl)pyrrolidin-2-one, 6b—85%; R_f 0.4 (10% MeOH/EtOAc); $[\alpha]_D^{23}$ = −95.7 (*c* 0.02, CH_3OH); ^{1}H NMR (D_2O) δ 7.15 (d, 2H, *J* = 8.5 Hz), 6.85 (d, 2H, *J* = 8.5 Hz), 3.90 (m, 1H), 3.77 – 3.65 (m, 4H), 3.16 (m, 1H), 3.06 (dd, 1H, *J* = 6.9, 10.4 Hz), 2.68 (dd, 1H, *J* = 9.3, 17.0 Hz), 2.50 (dd, 1H, *J* = 8.7, 16.8 Hz); ^{13}C NMR (D_2O) δ 180.9, 157.9, 130.5, 129.2, 114.0, 61.8, 59.6, 55.4, 41.0, 35.5. HRMS m/z (ESI) calcd for $C_{12}H_{15}NO_3$ $(M+H)^+$ 222.1130, found 222.1122.

4.5.3. (4*R*,5*R*)-4-(4-Fluorophenyl)-5-(hydroxymethyl)pyrrolidin-2-one, 6c—82%; R_f 0.49 (5% MeOH/EtOAc); $[\alpha]_D^{23}$ = −105.7 (*c* 0.03, CH_3OH); ^{1}H NMR (D_2O) δ 7.25 (br t, 2H), 7.05 (br t, 2H), 3.97 (m, 1H), 3.7 (br dd, 1H, *J* = 8.5, 17.3 Hz), 3.24 (br dd, 1H, *J* = 3.5, 13.6 Hz), 3.12 (br dd, 1H, *J* = 6.6, 11.5 Hz), 2.78 (br dd, 1H, *J* = 9.1, 16.7 Hz), 2.6 (br dd, 1H, *J* = 8.8, 16.8 Hz); ^{13}C NMR (D_2O) δ 180.9, 157.9, 129.2, 114.0, 61.8, 59.6, 55.4, 41.0, 35.5; HRMS m/z (ESI) calcd for $C_{11}H_{12}FNO_2$ $(M+H)^+$ 210.0930, found 210.0927.

4.5.4. (4*R*,5*R*)-4-(4-Chlorophenyl)-5-(hydroxymethyl)pyrrolidin-2-one, 6d—75%; R_f 0.44 (5% MeOH/EtOAc); $[\alpha]_D^{23}$ = −113.7 (*c* 0.01, CH_3OH); ^{1}H NMR (D_2O) δ 7.35 (br d, 2H, *J* = 7.9 Hz), 7.24 (br d, 2H, *J* = 8.2), 3.95 (m, 1H), 3.84 (dd, 1H, *J* = 7.98, 17.1 Hz), 3.2 (br dd, 1H, *J* = 3.0, 12.1 Hz), 3.08 (br dd, 1H, *J* = 6.0, 12.5 Hz), 2.74 (br dd, 1H, *J* = 8.8, 16.5 Hz), 2.56 (br dd, 1H, *J* = 8.8, 17.1 Hz); ^{13}C NMR (D_2O) δ 180.8, 138.8, 132.4, 129.6, 128.6, 61.5, 59.4, 41.2, 35.3; HRMS m/z (ESI) calcd for $C_{11}H_{12}ClNO_2$ $(M+H)^+$ 226.05, found 226.0643.

4.5.5. (4*R*,5*R*)-5-(Hydroxymethyl)-4-(3,4-dimethoxyphenyl)pyrrolidin-2-one, 6e —70%; R_f 0.47 (20% MeOH/EtOAc); $[\alpha]_D^{21}$ = −110.0 (*c* 0.01, CH_3OH); ^{1}H NMR (D_2O) δ 6.94 (br m, 3H), 3.89 (br s, 8H), 3.31 (br dd, 1H), 3.20 (br dd, 1H), 2.83 (br dd, 1H), 2.64 (br dd, 1H); ^{13}C NMR (D_2O) δ 181.0, 148.1, 147.3, 131.3, 120.5, 111.9, 61.8, 59.7, 55.9, 49.0, 41.5, 35.5; HRMS m/z (ESI) calcd for $C_{13}H_{17}NO_4$ $(M+H)^+$ 252.1236, found 252.1226.

4.5.6. (4*R*,5*R*)-4-(Benzo[d][1,3]dioxol-6-yl)-5-(hydroxymethyl)pyrrolidin-2-one, 6f—76%; R_f 0.35 (5% MeOH/EtOAc); $[\alpha]_D^{23}$ = −104.2 (*c* 0.003, CH_3OH); ^{1}H NMR (D_2O) δ 6.77 – 6.67 (m, 3H), 5.85 (s, 2H), 3.91 (m, 1H), 3.75 (dd, 1H, *J* = 8.5, 17.0 Hz), 3.19 (m, 2H), 2.70 (dd, 1H, *J* = 9.1, 16.7 Hz), 2.54 (dd, 1H, *J* = 8.8, 17.0 Hz); ^{13}C NMR (D_2O) δ 178.5, 148.0, 146.8, 131.7, 120.9, 108.3, 108.1, 101.2, 63.1, 59.7, 42.2, 36.2; HRMS m/z (ESI) calcd for $C_{12}H_{13}NO_4$ $(M+H)^+$ 236.0923, found 236.0921.

4.5.7. (4*R*,5*R*)-5-(Hydroxymethyl)-4-(4-methoxybenzo[d][1,3]dioxol-6-yl)pyrrolidin-2-one, 6g—70%; R_f 0.41(10% MeOH/EtOAc); $[\alpha]_D^{24}$ = −123.4 (*c* 0.01,

CH_3OH); ^1H NMR (D_2O) δ 6.55 (d, 2H, J = 14.0 Hz), 5.93 (s, 2H), 3.96 (m, 1H), 3.85 (m, 4H), 3.30 (br m, 1H), 3.22 (br dd, 1H), 2.79 (dd, 1H, J = 9.1, 16.5 Hz), 2.63 (dd, 1H, J = 8.8, 1.8 Hz); ^{13}C NMR (D_2O) δ 180.8, 153.8, 146.1, 142.9, 107.7, 102.3, 101.7, 61.7, 59.6, 56.6, 41.9, 35.5; HRMS m/z (ESI) calcd for $C_{13}H_{15}NO_5$ $(M+H)^+$ 266.1028, found 266.1032.

4.6. Stereochemistry assignment by acetylation of 5b and 5f

Hydroxymethyl pyrrolidine-2-ones **5b** and **5f** (0.0185 g, 0.08 mmol) were dissolved in pyridine (1.5 ml) and stirred with Ac_2O (0.224 ml, 2.37 mmol) in the presence of DMAP (0.5 mg) for 16 h at rt. The solution was concentrated under reduced pressure and the residual oil was presorbed on silica gel. The two acetylated products were purified by column chromatography (15% EtOAc/Hexane and 70 % EtOAc/Hexane).

4.6.1. (4*R*,5*R*)-1-Acetyl-4-(benzo[d][1,3]dioxol-6-yl)-5-(hydroxymethyl)pyrrolidin-2-one, 7f—45%; R_f 0.41 (50 % EtOAc/Hexane); ^1H NMR δ 6.64 (m, 3H), 5.91 (s, 2H), 4.14 – 4.02 (m, 3H), 3.89 (dd, 1H, J = 3.3, 8.3 Hz), 3.79 (dd, 1H J = 8.3, 8.5 Hz), 3.54 (dd, 1H, J = 8.3, 11.3 Hz), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 176.9, 170.5, 148.2, 147.1, 131.0, 120.8, 108.5, 107.9, 101.3, 65.0, 56.4, 41.9, 35.6, 20.8; HRMS m/z (ESI) calcd for $C_{14}H_{15}NO_5$ $(M+H)^+$ 278.1028, found 278.1024.

4.6.2. ((2*R*,3*R*)-1-Acetyl-3-(4-methoxyphenyl)-5-oxopyrrolidin-2-yl)methyl acetate, 8b—55%; R_f 0.56, (60 % EtOAc/Hexane); ^1H NMR δ 7.13 (d, 2H, J = 8.5 Hz), 6.88 (d, 2H, J = 8.5 Hz), 4.76 (m, 1H), 4.41 (dd, 1H, J = 2.8, 12.1 Hz), 3.8 (m, 4H), 3.62 (dd, 1H, J = 2.8, 12.1 Hz), 3.24 (dd, 1H, J = 15.2, 16.9 Hz), 2.72 (dd, 1H, J = 8.3, 16.9 Hz), 2.40 (s, 3H), 1.96 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 174.5, 171.0, 170.0, 159.9, 128.5, 127.2, 114.4, 61.5, 58.7, 55.3, 39.5, 36.8, 25.4, 21.0; HRMS m/z (ESI) calcd for $C_{16}H_{19}NO_5$ $(M+Na)^+$ 328.1161, found 328.1149.

4.6.3. ((2*R*,3*R*)-1-Acetyl-3-(benzo[d][1,3]dioxol-6-yl)-5-oxopyrrolidin-2-yl)methyl acetate, 8f—25%; R_f 0.58, (50 % EtOAc/Hexane); ^1H NMR δ 6.79 (d, 1H, J = 8.0 Hz), 6.69 – 6.66 (m, 2H), 5.97 (s, 2H), 4.73 (ddd, 1H, J = 2.8, 2.8, 8.2 Hz), 4.44 (dd, 1H, J = 2.8, 12.1 Hz), 3.75 (ddd, 1H, J = 8.2, 8.3, 15.2 Hz), 3.67 (dd, 1H, J = 2.8, 12.1 Hz), 3.20 (dd, 1H, J = 15.2, 16.9 Hz), 2.69 (dd, 1H, J = 8.3, 16.9 Hz); ^{13}C NMR ($CDCl_3$) δ 174.4, 169.9, 148.3, 147.2, 129.1,120.7, 108.6, 107.7, 101.3, 61.5, 58.7, 39.9, 36.9, 20.9; HRMS m/z (ESI) calcd for $C_{21}H_{29}NO_7$ $(M+Na)^+$ 342.0954, found 342.0946.

4.6.4. (4*R*,5*R*)-5-(Dibenzylamino)-tetrahydro-4-phenylpyran-2-one, 9a— Tetrabutylammonium fluoride (1M solution in THF, 0.498 ml, 0.5 mmol) was added dropwise to a solution of phenyl cuprate adduct **3a** (62.5 mg, 0.1 mmol) in THF (3 ml). The reaction mixture was stirred for 16 h at rt. After completion of reaction (monitored by TLC) EtOAc (10 ml) was added and solution was washed with water (2 ml × 2) and with brine (2 ml × 2). This solution was dried over anhydrous $MgSO_4$ and the solvent was concentrated under reduced pressure. The residue was presorbed on silica gel and purified by column chromatography (4% EtOAc//Hexane) to afford **9a** (19.5 mg, 55% yield). R_f 0.38 (20% EtOAc/Hexane); ^1H NMR ($CDCl_3$) δ 7.44 - 6.99 (m, 15H), 4.47 (m, 2H), 3.75 (d, 2H, J = 13.8 Hz), 3.52 (d, 2H, J = 13.8 Hz), 3.35 (m, 2H), 2.82 (br dd, 1H), 2.60 (br dd, 1H); ^{13}C NMR ($CDCl_3$) δ 171.6, 142.1, 138.7, 128.8, 128.4, 128.3, 127.7, 127.3, 127.2; HRMS m/z (ESI) calcd for $C_{25}H_{25}NO_2$ $(M+H)^+$ 372.1964, found 372.1946.

4.6.5. (4*R*,5*R*)-5-Amino-tetrahydro-4-phenylpyran-2-one, 10a—To a solution of lactone **9a** (15.2 mg, 0.041 mmol) in water/dioxane (2:1, 3 ml) were added 2 drops of AcOH and 10% Pd/C (10 mg). The solution was stirred under an H_2 atmosphere (1 atm pressure) at rt for 24 h. The completion of the reaction was monitored by TLC. The reaction mixture was

filtered through a celite pad and the filtrate was concentrated to give 4.7 mg of debenzylated lactone **10a** (62% yield). ^{1}H NMR ($CDCl_3$) δ 7.41 (m, 5H), 3.96 (dd, 1H, *J* = 3.0, 12.7 Hz), 3.81 (dd, 1H, *J* = 5.8, 12.4 Hz), 3.64 (m, 1H), 3.37 (m, 1H), 2.94 (dd, 1H, *J* = 4.7, 15.4), 2.75 (dd, 1H, *J* = 10.5, 15.1); ^{13}C NMR ($CDCl_3$) δ 176.0, 137.8, 129.6, 128.6, 128.5, 59.4, 56.8, 41.5, 37.5; HRMS m/z (ESI) calcd for $C_{11}H_{13}NO_2 \cdot H_2O$ $(M+H)^+$ 210.1130, found 210.1133.

4.6.6. (4*R*,5*R*)-5-Hydroxymethyl-4-phenylpyrrolidin-2-one, 6a—Amino lactone **10a** was stirred in a solution of freshly prepared NaOMe in MeOH (2 ml, pH ~ 9) at rt for 1 h. The reaction mixture was stirred with Amberlyst 15 (dry) ion-exchange resin (200 mg) at rt for 10 min. The solution was filtered and the filtrate was concentrated under reduced pressure. This afforded 3.2 mg of **6a** (80 % yield), whose NMR spectra were identical to those recorded with the material obtained from **5a**.

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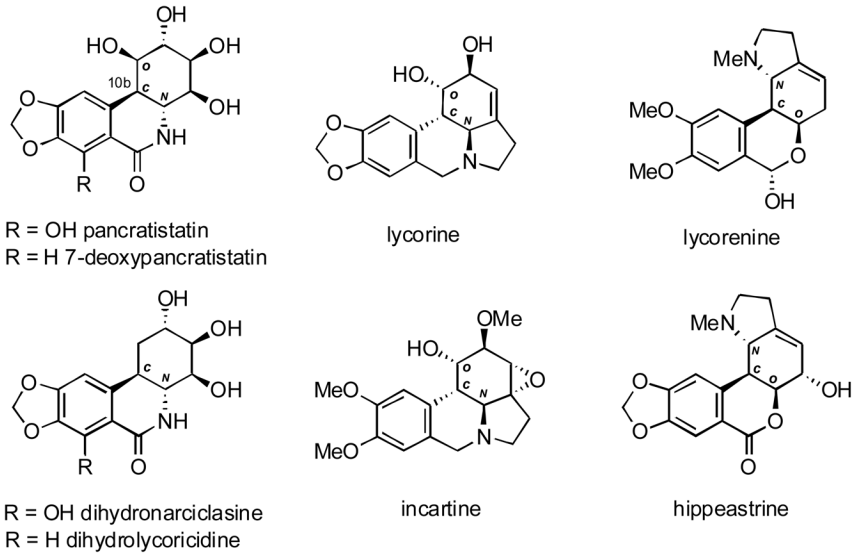


Figure 1.
Selected amaryllidaceae constituents.

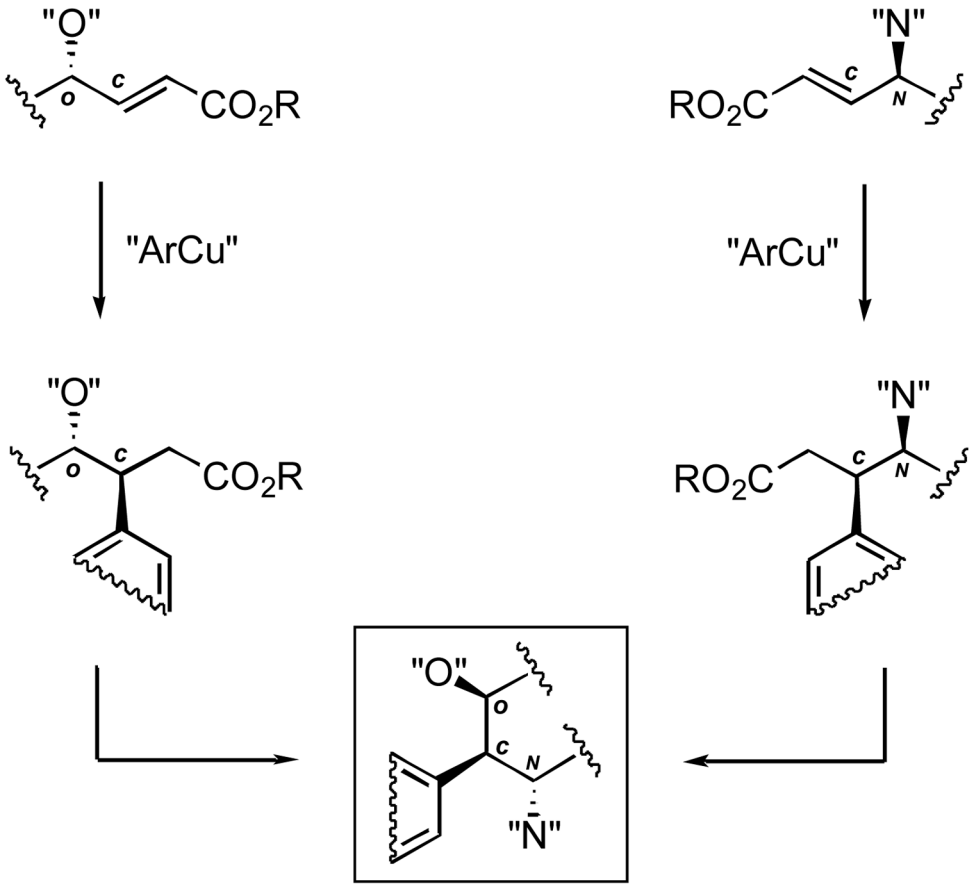


Figure 2.
Correlation of stereochemical relationships in open-chain and cyclic structures.

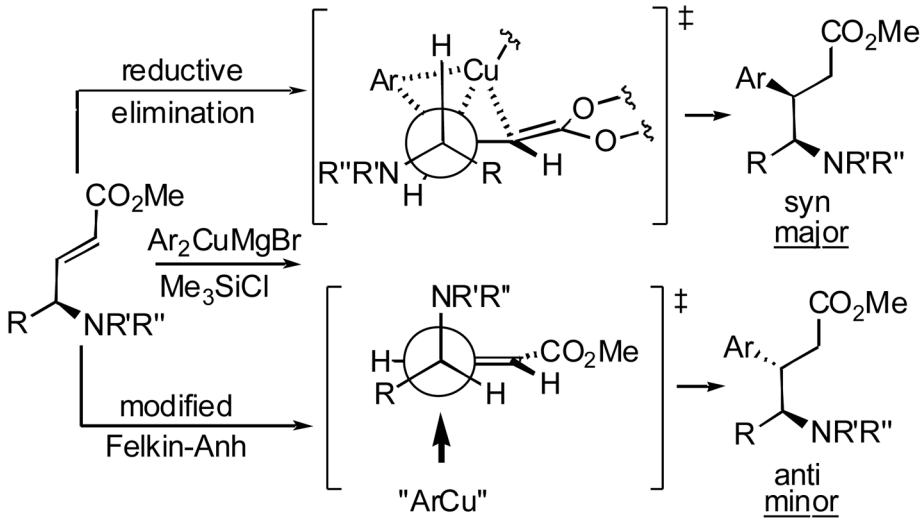
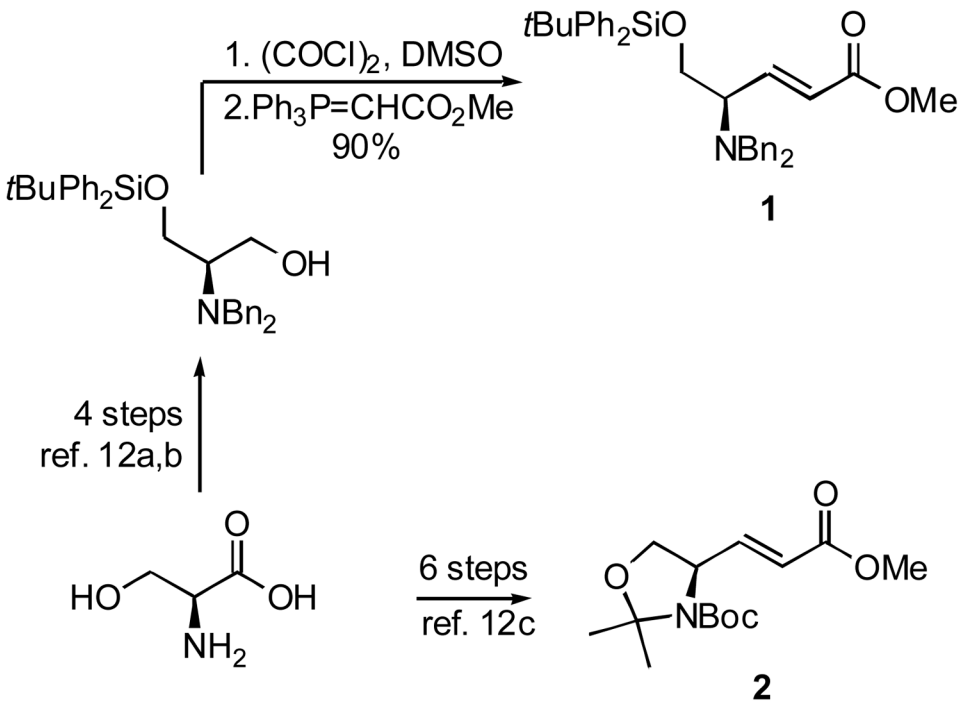
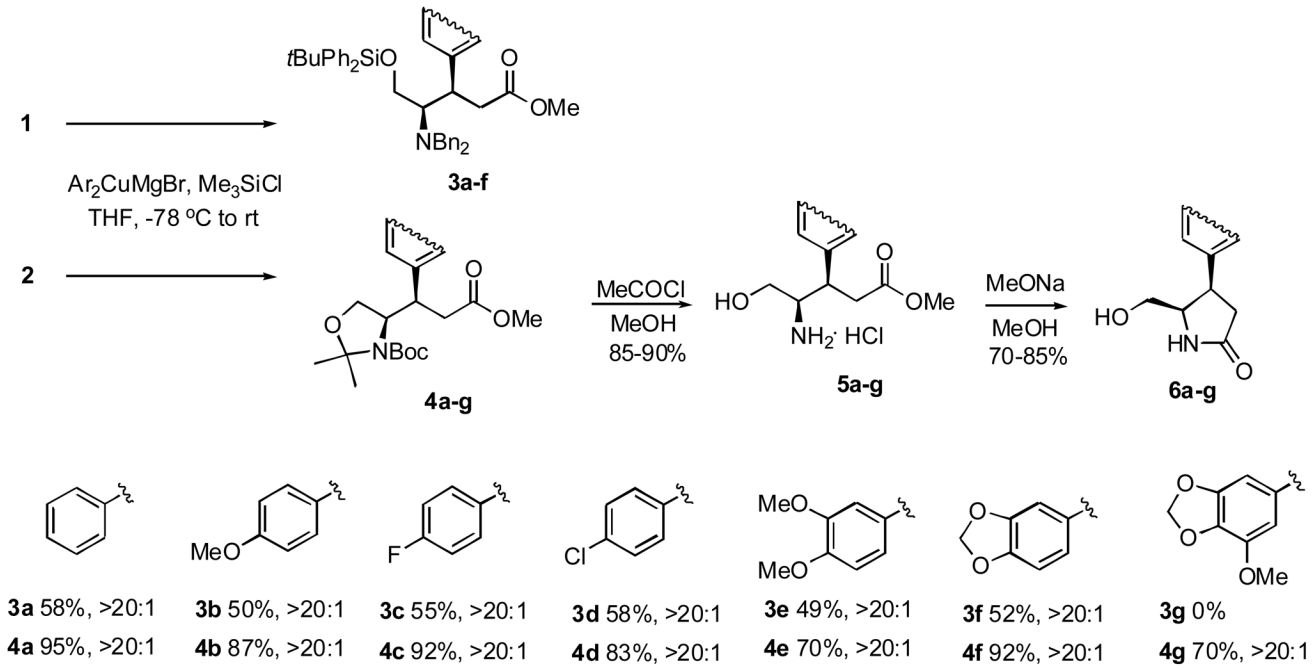


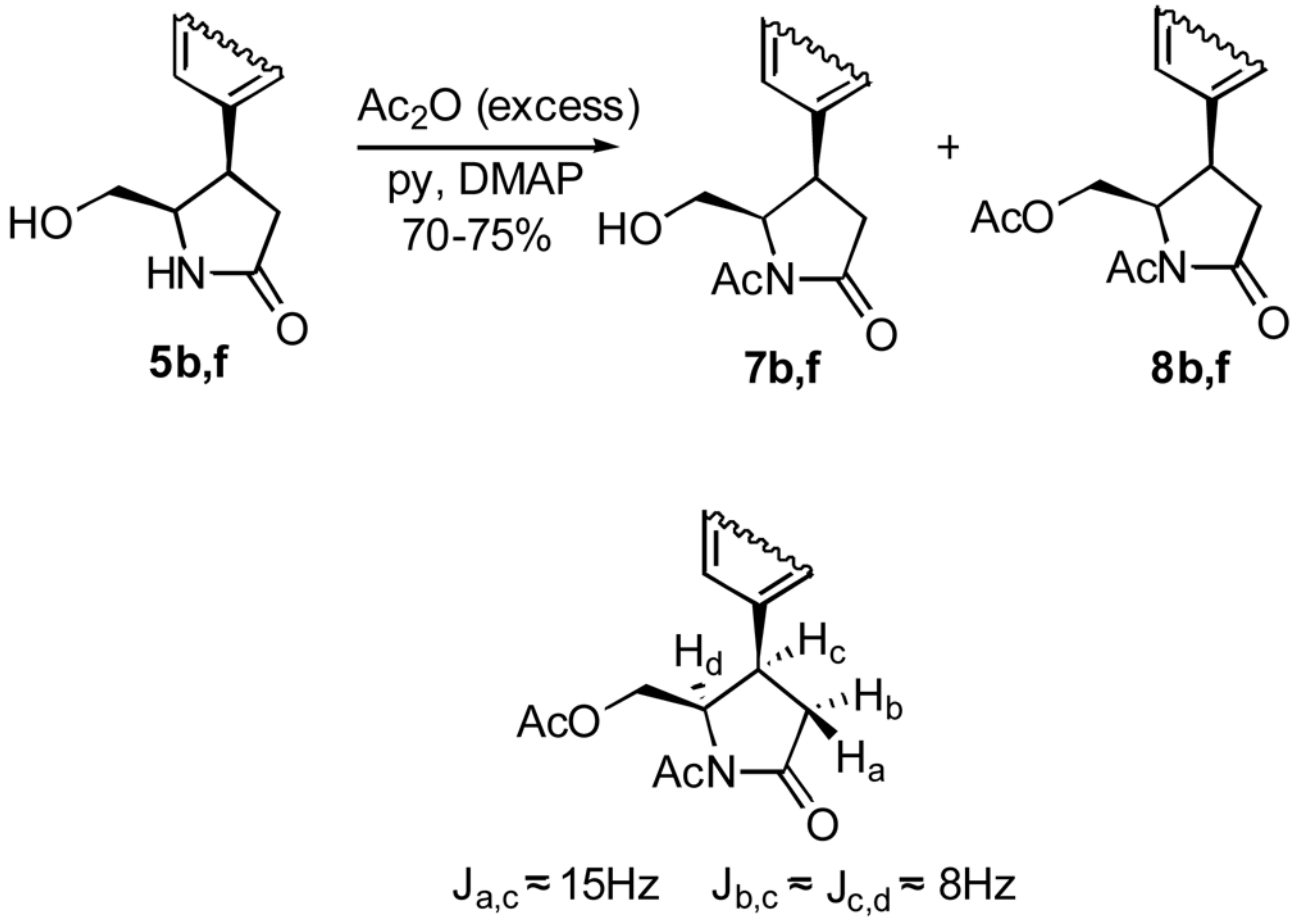
Figure 3.
Reductive elimination and modified Felkin-Anh stereochemical models.



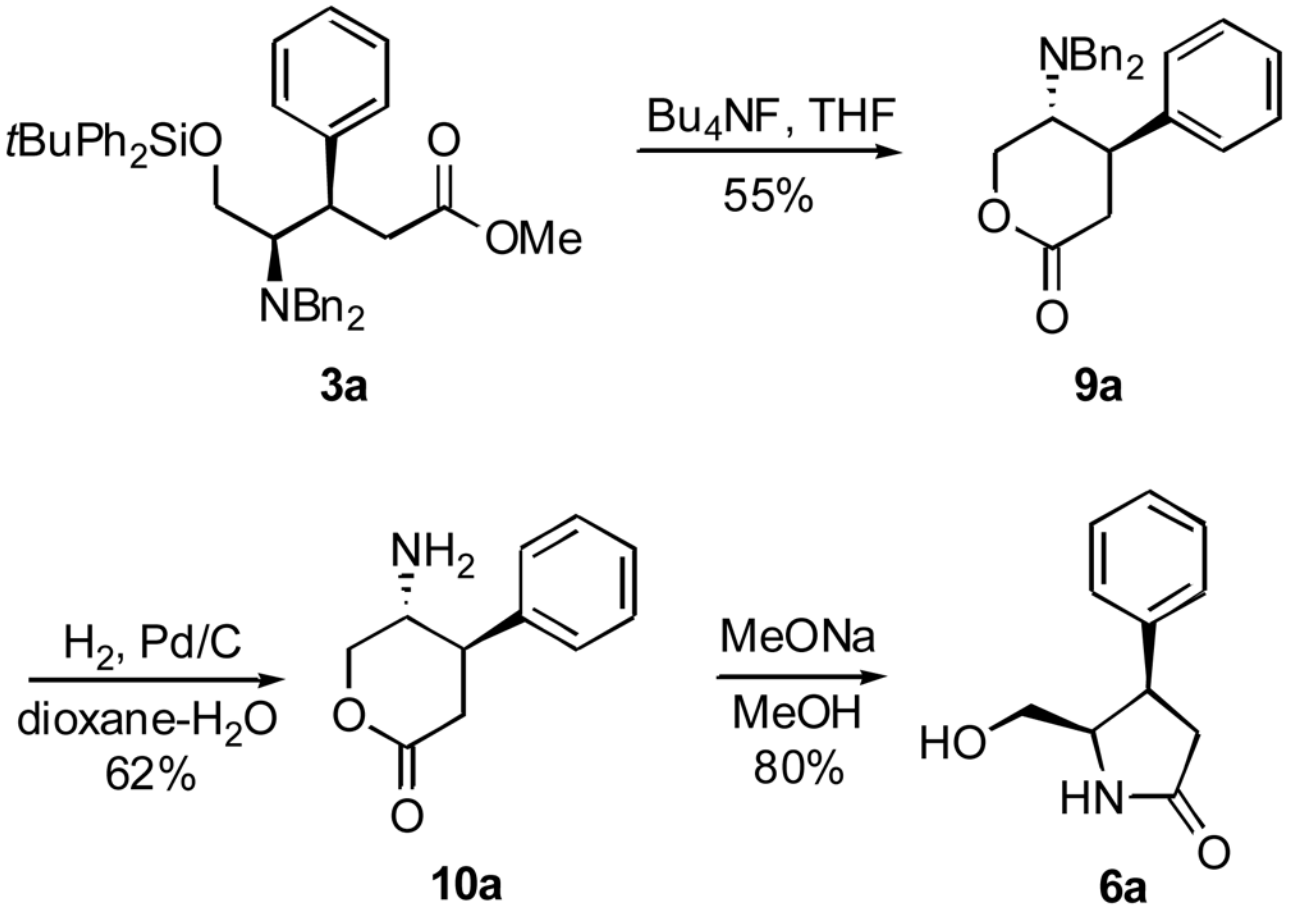
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.