Available online at www.sciencedirect.com
ScienceDirect
C. R. Chimie 11 (2008) 5–18
COMPTES RENDUS CHIMIE
http://france.elsevier.com/direct/CRAS2C/

Full paper / Mémoire

A versatile approach to (4*S*,5*R*)-4-benzyloxy-5-(α-hydroxyalkyl)-2-pyrrolidinones: Experimental evidences to the computational predictions

Xiang Zhou, Pan-Yuan Zhang, Jian-Liang Ye*, Pei-Qiang Huang*

Department of Chemistry and The Key Laboratory for Chemical Biology of Fujian Province, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, PR China

Received 8 December 2006; accepted after revision 13 February 2007
Available online 23 May 2007

Abstract

A versatile and highly diastereoselective four-step approach to (4*S*,5*R*)-*N*-benzyl-4-benzyloxy-5-(α-hydroxyalkyl)-2-pyrrolidinones **2**, which starts from readily available (*S*)-*N*,*O*-dibenzylmalimide (**5**), is reported. Substituted 2-pyrrolidinones **2** are valuable building blocks for the asymmetric synthesis of hydroxylated pyrrolidine alkaloids. The method demonstrates high diastereoselectivities at the pyrrolidinone ring (C-4/C-5 *trans*), and low diastereoselectivities at the carbinolic center. Some interesting phenomena such as a remarkable difference in reactivity between the two diastereomeric *N*,*O*-acetals **6** towards the dehydration reactions, the isomerization of *trans*-diastereomers to *cis*-diastereomers (**6**), and the exclusive formation of (*E*)-enamides **8** were observed. These results provide experimental proofs to our previous computational predictions, or have been rationalized by calculations. ***To cite this article: X. Zhou et al., C. R. Chimie 11 (2008).***

Résumé

Nous présentons dans cet article une voie souple pour la synthèse des (4*S*,5*R*)-*N*-benzyl-4-benzyloxy-5-(α-hydroxyalkyl)-2-pyrrolidinones **2** en quatre étapes à partir d'imide (*S*)-malique *N*,*O*-dibenzylée (**5**). Les produits sont des briques moléculaires de valeur pour la synthèse asymétrique des alkaloïdes pyrrolidiniques hydroxylés. Les diastéréosélectivités sont excellentes au niveau du cycle pyrrolidinonique (C-4/C-5 *trans*) et faibles à celui du centre carbinolique. Les différences de réactivité notables observées entre les deux *N*,*O*-acétals (**6**) diastéréomères vis-à-vis de la réaction de déshydratation, de l'isomérisation des *trans*-diastéréomères en *cis*-diastéréomères (**6**) et de la formation exclusive des (*E*)-énamides **8** sont en bon accord avec les resultats des calculs sur ordinateur, ou ont été expliquées à l'aide de ces derniers. ***Pour citer cet article : X. Zhou et al., C. R. Chimie 11 (2008).***

* Corresponding authors.
E-mail address: pqhuang@xmu.edu.cn (P.-Q. Huang).

1631-0748/$ - see front matter © 2007 Académie des sciences. Published by Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.crci.2007.02.018

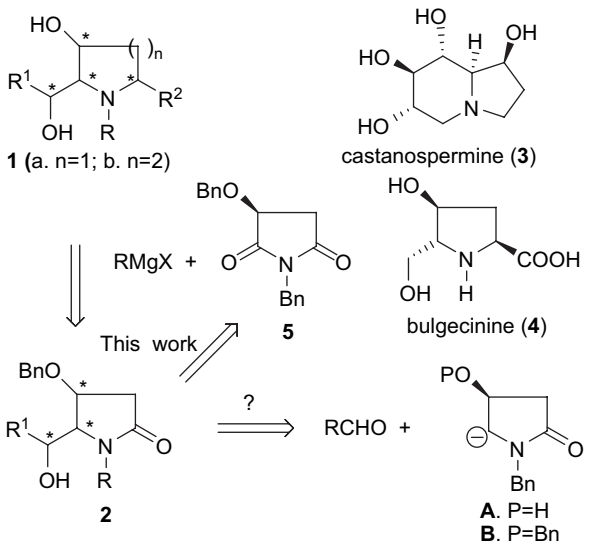
Keywords: Dehydration; Enamides; 2-Pyrrolidinones; Epoxidation; Asymmetric synthesis; Stereoelectronic effects; Computations; Reaction mechanism

Mots-clés : Déshydratation ; Énamides ; 2-Pyrrolidinones ; Époxydation ; Synthèse asymétrique ; Effets stéréoélectroniques ; Calculs sur ordinateur ; Mécanisme réactionnel

1. Introduction

2-(α-Hydroxyalkyl) 5-substituted 3-pyrrolidinols and their higher homologues **1a/1b** are key structural features found in a number of polyhydroxylated bioactive alkaloids [1], and azasugars [2]. Castanospermine [3] (**3**) and bulgecinine [4] (**4**) are two typical examples among many others. For the asymmetric synthesis of such polyhydroxylated pyrrolidines, carbanion **A** represents a highly desirable synthon according to a conceptually attractive retrosynthetic analysis displayed in Scheme 1. However, although a huge number of methods have been developed for the carbanion-based C–C bond formation [5], and generation of chiral non-racemic *N*-α-carbanion of 4-hydroxy-2-pyrrolidinone **A** has been reported [6], the C–C bond formation based on synthon **A**, as well as generation and C–C bond formation of chiral non-racemic *N*-α-carbanion of 4-benzyloxy-2-pyrrolidinone **B**, remains as a challenging problem in carbanion chemistry [7,8].

In recent years, we have been engaged [6] in the development of carbanion-based asymmetric approaches to 5-alkyl 4-hydroxy-2-pyrrolidinones (via tetramates) [9], 2-(α-hydroxyalkyl)-3-pyrrolidinols [7,10], 2,5-dialkyl-3-pyrrolidinols [9a], and 2-(α-hydroxyalkyl) 3-amino-pyrrolidines [11]. As a continuation of these studies and in connection with a related project [12], we have communicated recently a flexible approach to 5-(α-hydroxyalkyl) 4-benzyloxy-2-pyrrolidinones **2** [13], and we now report the full details of this method, and the results of further investigations on the key dehydration of diastereomeric *N*,*O*-acetals **6**.



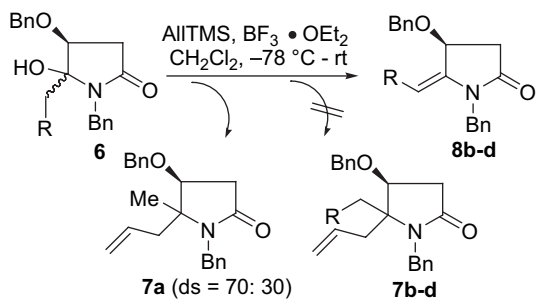
Scheme 1.

2. Results and discussion

Our approach to **2** stemmed from some unexpected results obtained in a related project [12]. When we attempted the α-amidoallylation (AllTMS, $BF_3 \cdot OEt_2$, CH_2Cl_2, −78 °C to rt, 15 h) of *N*,*O*-acetals **6a–d**, only **6a** led to the desired α-amidoallylation product **7a**, the reaction of **6b–d** gave the dehydrated products **8b–d**, respectively, in 75–82% yields (Scheme 2 and Table 1). In view of the recent advances in the enamide chemistries [14,15], it was realized that these findings would found a basis for a versatile approach to 5-(α-hydroxyalkyl)-4-benzyloxy-2-pyrrolidinones **2**, and thus provide an alternative solution to the challenging problem of generating and reaction of synthon **B**.

To this end, further investigations [13] on the acid catalyzed dehydrations [14] of *N*,*O*-acetals **6** [12] have been undertaken and $TsOH \cdot H_2O$ turned out to be an effective and simple catalyst, which was used for further investigations.

The requisite *N*,*O*-acetals **6** were obtained by Grignard reaction of (*S*)-*N*,*O*-dibenzylmalimide (**5**) as described previously [12] (Scheme 3). Most of the *N*,*O*-acetals (**6a–h**) were obtained with excellent C-2 regioselectivities (only one regioisomer was obtained



Scheme 2.

Table 1
Results of the attempted α-amidoallylations of **6a–d**[a]

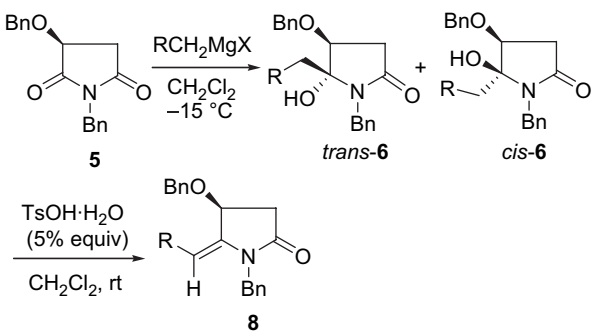
Entry	Starting material (alkyl group)	Product (yield, %)
1	**6a** (R = H)	**7a** (86)
2	**6b** (R = *n*-Pr)	**8b** (78)
3	**6c** (R = *i*-Pr)	**8c** (75)
4	**6d** (R = *n*-C_6H_{13})	**8d** (82)

[a] Reaction conditions: AllTMS, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C to rt, 15 h.

in each case) and with diastereoselectivities ranging from 6:1 to 8:1. Recent single-crystal X-ray crystallographic analysis and NOESY experiments showed that the major diastereomer is *trans*-**6** [16]. One exception is the reaction with benzyl magnesium bromide, which led to **6i** as a 1:1 diastereomeric mixture. The results of the TsOH (5% mol. equiv)-promoted dehydration reactions of the major diastereomers of **6** are displayed in Table 2.

It is worth noting that the dehydration of **6a** was unsuccessful under several acidic conditions (TsOH; TFA; CSA; HCl; H_2SO_4) [14c,14d]. To our delight, the desired dehydration product **8a** (yield: 67%) was obtained by refluxing a mixture of **6a** and Ac_2O/py in CH_2Cl_2 for 2 days [14e]. If a catalytic amount of DMAP was added, higher yield (78%) of **8a** was obtained (Table 2, entry 1).

More importantly, all the dehydration reactions were incomplete, and partial epimerization of *trans*-diastereomer (*trans*-**6**) to *cis*-diastereomer (*cis*-**6**) was observed according to TLC monitoring. To gain an insight into the reactivity difference between two pairs of diastereomers (*cis*-**6**/*trans*-**6**), the dehydration of either pure diastereomer or diastereomeric mixtures of *cis*-**6e**/*trans*-**6e** were performed separately. Pure diastereomer *trans*-**6e** provided the dehydration product **8e** in 69% yield, alongside with 29% of *cis*-**6e** (Table 3, entry 1). The result implicates clearly partial epimerization of *trans*-**6e** to *cis*-**6e** under the reaction conditions. Starting from a 25:75 mixture of *cis*-**6e**/*trans*-**6e**, **8e** and *cis*-**6e** were obtained in 62% and 34% yield,



Scheme 3.

Table 2
Grignard reactions with **5** and the subsequent TsOH-mediated dehydration reactions of **6**

Entry	RCH_2MgX	Product **6** (yield %)	Product **8** (yield %)
1	CH_3MgI	**6a** (95)[a]	**8a** (78[c], 88[d])[e]
2	*n*-$PrCH_2MgBr$	**6b** (95)[a]	**8b** (74[c], 97[d])
3	*i*-$PrCH_2MgBr$	**6c** (86)[a]	**8c** (83[c], 95[d])
4	*n*-$C_6H_{13}CH_2MgBr$	**6d** (90)[a]	**8d** (63[c], 92[d])
5	*n*-$BuCH_2MgBr$	**6e** (81)[a]	**8e** (69[c], 91[d])
6	$MeCH_2MgBr$	**6f** (83)[a]	**8f** (67[c], 95[d])
7	$EtCH_2MgBr$	**6g** (99)[a]	**8g** (79[c], 93[d])
8	$BnCH_2MgBr$	**6h** (95)[a]	**8h** (55[c], 89[d])
9	$PhCH_2MgBr$	**6i** (92)[b]	**8i** (77[c], 93[d])

[a] Diastereomeric ratios: 6:1–8:1, only the major diastereomers were used for the dehydration.
[b] Diastereomeric ratio: *ca.* 1:1.
[c] Isolated yields.
[d] Yield based on the recovered starting material (*cis*-diastereomer).
[e] Conditions used: Ac_2O/py/DMAP (cat), CH_2Cl_2, reflux, 2 days.

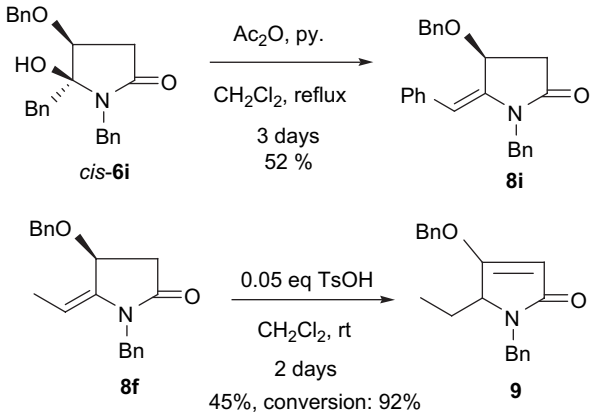
respectively (entry 2). A 1:1 mixture of *cis*-**6e** and *trans*-**6e** gave lower yield (48%) of **8e** and higher portion of *cis*-**6e** (50%, entry 3). When started from pure diastereomer *cis*-**6e** (entry 4), little desired dehydration product **8e** was observed. These results suggested that the yields of **8e** are depended on the content of the *trans*-diastereomer in the starting diastereomeric mixture (*cis*-**6e**/*trans*-**6e**), namely, only the *trans*-diastereomer (*trans*-**6e**) can be readily converted into **8e**.

When performing the reaction under modified conditions (Ac_2O, py) and at higher temperature with longer reaction time, the dehydration of the *cis*-diastereomer (*cis*-**6i**) was also observed (Scheme 4). However, prolonged reaction time led to the migration of the double bond yielding 3-pyrroline **9** (Scheme 4). Unexpectedly, when pure diastereomer *cis*-**6e** and a catalytic amount of TsOH were mixed in $CDCl_3$ in a NMR tube for 20 min at rt, ^1H NMR monitoring showed that the

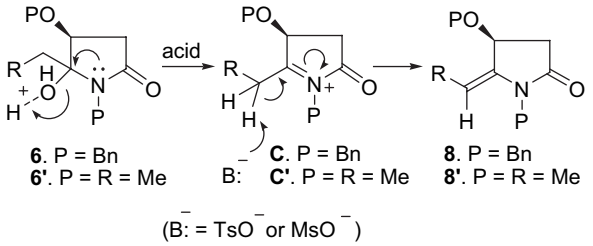
Table 3
The reactivity difference between diastereomers (*cis*-**6e** and *trans*-**6e**) in the dehydration reaction[a]

Entry	Ratio of starting **6e** (*cis*/*trans*)	Reaction time	Yield (%) of **8e**/(recovered *cis*-**6e**)
1	0:100	1 h	69 (29)[b]
2	25:75	1 h	62 (34)[b]
3	50:50	1 h	48 (50)[b]
4	100:0	1–12 h	[c]
5	100:0	20 min[d]	67 (33)[e]

[a] Reaction conditions: 0.05 mol. equiv. TsOH, CH_2Cl_2, rt.
[b] Isolated yield.
[c] Detected by TLC monitoring, little product formed, most of the starting material remained unchanged.
[d] Reaction run in $CDCl_3$ in a NMR tube and monitored by ^1H NMR.
[e] Ratio of the two diastereomers determined by ^1H NMR.



Scheme 4.



Scheme 5.

dehydrated product **8e** was formed and the **8e**/*cis*-**6e** ratio was 67:33 (Table 3, entry 5). This unexpected result can be attributed to the presence of a small amount of strongly acidic impurity in $CDCl_3$.

These results suggest that *cis*-**6** is the thermodynamically more stable diastereomer, which is in agreement with our computation prediction [16]. The computational studies showed that after chelation of Mg with two vicinal oxygens, the *cis*-addition (leading to *trans*-diastereomer) is kinetically more favorable over the corresponding *trans*-addition (leading to the *cis*-diastereomer), while the formation of the latter is more exothermic, demonstrating that it is the more thermodynamically stable isomer [16]. The different reactivities of the diastereomeric *N*,*O*-acetals under acidic conditions have been observed previously in a tricyclic oxazolidinolactam system [17]. This phenomenon can be attributed to a stereoelectronic effect [17,18].

Another feature of the dehydration reaction is that the reaction is highly stereoselective, and only (*E*)-enamides **8** were obtained. The stereochemistry of **8b** was determined by NOESY experiments. The formation of enamides **8** was considered to proceed in two steps, namely dehydroxylation leading to an *N*-acyliminium intermediate **C** followed by a deprotonation-driven double-bond migration (Scheme 5).

The exclusive formation of the (*E*)-enamides **8** could be understood in the light of the computational studies. It has been shown [16] that the delocalization of δ-electrons of the amide group (partial structure in the imide system) results in a C2−N1−C5 plane, which in turn gives rise to the rigidity of the five-membered ring, and hinders rotation of the RO−C3 around the C2−C3 bond. Because **8** is geometrically similar to a protected malimide, steric constrain between the alkyl group and *N*-Bn group in the (*Z*)-enamide is much more important compared with that between the alkyl group and *O*-Bn group in the (*E*)-enamide. As a result, (*E*)-enamide is the more thermodynamically stable isomer. This is confirmed by computational results, which shows that (*E*)-enamide **8f** is more stable than (*Z*)-enamide **8f** by 3.80 kcal/mol.

To get an insight into the stereoselective enamides formation, four possible transition states of mesylate promoted deprotonative double bond migration of model *N*-acyliminium intermediate **C′** (Scheme 5) were located. As shown in Fig. 1, due to the steric interactions between MeO and mesylate in (*E*)-TS2 and (*Z*)-TS2, and R-C5 and the *N*-methyl group in (*Z*)-TS1, the relative energies increased in the sequence (*E*)-TS1 < (*Z*)-TS1 < (*E*)-TS2 < (*Z*)-TS2, and the (*E*)-TS1 is the preferred transition state. Consequently, the formation of the (*E*)-enamide is both thermodynamically and dynamically favored.

Next, the one-pot epoxidation-ring opening reactions of compounds **8** were investigated by using the method of Nagasaka and co-workers [15]. Thus when **8b** was treated with 3 equiv MCPBA in a mixed solvent system of absolute MeOH and CH_2Cl_2 at −78 °C for 1 h, then warmed-up and stirred at rt for 10 h, the desired products **11b** were obtained as a mixture of four diastereomers with a combined yield of 83% (Scheme 6). To confirm the structures of the products, flash column chromatography separation of a sample of diastereomeric mixture of **11b** was undertaken, two pure diastereomers, and an inseparable mixture of the other two diastereomers were isolated and characterized.

The diastereomeric mixture of **11b** (four diastereomers) was then subjected to Lewis acid mediated ionic hydrogenation ($F_3B\cdot OEt_2$, Et_3SiH, CH_2Cl_2, −78 °C to rt) [19,14], which gave two separable diastereomers *trans*-**2b** in 1:2 ratio with a combined yield of 78%. The fact that the reductive demethoxylation of a mixture of four diastereomers (**11b**) led to only two diastereomers (**2b**) might implicate that the transformation of **11b** to **2b** proceeded via the intermediacy of *N*-acyliminium ion [20] **D** (R = *n*-Pr), and the stereoselectivity at the C-5 of the 2-pyrrolidinone ring was higher than

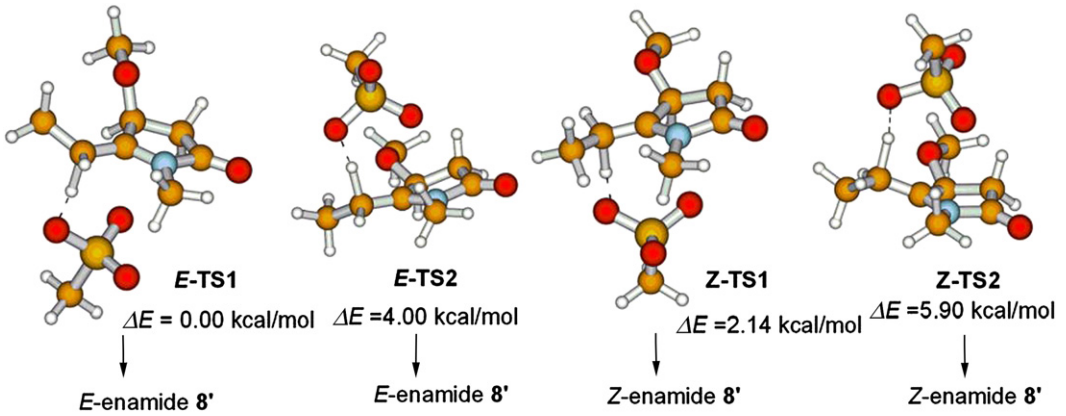
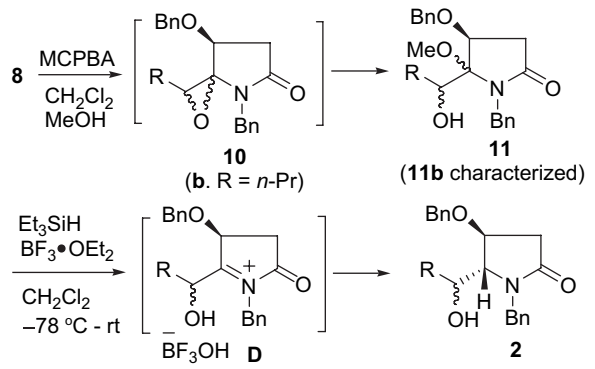


Fig. 1. B3LYP/6-31G*-optimized structures and relative energies of the transition states of mesylate-promoted deprotonative double-bond migration from the model *N*-acyliminium intermediate **C**′.

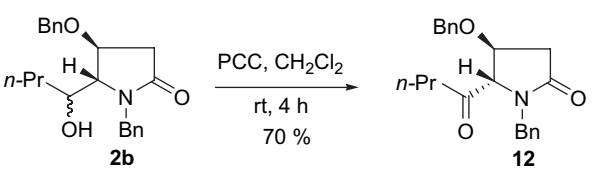
95%. Both the two diastereomers of **2b** were assigned to *trans* according to the observed vicinal coupling constant [21,13] (both $J_{4,5}$ = ca. 0 Hz). To further confirm this point, a diastereomeric mixture of **2b** (in 1:2 ratio) was treated with PCC (CH_2Cl_2, rt, 4 h, yield: 70%) (Scheme 7), and indeed, ketone (4*S*,5*R*)-**12** was obtained as the sole diastereomer ($J_{4,5}$ = 2.0 Hz) [21]. It allows us to conclude that the ionic hydrogenation resulted in high *trans*-stereoselectivity at the C-5 of 2-pyrrolidinone (**2**) and low selectivity at the C-1′. The stereochemistries at the C-1′of the two diastereomers of **2b** were not determined.

With the MCPBA epoxidation-ring opening of **8b** and the subsequent reductive demethoxylation reactions secured, the syntheses of other homologues or analogues of **2b** were investigated and the results were outlined in Table 4. The results displayed in Table 4 showed that the one-pot epoxidation-ring openings of other enamides **8** worked similarly as **8b** did in terms of chemical yields and diastereoselectivities, which demonstrated the flexibility of the method. Surprisingly, although the MCPBA epoxidation−MeOH ring opening reaction of **8a** proceeded smoothly to give the desired *N*,*O*-acetal **11a** in excellent yield, the subsequent reductive demethoxylation of **11a** gave **2a** in only 82:18 *trans*/*cis* diastereoselectivity.

As can be seen from Scheme **6**, the diastereoselectivity at the C-1′ during the transformation of **8** to **2** is determined in the epoxidation step. The observed low diastereoselectivity of the epoxidation might be attributed to two plausible competing transition states **E** and **F** (Scheme 8). While transition state **E** is favoured by avoiding the steric interaction between the incoming MCPBA and the C-4 benzyloxy group, possible hydrogen bond formation in the transition state **F** recompenses the steric interaction and the resultant hinge effect led the epoxidation to occur from the β-face. On the basis of these mechanistic considerations, investigations were carried out to improve the diastereoselectivity of the epoxidation by trying to alert the hydrogen bond formation. First, the reaction was performed at rt and in CH_2Cl_2 (instead of using a mixed solvent system: MeOH/CH_2Cl_2) for 2 h. However, only degradation [22] product **5** was obtained in 71% yield. When running the reaction at −78 °C for 1 h, then warmed-up and stirred at rt for 10 h, namely under the standard conditions (vide supra) except CH_2Cl_2 was used as the



Scheme 6.



Scheme 7.

Table 4
Results of the MCPBA-mediated epoxidation–ring-opening reactions of **8** and the subsequent reductive demethoxylation reactions leading to **2**

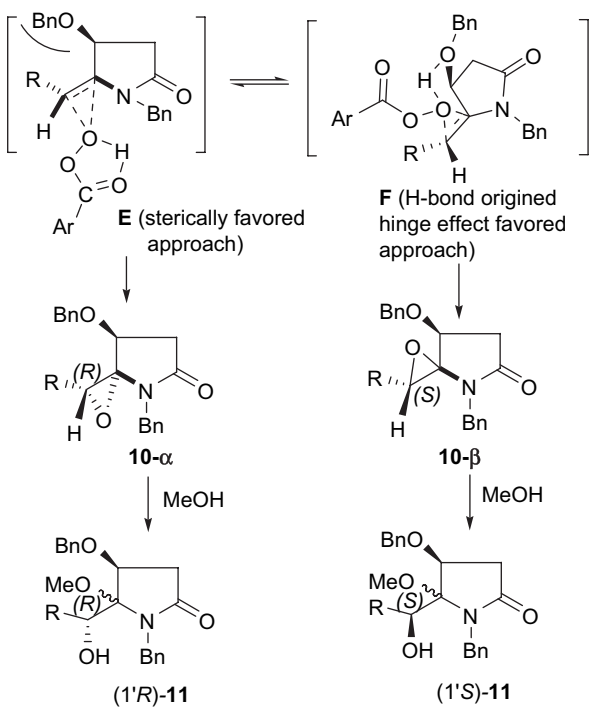
Entry	Starting material	Product **11** (yield %)[a]	Product **2** (yield %)[a]	Stereoselectivity at C-1′
1	**8a**	**11a** (91)	**2a** (93)[b,c]	–
2	**8b**	**11b** (83)	**2b** (78)	1:2[c]
3	**8c**	**11c** (80)	**2c** (85)	1:4[d]
4	**8d**	**11d** (86)	**2d** (81)	1:4[c]
5	**8e**	**11e** (86)	**2e** (78)	1:1[c]
6	**8f**	**11f** (85)	**2f** (85)	1:1.6[d]
7	**8g**	**11g** (90)	**2g** (74)	1:2[c]
8	**8h**	**11h** (93)	**2h** (98)	1:1.5[c]
9	**8i**	**11i** (90)	**2i** (98)	1:2.6[e]

[a] Combined yield of the diastereomers.
[b] Two diastereomers (*trans*/*cis* = 82:18) were obtained.
[c] Diastereomeric ratio determined by chromatography separation.
[d] diastereomeric ratio determined by ^{1}H NMR.
[e] Ratio determined by HPLC.

solvent, **5** was obtained once again in 72% yield. Next, we also tried the Ag_2O/I_2 system [23] under two types of conditions. Unfortunately, all led to complex mixture of products.

3. Conclusions

In summary, a flexible four-step *trans*-diastereoselective approach to (4*S*,5*R*)-*N*-benzyl-4-benzyloxy-5-hydroxyalkyl-2-pyrrolidinones **2** has been developed starting from (*S*)-*N*,*O*-dibenzyl malimide (**5**). To the best of our knowledge, this represents the first flexible asymmetric approach to the substituted 2-pyrrolidinone derivatives **2**, and provides an alternative solution to the challenging problems showed retrosynthetically in Scheme 1. Importantly, the observed higher reactivity of the *trans*-diastereomer of **6** towards the dehydration reaction, the isomerization of *trans*-diastereomers to *cis*-diastereomers, as well as the exclusive formation of the (*E*)-enamides **8**, provides experimental proofs to our previous predictions made on the basis of computational studies, or has been rationalized by calculations.



Scheme 8.

4. Experimental

4.1. General

Melting points were determined on a Yanaco MP-500 micromelting point apparatus and were uncorrected. Infrared spectra were measured with a Nicolet Avatar 330 FT-IR spectrometer using the film KBr pellet technique. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AV400 or a Varian Unity$^+$ 500 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded by Bruker Dalton Esquire 3000 plus LC-MS apparatus. Optical rotations were measured with a PerkinElmer 341 automatic polarimeter. Flash column chromatography was carried out on silica gel (300–400 mesh). THF was distilled over sodium. Dichloromethane was distilled over P_2O_5.

4.2. General procedure for the preparation of *6a–i* from (S)-N,O-dibenzyl malimide (*5*)

To a cooled (−15 to −10 °C) solution of *N*,*O*-dibenzylmalimide **5** (1.0 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise a Grignard reagent (3.0 mmol) in diethyl ether under nitrogen atmosphere. After being stirred at the same temperature for 4 h, the reaction was quenched with a saturated aqueous solution of ammonium chloride (6 mL) and extracted with dichloromethane (3 × 30 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. Filtration through a short pad of SiO_2 eluting with ethyl acetate–petroleum ether gave a mixture of two diastereomers **6** (yield: 81–99%), which, without separation, was used in the next step as it was. The diastereomeric ratios were determined either by flash chromatographic separation or by ^{1}H NMR spectroscopy of the crude mixture.

4.3. (S)-1-Benzyl-4-(benzyloxy)-5-methylenepyrrolidin-2-one (**8a**)

To a solution of **6a** (1.0 mmol) and DMAP (0.05 mmol) in CH_2Cl_2 (10 mL) were added pyridine (0.8 mL, 10.0 mmol) and Ac_2O (0.47 mL, 5.0 mmol). The mixture was heated at reflux for 2 days, then cooled to room temperature, diluted with CH_2Cl_2, and washed successively with 1.0 M HCl and water. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel eluting with ethyl acetate/PE (1:2) to give **8a** (yield 78%) as a colorless oil: $[\alpha]_D^{20}$ +60.0 (*c* 0.4, $CHCl_3$); IR (film): 3030, 2923, 1722, 1648, 1449, 1394, 1341, 1211, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.65 (dd, $J = 3.0$, 17.5 Hz, 1H, $COCH_2$), 2.79 (dd, $J = 7.3$, 17.5 Hz, 1H, $COCH_2$), 4.40 (dd, $J = 1.4$, 1.9 Hz, 1H, $=CH_2$), 4.45 (dd, $J = 1.0$, 1.9 Hz, 1H, $=CH_2$), 4.51–4.53 (m, 1H, BnOCH), 4.54 (d, $J = 11.6$ Hz, 1H, $PhCH_2O$), 4.59 (d, $J = 11.6$ Hz, 1H, $PhCH_2O$), 4.65 (d, $J = 15.5$ Hz, 1H, $PhCH_2N$), 4.75 (d, $J = 15.5$ Hz, 1H, $PhCH_2N$), 7.20–7.40 (m, 10H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.2, 43.4, 70.5, 72.6, 89.5, 127.1, 127.4, 127.9, 128.0, 128.5, 128.6, 135.6, 137.4, 146.4, 173.3 ppm; MS (ESI, *m/z*): 316 ($M + Na^+$, 6), 294 ($M + H^+$, 100); Anal. calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.74; H, 6.39; N, 4.42.

4.4. Representative procedure for the dehydration of N,O-acetals **8b–i**

To a solution of **6b** (62 mg, 0.2 mmol) in CH_2Cl_2 (3 mL) was added a catalytic amount of *p*-toluenesulfonic acid monohydrate. The mixture was stirred at rt for 2 h. The reaction was quenched by a saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×5 mL). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel eluting with ethyl acetate/PE (1:2) to give **8b** (44 mg, yield 74%) as a colorless oil.

4.4.1. (S,E)-1-Benzyl-4-(benzyloxy)-5-butylidenepyrrolidin-2-one (**8b**)

Compound **8b**: yield, 74%. Colorless oil; $[\alpha]_D^{20}$ +62.0 (*c* 0.4, $CHCl_3$); IR (film): 3060, 3023, 2957, 2929, 2870, 1719, 1674, 1496, 1454, 1409, 1340, 1230, 1201, 1070, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.80 (t, $J = 7.3$ Hz, 3H, CH_3), 1.22–1.38 (m, 2H, $MeCH_2$), 1.94–2.12 (m, 2H, $EtCH_2$), 2.68 (dd, $J = 1.7$, 17.8 Hz, 1H, $COCH_2$), 2.78 (dd, $J = 7.0$, 17.8 Hz, 1H, $COCH_2$), 4.42 (d, $J = 11.2$ Hz, 1H, $PhCH_2O$), 4.53 (d, $J = 11.2$ Hz, 1H, $PhCH_2O$), 4.70 (s, 2H, $PhCH_2N$), 4.74 (dd, $J = 1.7$, 7.0 Hz, 1H, BnOCH), 4.84 (t, $J = 7.5$ Hz, 1H, $=CH$), 7.20–7.40 (m, 10H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 23.3, 28.7, 36.6, 43.4, 69.9, 70.2, 108.0, 127.0, 127.2, 128.0, 128.1, 128.3, 128.4, 128.5, 135.8, 137.3, 138.9, 173.1 ppm; MS (ESI, *m/z*): 336 ($M + H^+$, 100); Anal. calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.81; H, 7.47; N, 4.00.

4.4.2. (S,E)-1-Benzyl-4-(benzyloxy)-5-(2-methylpropylidenepyrrolidin-2-one (**8c**)

Compound **8c**: yield, 83%. Colorless oil; $[\alpha]_D^{20}$ +38.8 (*c* 1.0, $CHCl_3$); IR (film): 3030, 2957, 2867, 1718, 1673, 1410, 1339 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, $J = 6.5$ Hz, 3H, CH_3), 0.96 (d, $J = 6.5$ Hz, 3H, CH_3), 2.48–2.58 (m, 1H, Me_2CH), 2.68 (dd, $J = 2.0$, 17.9 Hz, 1H, $COCH_2$), 2.78 (dd, $J = 7.0$, 17.9 Hz, 1H, $COCH_2$), 4.44 (d, $J = 11.2$ Hz, 1H, $PhCH_2O$), 4.52 (d, $J = 11.2$ Hz, 1H, $PhCH_2O$), 4.67 (dd, $J = 2.0$, 7.0 Hz, 1H, BnOCH), 4.68 (s, 2H, $PhCH_2N$), 4.77 (d, $J = 7.0$, 1.8 Hz, 1H, $=CH$), 7.20–7.40 (m, 10H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.6, 23.7, 26.7, 36.5, 43.4, 69.9, 70.4, 115.5, 127.0, 127.2, 127.9, 128.0, 128.4, 135.8, 137.1, 137.3, 173.0 ppm; MS (ESI, *m/z*): 337 [$(M + 2H)^+$, 24], 358 ($M + Na^+$, 36), 336 ($M + H^+$, 100); Anal. calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.21; H, 7.37; N, 4.36.

4.4.3. (S,E)-1-Benzyl-4-(benzyloxy)-5-heptylidenepyrrolidin-2-one (**8d**)

Compound **8d**: yield, 63%. Colorless oil; $[\alpha]_D^{20}$ +68.7 (*c* 0.9, $CHCl_3$); IR (film): 3030, 2925, 2857, 1720, 1674, 1495, 1453, 1409, 1338, 1204, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, $J = 7.0$ Hz, 3H, CH_3), 1.10–1.32 (m, 8H, $Me(CH_2)_5$), 1.96–2.12 (m, 2H, $Me(CH_2)_5$), 2.68 (dd, $J = 2.0$, 17.9 Hz, 1H, $COCH_2$), 2.77 (dd, $J = 7.0$, 17.9 Hz, 1H, $COCH_2$), 4.44 (d, $J = 11.2$ Hz, 1H, $PhCH_2O$), 4.53 (d, $J = 11.2$ Hz, 1H, $PhCH_2O$), 4.69 (s, 2H, $PhCH_2N$), 4.74 (dd, $J = 2.0$, 7.0 Hz, 1H, BnOCH), 4.83 (td, $J = 7.3$, 1.0 Hz, 1H, $=CH$), 7.20–7.40 (m, 10H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.6, 26.8, 28.8, 30.1, 31.6, 36.6, 43.5, 69.9, 70.2, 108.3, 127.0, 127.2, 128.0, 128.1, 128.4, 128.5, 135.9, 137.3, 138.7, 173.1; MS (ESI, *m/z*): 400 ($M + Na^+$, 11), 379 [$(M + 2H)^+$, 28], 378 ($M + H^+$, 100) ppm; Anal. calcd for $C_{25}H_{31}NO_2$: C, 79.54; H, 8.28; N, 3.71. Found: C, 79.25; H, 8.29; N, 3.84.

*4.4.4. (S,E)-1-Benzyl-4-(benzyloxy)-5-pentylidenepyrrolidin-2-one (**8e**)*

Compound **8e**: yield, 69%. Colorless oil; $[\alpha]_D^{20}$ +51.6 (*c* 0.5, $CHCl_3$); IR (film): 3030, 2926, 2861, 1719, 1675, 1496, 1453, 1409, 1338, 1202, 1071, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, $J = 7.2$ Hz, 3H, CH_3), 1.15–1.35 (m, 4H, $Me(CH_2)_3$), 1.98–2.12 (m, 2H, $Me(CH_2)_3$), 2.68 (dd, $J = 1.7$, 17.8 Hz, 1H, $COCH_2$), 2.78 (dd, $J = 7.1$, 17.8 Hz, 1H, $COCH_2$), 4.45 (d, $J = 11.2$ Hz, 1H, $PhCH_2O$), 4.54 (d, $J = 11.2$ Hz, 1H, $PhCH_2O$), 4.70 (s, 2H, $PhCH_2N$), 4.76 (dd, $J = 1.7$, 7.1 Hz, 1H, BnOCH), 4.84 (t, $J = 7.5$ Hz, 1H, =CH), 7.16–7.40 (m, 10H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.2, 26.5, 32.3, 36.6, 43.5, 69.9, 70.2, 108.2, 127.0, 127.2, 128.0, 128.1, 128.4, 128.5, 135.9, 137.3, 138.7, 173.0 ppm; MS (ESI, *m/z*): 351 [$(M + 2H)^+$, 27], 350 ($M + H^+$, 100); Anal. calcd for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79; N, 4.01. Found: C, 78.57; H, 7.69; N, 4.20.

*4.4.5. (S,E)-1-Benzyl-4-(benzyloxy)-5-ethylidenepyrrolidin-2-one (**8f**)*

Compound **8f**: yield, 67%. Colorless oil; $[\alpha]_D^{20}$ +99.7 (*c* 0.3, $CHCl_3$); IR (film): 3031, 2923, 2861, 1718, 1677, 1496, 1412, 1337, 1205, 1069 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.70 (d, $J = 7.1$ Hz, 3H, CH_3), 2.70 (dd, $J = 1.9$, 17.9 Hz, 1H, $COCH_2$), 2.80 (dd, $J = 7.1$, 17.9 Hz, 1H, $COCH_2$), 4.44 (d, $J = 11.3$ Hz, 1H, $PhCH_2O$), 4.54 (d, $J = 11.3$ Hz, 1H, $PhCH_2O$), 4.70 (d, $J = 15.6$ Hz, 1H, $PhCH_2N$), 4.74 (d, $J = 15.6$ Hz, 1H, $PhCH_2N$), 4.78 (dd, $J = 1.9$, 7.1 Hz, 1H, BnOCH), 4.90 (qd, $J = 7.1$, 1.1 Hz, 1H, =CH), 7.20–7.40 (m, 10H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.0, 36.5, 43.4, 70.0, 70.1, 101.9, 127.0, 127.2, 127.9, 128.0, 128.4, 128.5, 135.9, 137.3, 139.6, 173.0 ppm; MS (ESI, *m/z*): 330 ($M + Na^+$, 90), 308 ($M + H^+$, 100); Anal. calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.99; H, 6.83; N, 4.84.

*4.4.6. (S,E)-1-Benzyl-4-(benzyloxy)-5-propylidenepyrrolidin-2-one (**8g**)*

Compound **8g**: yield, 79%. Colorless oil; $[\alpha]_D^{20}$ +42.7 (*c* 0.3, $CHCl_3$); IR (film): 3030, 2962, 2927, 2867, 1717, 1673, 1496, 1450, 1409, 1338, 1256, 1200, 1072, 1016 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.60 (t, $J = 7.5$ Hz, 3H, CH_3), 2.02–2.14 (m, 2H, $MeCH_2$), 2.66 (dd, $J = 1.8$, 17.8 Hz, 1H, $COCH_2$), 2.76 (dd, $J = 7.1$, 17.8 Hz, 1H, $COCH_2$), 4.44 (d, $J = 11.2$ Hz, 1H, $PhCH_2O$), 4.52 (d, $J = 11.2$ Hz, 1H, $PhCH_2O$), 4.69 (s, 2H, $PhCH_2N$), 4.76 (dd, $J = 1.8$, 7.1 Hz, 1H, BnOCH), 4.83 (td, $J = 7.5$, 1.0 Hz, 1H, =CH), 7.18–7.40 (m, 10H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.9, 20.2, 36.6, 43.4, 69.9, 70.2, 109.6, 127.0, 127.2, 127.9, 128.0, 128.4, 128.5, 135.9, 137.3, 138.5, 173.1 ppm; MS (ESI, *m/z*): 321 (M^+, 100); Anal. calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.07; H, 7.13; N, 4.68.

*4.4.7. (S,E)-1-Benzyl-4-(benzyloxy)-5-(2-phenylethylidene)pyrrolidin-2-one (**8h**)*

Compound **8h**: yield, 55%. Colorless oil; $[\alpha]_D^{20}$ +85.7 (*c* 0.6, $CHCl_3$); IR (film): 3028, 2920, 1719, 1672, 1495, 1449, 1406, 1337, 1205, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.73 (dd, $J = 2.3$, 17.8 Hz, 1H, $COCH_2$), 2.82 (dd, $J = 7.0$, 17.8 Hz, 1H, $COCH_2$), 3.38 (dd, $J = 8.1$, 16.0 Hz, 1H, $PhCH_2CH$=), 3.44 (dd, $J = 7.8$, 16.0 Hz, 1H, $PhCH_2CH$=), 4.44 (d, $J = 11.3$ Hz, 1H, $PhCH_2O$), 4.54 (d, $J = 11.3$ Hz, 1H, $PhCH_2O$), 4.69 (d, $J = 16.4$, 1H, $PhCH_2N$), 4.74 (d, $J = 16.4$, 1H, $PhCH_2N$), 4.82 (dd, J = 2.3, 7.0 Hz, 1H, BnOCH), 5.01 (td, $J = 7.8$, 1.2 Hz, 1H, =CH), 7.00–7.40 (m, 15H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.4, 36.4, 43.5, 70.2 (2C), 106.0, 126.0, 127.1, 127.3, 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 135.7, 137.1, 140.0, 140.5, 173.0 ppm; MS (ESI, *m/z*): 385 [$(M + 2H)^+$, 23], 384 ($M + H^+$, 100). Anal. calcd for $C_{26}H_{25}NO_2$: C, 81.43; H, 6.57; N, 3.65. Found: C, 81.23; H, 6.88; N, 3.69.

*4.4.8. (S,E)-1-Benzyl-5-benzylidene-4-(benzyloxy)pyrrolidin-2-one (**8i**)*

Compound **8i**: yield, 77%. Colorless oil; $[\alpha]_D^{20}$ +276.7 (*c* 0.7, $CHCl_3$); IR (film): 3029, 2924, 1718, 1652, 1495, 1449, 1410, 1344, 1222, 1283, 1064 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.72 (d, $J = 17.8$ Hz, 1H, $COCH_2$), 2.76 (dd, $J = 1.7$, 17.8 Hz, 1H, $COCH_2$), 4.35 (d, $J = 11.1$ Hz, 1H, $PhCH_2O$), 4.38 (d, $J = 11.1$ Hz, 1H, $PhCH_2O$), 4.74 (d, $J = 15.8$, 1H, $PhCH_2N$), 4.80 (d, $J = 15.8$, 1H, $PhCH_2N$), 4.86 (m, 1H, BnOCH), 5.90, (s, 1H, =CH), 7.10–7.30 (m, 15H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.2, 43.9, 69.6, 71.0, 108.9, 126.5, 127.0, 127.5, 128.0, 128.1, 128.2, 128.4, 128.7, 135.4, 135.5, 136.9, 141.0, 173.1; MS (ESI, *m/z*): 371 ($M + 2H^+$, 29), 370 ($M + H^+$, 100); Anal. calcd for $C_{25}H_{23}NO_2$: C, 81.27; H, 6.27; N, 3.79. Found: C, 80.99; H, 6.40; N, 3.93.

*4.5. General procedure for preparation of **11** from **8** utilizing MCPBA as an oxidant*

To a solution of **8** (1.0 mmol) in abs. MeOH (20 mL) and dry CH_2Cl_2 (10 ml) was added dropwise a solution of MCPBA (3.0 mmol) in CH_2Cl_2 (10 ml) at −78 °C under nitrogen atmosphere. After being stirred for 1 h

at the same temperature, and then at room temperature overnight, the reaction was quenched by addition of a solution of aqueous 10% $Na_2S_2O_3$ and saturated $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3×40 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. Filtration through a short pad of SiO_2 eluting with ethyl acetate–petroleum ether gave a mixture of diastereomers **11**. The diastereomeric ratios were determined either by flash chromatographic separation or by ^{1}H NMR spectra of the crude mixture.

*4.5.1. (4S,5R/S,1′R/S)-1-Benzyl-4-(benzyloxy)-5-(1-hydroxybutyl)-5-methoxy-pyrrolidin-2-one (**11b**)*

The oxidation of **8b** (470 mg, 1.4 mmol) under the conditions described in the general procedure and subsequent chromatography on silica gel eluting with ethyl acetate/PE (1:2) gave four diastereomers **11b** (combined yield 83%). The first diastereomer: R_f: 0.50 (AcOEt:PE = 1:2). White crystals, mp 88–89 °C (ethyl acetate/PE). $[\alpha]_D^{20}$ −33.2 (*c* 0.2, $CHCl_3$). IR (KBr pellet): 3438, 2955, 2925, 1696, 1505, 1398, 1356, 1088 cm^{-1}. ^{1}H NMR (500 MHz, CD_3CN) δ 0.64 (t, $J = 6.8$ Hz, 3H, CH_3), 0.98–1.16 (m, 2H, $Me(CH_2)_2$), 1.26–1.38 (m, 2H, $Me(CH_2)_2$), 2.49 (dd, $J = 6.6$, 17.8 Hz, 1H, $COCH_2$), 2.88 (dd, $J = 9.3$, 17.8 Hz, 1H, $COCH_2$), 2.95 (d, $J = 4.4$ Hz, 1H, OH), 3.26 (s, 3H, CH_3O), 3.60 (ddd, $J = 1.6$, 4.4, 10.4 Hz, 1H, C*H*OH), 4.13 (d, $J = 15.2$ Hz, 1H, $PhCH_2N$), 4.32 (dd, $J = 6.6$, 9.3 Hz, 1H, BnOCH), 4.62 (d, $J = 11.6$ Hz, 1H, $PhCH_2O$), 4.73 (d, $J = 11.6$ Hz, 1H, $PhCH_2O$), 5.00 (d, $J = 15.2$ Hz, 1H, $PhCH_2N$), 7.20–7.50 (m, 10H, Ar) ppm; ^{13}C NMR (125 MHz, CD_3CN) δ 14.7, 20.7, 34.4, 38.7, 44.7, 52.8, 73.5, 74.5, 76.3, 97.9, 128.5, 129.1, 129.4, 129.7, 129.8, 129.9, 140.0, 140.1, 175.0 ppm; MS (ESI, *m/z*): 384 ($M + H^+$, 9), 406 ($M + Na^+$, 100); Anal. calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 71.72; H, 7.70; N, 3.47. The second diastereomer: R_f: 0.26 (AcOEt:PE = 1:2). Colorless oil; $[\alpha]_D^{20}$ +24.7 (*c* 0.4, EtOH). IR (film): 3454, 3031, 2958, 2870, 1699, 1496, 1455, 1400, 1355, 1096, 1029 cm^{-1}. ^{1}H NMR (500 MHz, CD_3CN) δ 0.80 (t, $J = 7.2$ Hz, 3H, CH_3), 1.04–1.14 (m, 1H, $Me(CH_2)_2$), 1.33–1.60 (m, 3H, $Me(CH_2)_2$), 2.62 (dd, $J = 5.7$, 17.0 Hz, 1H, $COCH_2$), 2.78 (dd, $J = 7.6$, 17.0 Hz, 1H, $COCH_2$), 2.91 (d, $J = 8.0$ Hz, 1H, OH), 3.10 (s, 3H, CH_3O), 3.88 (dt, $J = 8.0$, 1.4 Hz, 1H, C*H*OH), 4.36 (dd, $J = 5.7$, 7.6 Hz, 1H, BnOCH), 4.46 (d, $J = 15.6$ Hz, 1H, $PhCH_2N$), 4.58 (d, $J = 11.6$ Hz, 1H, $PhCH_2O$), 4.62 (d, $J = 15.6$ Hz, 1H, $PhCH_2N$), 4.70 (d, $J = 11.6$ Hz, 1H, $PhCH_2O$), 7.20–7.50 (m, 10H, Ar) ppm; ^{13}C NMR (125 MHz, CD_3CN) δ 14.7, 20.7, 34.4, 38.7, 44.7, 52.8, 73.5, 74.5, 76.3, 97.9, 128.5, 129.1, 129.4, 129.7, 129.8, 129.9, 140.0, 140.1, 175.0 ppm; MS (ESI, *m/z*): 384 ($M + H^+$, 23), 406 ($M + Na^+$, 100). HRESIMS calcd for $[C_{23}H_{29}NO_4+H]^+$: 384.2169; found: 384.2165. The third fraction of diastereomers (including two inseparable diastereomers): R_f: 0.38 (AcOEt:PE = 1:2). IR (KBr pellet): 3527, 3031, 2958, 2871, 1699, 1496, 1453, 1403, 1354, 1211, 1112 cm^{-1}. Major diastereomer: ^{1}H NMR (500 MHz, CD_3CN) δ 0.92 (t, $J = 7.3$ Hz, 3H, CH_3), 1.22–1.40 (m, 2H, $Me(CH_2)_2$), 1.44–1.63 (m, 2H, $Me(CH_2)_2$), 2.56 (dd, $J = 3.7$, 17.6 Hz, 1H, $COCH_2$), 2.80 (dd, $J = 7.2$, 17.6 Hz, 1H, $COCH_2$), 2.86 (s, 3H, CH_3O), 3.30 (d, $J = 9.5$ Hz, 1H, OH), 3.87 (dt, $J = 9.5$, 2.4 Hz, 1H, C*H*OH), 4.40 (dd, $J = 3.7$, 7.2 Hz, 1H, BnOCH), 4.45 (d, $J = 15.3$ Hz, 1H, $PhCH_2N$), 4.53 (d, $J = 11.2$ Hz, 1H, $PhCH_2O$), 4.60 (d, $J = 15.3$ Hz, 1H, $PhCH_2O$), 4.68 (d, $J = 15.3$ Hz, 1H, $PhCH_2N$), 7.20–7.50 (m, 10H, Ar) ppm. Minor diastereomer: ^{1}H NMR (500 MHz, CD_3CN) δ 0.92 (t, $J = 6.8$ Hz, 3H, CH_3), 1.22–1.40 (m, 2H, $Me(CH_2)_2$), 1.64–1.81 (m, 2H, $Me(CH_2)_2$), 2.50 (dd, $J = 7.5$, 17.1 Hz, 1H, $COCH_2$), 2.82 (d, $J = 4.3$ Hz, 1H, OH), 2.84 (dd, $J = 8.9$, 17.1 Hz, 1H, $COCH_2$), 3.07 (s, 3H, CH_3O), 3.70 (ddd, $J = 2.0$, 4.3, 6.4 Hz, 1H, C*H*OH), 4.34 (d, $J = 15.1$ Hz, 1H, $PhCH_2N$), 4.36, (dd, $J = 7.5$, 8.9 Hz, 1H, BnOCH), 4.38 (d, $J = 11.3$ Hz, 1H, $PhCH_2O$), 4.56 (d, $J = 15.1$ Hz, 1H, $PhCH_2N$), 4.65 (d, $J = 11.3$ Hz, 1H, $PhCH_2O$), 7.20–7.50 (m, 10H, Ar) ppm. ^{13}C NMR (125 MHz, CD_3CN) for the two diastereomers: δ 14.8 (2C), 20.8, 21.0, 34.2, 35.1, 38.1 (2C), 43.6, 44.7, 50.8, 52.5, 72.6, 72.9, 73.0, 73.1, 74.4, 78.6, 98.3, 99.1, 128.3, 128.9, 129.3, 129.4, 129.5, 129.6, 129.7, 129.8, 130.0, 130.1, 138.8, 139.6, 139.8, 175.0, 177.4 ppm; MS (ESI, *m/z*): 384 ($M + H^+$, 13), 406 ($M + Na^+$, 100). HRESIMS calcd for $[C_{23}H_{29}NO_4+H]^+$: 384.2169; found: 384.2165.

*4.6. General procedure for preparation of **2** from **11** utilizing $Et_3SiH/F_3B\cdot OEt_2$*

To a cooled (−78 °C) solution of diastereomer mixture **11** (1.0 mmol) in dry dichloromethane (10 ml) was added dropwise triethylsilane (10 mmol) and boron trifluoride etherate (10.0 mmol) under nitrogen atmosphere. After being stirred for 6 h at the same temperature, the reaction was allowed to warm up and stirred at rt overnight. The reaction was quenched by saturated aqueous sodium bicarbonate and extracted with dichloromethane (3×20 ml). The combined extracts were washed with brine, dried over anhydrous

Na_2SO_4, filtered and concentrated in vacuum. The crude was purified by flash column chromatography on silica gel eluting with ethyl acetate–petroleum ether to give **2**.

*4.6.1. (4S,5S)-1-Benzyl-4-(benzyloxy)-5-hydroxymethyl-pyrrolidin-2-one (cis-**2a**), (4S,5R)-1-Benzyl-4-(benzyloxy)-5-hydroxymethyl-pyrrolidin-2-one (trans-**2a**)*

Reduction of **8a** gave *cis*-**2a** and *trans*-**2a** in 18:82 ratio with a combined yield of 93%. (4*S*,5*R*)-*trans*-**2a** (major diastereomer): R_f: 0.12 (AcOEt:PE = 1:1). White crystals, mp 89–90 °C (ethyl acetate/PE). $[\alpha]_D^{20}$ +66.7 (*c* 0.6, $CHCl_3$). IR (KBr pellet): 3261, 2916, 2865, 1659, 1453, 1345, 1298, 1261, 1083, 1051 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.52 (dd, $J = 1.7$, 17.3 Hz, 1H, $COCH_2$), 2.67 (br s, 1H, OH), 2.80 (dd, $J = 6.7$, 17.3 Hz, 1H, $COCH_2$), 3.54–3.60 (m, 2H, BnNCH, CH_2OH), 3.72 (dd, $J = 3.4$, 12.6 Hz, 1H, CH_2OH), 4.16 (dd, $J = 1.7$, 6.7 Hz, 1H, BnOCH), 4.22 (d, $J = 15.3$ Hz, 1H, $PhCH_2N$), 4.43 (d, $J = 11.7$ Hz, 1H, $PhCH_2O$), 4.50 (d, $J = 11.7$ Hz, 1H, $PhCH_2O$), 4.93 (d, $J = 15.3$ Hz, 1H, $PhCH_2N$), 7.20–7.40 (m, 10H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.1, 44.4, 60.5, 65.4, 70.8, 74.5, 127.6, 127.7, 127.9, 128.5, 128.9, 136.4, 137.6, 174.0 ppm; MS (ESI, *m/z*): 334 ($M + Na^+$, 21), 313 [$(M + 2H)^+$, 24], 312 ($M + H^+$, 100); Anal. calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.20; H, 6.97; N, 4.60. (4*S*,5*S*)-*cis*-**2a** (minor diastereomer): R_f: 0.24 (AcOEt:PE = 1:1). White crystals, mp 65–67 °C (ethyl acetate/PE). $[\alpha]_D^{20}$ −15.6 (*c* 0.4, $CHCl_3$). IR (KBr pellet): 3404, 3031, 2927, 1679, 1495, 1447, 1355, 1259, 1109, 1069 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.58 (br s, 1H, OH), 2.60 (d, $J = 6.6$ Hz, 2H, $COCH_2$), 3.56–3.60 (m, 1H, BnNCH), 3.80–3.85 (m, 2H, CH_2OH), 4.02 (d, $J = 15.2$ Hz, 1H, $PhCH_2N$), 4.34 (dt, $J = 6.8$, 6.6 Hz, 1H, BnOCH), 4.46 (d, $J = 11.6$ Hz, 1H, $PhCH_2O$), 4.64 (d, $J = 11.6$ Hz, 1H, $PhCH_2O$), 5.12 (d, $J = 15.2$ Hz, 1H, $PhCH_2N$), 7.20–7.40 (m, 10H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.1, 44.3, 59.2, 60.4, 71.9, 74.1, 127.6, 127.7, 128.0, 128.3, 128.7, 136.3, 136.7, 172.3 ppm; MS (ESI, *m/z*): 334 ($M + Na^+$, 18), 312 ($M + H^+$, 100); Anal. calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.30; H, 7.04; N, 4.53.

*4.6.2. (4S,5R,1′R/S)-1-Benzyl-4-(benzyloxy)-5-(1-hydroxy-n-butyl)pyrrolidin-2-one (**2b**)*

Combined yields of the diastereomers: 83% (**11b**); 78% (**2b**), separable diastereomeric mixture in 1.0:2.0 ratio. **2b** (major diastereomer): R_f: 0.29 (AcOEt:PE = 1:1.5). Colorless oil. $[\alpha]_D^{20}$ +44.2 (*c* 1.0, $CHCl_3$). IR (film): 3378, 3063, 3031, 2928, 2868, 1671, 1494, 1452, 1353, 1259, 1085, 1020 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, $J = 7.1$ Hz, 3H, CH_3), 1.22–1.48 (m, 4H, $Me(CH_2)_2$), 1.69 (br s, 1H, OH), 2.50 (dd, $J = 1.4$, 17.5 Hz, 1H, $COCH_2$), 2.78 (dd, $J = 6.8$, 17.5 Hz, 1H, $COCH_2$), 3.40 (s, 1H, BnNCH), 3.78–3.84 (m, 1H, C*H*OH), 4.18 (d, $J = 15.3$ Hz, 1H, $PhCH_2N$), 4.19 (dd, $J = 1.4$, 6.8 Hz, 1H, BnOCH), 4.40 (d, $J = 11.8$ Hz, 1H, $PhCH_2O$), 4.48 (d, $J = 11.8$ Hz, 1H, $PhCH_2O$), 5.00 (d, $J = 15.3$ Hz, 1H, $PhCH_2N$), 7.20–7.40 (m, 10H, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 19.3, 34.8, 38.6, 44.2, 68.0, 67.9, 70.4, 71.9, 127.7, 127.8, 128.4, 128.8, 136.2, 137.5, 174.3 ppm; MS (ESI, *m/z*): 355 [$(M + 2H)^+$, 22], 354 ($M + H^+$, 84), 376 ($M + Na^+$, 100); Anal. calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.28; H, 7.52; N, 3.98. **2b** (minor diastereomer): R_f: 0.36 (AcOEt:PE = 1:1.5). White crystals, mp 77–79 °C (ethyl acetate/PE). $[\alpha]_D^{20}$ +13.9 (*c* 0.4, $CHCl_3$). IR (KBr pellet): 3394, 3062, 3031, 2928, 2869, 1669, 1495, 1452, 1357, 1259, 1175, 1073 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, $J = 7.3$ Hz, 3H, CH_3), 1.10–1.32 (m, 3H, $Me(CH_2)_2$), 1.42–1.52 (m, 1H, $Me(CH_2)_2$), 2.33 (br s, 1H, OH), 2.51 (d, $J = 17.7$ Hz, 1H, $COCH_2$), 2.75 (dd, $J = 6.4$, 17.7 Hz, 1H, $COCH_2$), 3.58 (d, $J = 4.6$ Hz, 1H, BnNCH), 3.61–3.65 (m, 1H, C*H*OH), 4.02 (d, $J = 6.4$ Hz, 1H, BnOCH), 4.18 (d, $J = 15.2$ Hz, 1H, $PhCH_2N$), 4.42 (s, 2H, $PhCH_2O$), 5.02 (d, $J = 15.2$ Hz, 1H, $PhCH_2N$), 7.20–7.40 (m, 10H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 19.2, 34.8, 38.2, 45.9, 67.8, 70.2, 71.3, 73.8, 127.5, 127.6, 127.7, 127.9, 128.4, 128.6, 136.3, 137.6, 174.3 ppm; MS (ESI, *m/z*): 354 ($M + H^+$, 67), 376 ($M + Na^+$, 100); Anal. calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.77; H, 7.94; N, 4.02.

*4.6.3. (4S,5R,1′R/S)-1-Benzyl-4-(benzyloxy)-5-(1-hydroxy-i-butyl)pyrrolidin-2-one (**2c**)*

Combined yields of the diastereomers: 80% (**11c**); 85% (**2c**), inseparable diastereomeric mixture in 1.0:4.0 ratio. R_f: 0.45 (AcOEt:PE = 1:1). White crystals, mp 65–66 °C (ethyl acetate/PE). IR (KBr pellet): 3376, 3031, 2957, 2871, 1672, 1451, 1353, 1312, 1257, 1074, 1027 cm^{-1}. **2c** (major diastereomer): ^1H NMR (500 MHz, $CDCl_3$) δ 0.76 (d, $J = 6.6$ Hz, 3H, CH_3), 0.98 (d, $J = 6.6$ Hz, 3H, CH_3), 1.68–1.72 (m, 1H, Me_2CH), 2.52 (dd, $J = 1.5$, 17.5 Hz, 1H, $COCH_2$), 2.78 (dd, $J = 6.7$, 17.5 Hz, 1H, $COCH_2$), 3.10 (br s, 1H, OH), 3.35–3.39 (m, 1H, C*H*OH), 3.62 (s, 1H, BnNCH), 4.10 (d, $J = 15.2$ Hz, 1H, $PhCH_2N$), 4.18 (dd, $J = 1.5$, 6.7 Hz, 1H, BnOCH), 4.36 (d, $J = 11.7$ Hz, 1H, $PhCH_2O$), 4.49 (d, $J = 11.7$ Hz, 1H, $PhCH_2O$), 5.01 (d, $J = 15.2$ Hz, 1H, $PhCH_2N$), 7.20–

7.40 (m, 10H, Ar) ppm; **2c** (minor diastereomer): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (d, $J = 6.6$ Hz, 3H, CH_3), 0.94 (d, $J = 6.6$ Hz, 3H, CH_3), 1.58–1.68 (m, 1H, Me_2CH), 2.50 (dd, $J = 3.8$, 17.3 Hz, 1H, $COCH_2$), 2.86 (dd, $J = 5.9$, 17.3 Hz, 1H, $COCH_2$), 3.20 (br s, 1H, OH), 3.22–3.26 (m, 1H, C*H*OH), 3.67 (d, $J = 5.6$ Hz, 1H, BnNCH), 3.95 (dd, $J = 3.8$, 5.9 Hz, 1H, BnOCH), 4.09 (d, $J = 15.5$ Hz, 1H, $PhCH_2N$), 4.37 (d, $J = 11.8$ Hz, 1H, $PhCH_2O$), 4.44 (d, $J = 11.8$ Hz, 1H, $PhCH_2O$), 5.27 (d, $J = 15.5$ Hz, 1H, $PhCH_2N$), 7.20–7.40 (m, 10H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) for the mixture: δ 18.0, 19.1, 19.6, 19.9, 30.4, 31.5, 37.9, 38.5, 44.2, 46.5, 64.7, 66.7, 70.3, 70.5, 72.0 (2C), 73.9, 79.0, 127.4, 127.5, 127.7, 127.8, 127.9, 128.4, 128.6, 128.8, 136.2, 137.6, 174.3, 175.4 ppm; MS (ESI, *m/z*): 355 $[(M + 2H)^+$, 23], 354 $(M + H^+$, 100); Anal. calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 75.04; H, 7.80; N, 3.91.

*4.6.4. (4S,5R,1′R/S)-1-Benzyl-4-(benzyloxy)-5-(1-hydroxy-n-heptyl)pyrrolidin-2-one (**2d**)*

Combined yields of the diastereomers: 86% (**11d**); 81% (**2d**), separable diastereomeric mixture in 1.0:4.0 ratio. **2d** (major diastereomer): R_f: 0.14 (AcOEt:PE = 1:2). White crystals, mp 77 °C (ethyl acetate/PE). $[\alpha]_D^{20}$ +34.1 (*c* 0.4, $CHCl_3$). IR (KBr pellet): 3374, 3031, 2927, 2859, 1674, 1451, 1352, 1082 cm^{-1}. ^{1}H NMR (500 MHz, CD_3CN) δ 0.94 (t, $J = 7.0$ Hz, 3H, CH_3), 1.22–1.50 (m, 10H, $Me(CH_2)_5$), 2.38 (d, $J = 17.3$ Hz, 1H, $COCH_2$), 2.74 (dd, $J = 6.6$, 17.3 Hz, 1H, $COCH_2$), 3.16 (d, $J = 4.6$ Hz, 1H, BnNCH), 3.40 (s, 1H, OH), 3.82–3.87 (m, 1H, C*H*OH), 4.07 (d, $J = 15.6$ Hz, 1H, $PhCH_2N$), 4.18 (d, $J = 6.6$ Hz, 1H, BnOCH), 4.44 (d, $J = 11.9$ Hz, 1H, $PhCH_2O$), 4.53 (d, $J = 11.9$ Hz, 1H, $PhCH_2O$), 5.02 (d, $J = 15.6$ Hz, 1H, $PhCH_2N$), 7.20–7.40 (m, 10H, Ar) ppm; ^{13}C NMR (125 MHz, CD_3CN) δ 14.9, 23.8, 27.2, 30.3, 32.9, 34.4, 39.7, 44.7, 69.3 (2C), 71.3, 73.8, 128.8, 129.1, 129.2, 129.3, 129.8, 130.1, 138.7, 139.8, 174.4 ppm; MS (ESI, *m/z*): 418 $(M + Na^+$, 16), 397 $[(M + 2H)^+$, 29], 396 $(M + H^+$, 100); Anal. calcd for $C_{25}H_{33}NO_3$: C, 75.91; H, 8.41; N, 3.54. Found: C, 75.81; H, 8.55; N, 3.64. **2d** (minor diastereomer): R_f: 0.21 (AcOEt:PE = 1:2). White crystals, mp 49–50 °C (ethyl acetate/PE). $[\alpha]_D^{20}$ +11.5 (*c* 0.7, $CHCl_3$). IR (KBr pellet): 3395, 2926, 2857, 1672, 1450, 1356, 1257, 1078 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, $J = 7.1$ Hz, 3H, CH_3), 1.06–1.44 (m, 10H, $Me(CH_2)_5$), 1.85 (br s, 1H, OH), 2.55 (d, $J = 17.7$ Hz, 1H, $COCH_2$), 2.76 (dd, $J = 6.4$, 17.7 Hz, 1H, $COCH_2$), 3.57 (d, $J = 4.6$ Hz, 1H, BnNCH), 3.62–3.68 (m, 1H, C*H*OH), 4.04 (d, $J = 6.4$ Hz, 1H, BnOCH), 4.23 (d, $J = 15.2$ Hz, 1H, $PhCH_2N$), 4.44 (s, 2H, $PhCH_2O$), 5.00 (d, $J = 15.2$ Hz, 1H, $PhCH_2N$), 7.20–7.40 (m, 10H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.5, 26.0, 29.1, 31.7, 32.7, 38.2, 46.0, 67.8, 70.3, 71.7, 73.8, 127.5, 127.6, 127.7, 127.8, 128.4, 128.6, 128.7, 136.4, 137.6, 174.2 ppm; MS (ESI, *m/z*): 418 $(M + Na^+$, 5), 397 $[(M + 2H)^+$, 25], 396 $(M + H^+$, 100); Anal. calcd for $C_{25}H_{33}NO_3$: C, 75.91; H, 8.41; N, 3.54. Found: C, 75.60; H, 8.70; N, 3.28.

*4.6.5. (4S,5R,1′R/S)-1-Benzyl-4-(benzyloxy)-5-(1-hydroxy-n-pentyl)pyrrolidin-2-one (**2e**)*

Combined yields of the diastereomers: 86% (**11e**); 78% (**2e**), separable diastereomeric mixture in 1.0:1.0 ratio. **2e** (major diastereomer): R_f: 0.12 (AcOEt:PE = 1:2). White crystals, mp 53–55 °C (ethyl acetate/PE). $[\alpha]_D^{20}$ +29.6 (*c* 1.1, $CHCl_3$). IR (KBr pellet): 3383, 3031, 2931, 2864, 1675, 1451, 1352, 1255, 1081 cm^{-1}. ^{1}H NMR (500 MHz, CD_3CN) δ 0.93 (t, $J = 7.0$ Hz, 3H, CH_3), 1.22–1.54 (m, 6H, $Me(CH_2)_3$), 2.39 (d, $J = 17.2$ Hz, 1H, $COCH_2$), 2.76 (dd, $J = 6.6$, 17.2 Hz, 1H, $COCH_2$), 3.28 (d, $J = 4.6$ Hz, 1H, BnNCH), 3.41 (s, 1H, OH), 3.84–3.88 (m, 1H, C*H*OH), 4.08 (d, $J = 15.5$ Hz, 1H, $PhCH_2N$), 4.20 (d, $J = 6.6$ Hz, 1H, BnOCH), 4.46 (d, $J = 11.7$ Hz, 1H, $PhCH_2O$), 4.54 (d, $J = 11.7$ Hz, 1H, $PhCH_2O$), 5.04 (d, $J = 15.5$ Hz, 1H, $PhCH_2N$), 7.24–7.44 (m, 10H, Ar) ppm; ^{13}C NMR (125 MHz, CD_3CN) δ 14.8, 23.8, 29.5, 34.1, 39.7, 44.7, 69.3, 69.4, 71.3, 73.8, 128.8, 129.1, 129.2, 129.3, 129.8, 130.1, 138.7, 139.8, 174.8 ppm; MS (ESI, *m/z*): 369 $[(M + 2H)^+$, 27], 368 $(M + H^+$, 100); Anal. calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.09; H, 8.02; N, 3.72. **2e** (minor diastereomer): R_f: 0.19 (AcOEt:PE = 1:2). Colorless oil. $[\alpha]_D^{20}$ +11.7 (*c* 0.6, $CHCl_3$). IR (film): 3396, 3031, 2932, 2865, 1672, 1451, 1356, 1256, 1075 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, $J = 7.4$ Hz, 3H, CH_3), 1.04–1.13 (m, 1H, $Me(CH_2)_3$), 1.20–1.46 (m, 5H, $Me(CH_2)_3$), 2.30 (br s, 1H, OH), 2.50 (d, $J = 17.6$ Hz, 1H, $COCH_2$), 2.76 (dd, $J = 6.2$, 17.6 Hz, 1H, $COCH_2$), 3.57 (d, $J = 4.4$ Hz, 1H, BnNCH), 3.62–3.66 (m, 1H, C*H*OH), 4.02 (d, $J = 6.2$ Hz, 1H, BnOCH), 4.20 (d, $J = 15.3$ Hz, 1H, $PhCH_2N$), 4.41 (d, $J = 12.0$ Hz, 1H, $PhCH_2O$), 4.44 (d, $J = 12.0$ Hz, 1H, $PhCH_2O$), 5.01 (d, $J = 15.3$ Hz, 1H, $PhCH_2N$), 7.20–7.40 (m, 10H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.5, 28.2, 32.5, 38.2, 46.0, 67.8, 70.2, 71.7, 73.9, 127.4, 127.6, 127.7, 127.8, 128.4, 128.6, 136.3, 137.6, 174.4 ppm; MS (ESI, *m/z*): 369 $[(M + 2H)^+$, 28], 368 $(M + H^+$, 100); Anal. calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.34; H, 8.12; N, 3.98.

*4.6.6. (4S,5R,1′R/S)-1-Benzyl-4-(benzyloxy)-5-(1-hydroxyethyl)pyrrolidin-2-one (**2f**)*

Combined yields of the diastereomers: 85% (**11f**); 85% (**2f**), inseparable diastereomeric mixture in 1.0:1.6 ratio. R_f: 0.31 (AcOEt:PE = 2:1). White crystals, mp 59–60 °C (ethyl acetate/PE). IR (KBr pellet): 3391, 3031, 2973, 2929, 1671, 1495, 1450, 1356, 1257, 1093 cm^{-1}. **2f** (major diastereomer): ^1H NMR (500 MHz, CD_3CN) δ 1.10 (d, $J = 7.5$ Hz, 3H, CH_3), 2.33 (d, $J = 17.4$ Hz, 1H, $COCH_2$), 2.72 (dd, $J = 6.6$, 17.4 Hz, 1H, $COCH_2$), 3.22 (d, $J = 5.3$ Hz, 1H, BnNCH), 3.38 (s, 1H, OH), 4.02–4.12 (m, 1H, C*H*OH), 4.13 (d, $J = 15.8$ Hz, 1H, $PhNCH_2$), 4.18 (d, $J = 6.6$ Hz, 1H, BnOCH), 4.42 (d, $J = 12.5$ Hz, 1H, $PhCH_2O$), 4.50 (d, $J = 12.5$ Hz, 1H, $PhCH_2O$), 4.98 (d, $J = 15.8$ Hz, 1H, $PhCH_2N$), 7.20–7.40 (m, 10H, Ar) ppm; **2f** (minor diastereomer): ^1H NMR (500 MHz, CD_3CN) δ 1.04 (d, $J = 7.5$ Hz, 3H, CH_3), 2.33 (d, $J = 17.4$ Hz, 1H, $COCH_2$), 2.72 (dd, $J = 6.6$, 17.4 Hz, 1H, $COCH_2$), 3.30 (d, $J = 4.9$ Hz, 1H, BnNCH), 3.48 (d, $J = 5.4$ Hz, 1H, OH), 3.84–3.94 (m, 1H, C*H*OH), 4.11 (d, $J = 15.8$ Hz, 1H, $PhCH_2N$), 4.19 (d, $J = 6.6$ Hz, 1H, BnOCH), 4.42 (d, $J = 12.5$ Hz, 1H, $PhCH_2O$), 4.50 (d, $J = 12.5$ Hz, 1H, $PhCH_2O$), 4.98 (d, $J = 15.8$ Hz, 1H, $PhCH_2N$), 7.20–7.40 (m, 10H, Ar) ppm; ^{13}C NMR (125 MHz, CD_3CN) for the mixture: δ 19.1, 19.5, 38.9, 39.2, 44.4, 46.0, 65.1, 67.3, 69.2, 69.7, 70.7, 70.9, 73.4, 74.5, 128.3, 128.5, 128.6, 128.7, 128.8, 128.9, 129.3, 129.4, 129.5, 129.6, 138.3, 139.4, 174.4 (2C) ppm; MS (ESI, *m/z*): 326 ($M + H^+$, 25), 348 ($M + Na^+$, 100); Anal. calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.89; H, 7.21; N, 4.49.

*4.6.7. (4S,5R,1′R/S)-1-Benzyl-4-(benzyloxy)-5-(1-hydroxy-n-propyl)pyrrolidin-2- one (**2g**)*

Combined yields of the diastereomers: 90% (**11g**); 74% (**2g**), separable diastereomeric mixture in 1.0:2.0 ratio. **2g** (major diastereomer): R_f: 0.19 (AcOEt:PE = 1:1). White crystals, mp 66–67 °C (ethyl acetate/PE). $[\alpha]_D^{20}$ +51.4 (*c* 0.4, $CHCl_3$). IR (KBr pellet): 3379, 3031, 2929, 2873, 1673, 1452, 1353, 1258, 1085 cm^{-1}. ^1H NMR (500 MHz, CD_3CN) δ 0.90 (t, $J = 7.4$ Hz, 3H, CH_3), 1.34–1.50 (m, 2H, $MeCH_2$), 2.32 (dd, $J = 1.1$, 17.3 Hz, 1H, $COCH_2$), 2.71 (dd, $J = 6.7$, 17.3 Hz, 1H, $COCH_2$), 3.24 (d, $J = 4.6$ Hz, 1H, BnNCH), 3.40 (s, 1H, OH), 3.70–3.76 (m, 1H, C*H*OH), 4.03 (d, $J = 15.5$ Hz, 1H, $PhCH_2N$), 4.14 (dd, $J = 1.1$, 6.7 Hz, 1H, BnOCH), 4.40 (d, $J = 11.9$ Hz, 1H, $PhCH_2O$), 4.48 (d, $J = 11.9$ Hz, 1H, $PhCH_2O$), 5.00 (d, $J = 15.5$ Hz, 1H, $PhCH_2N$), 7.20–7.40 (m, 10H, Ar) ppm; ^{13}C NMR (125 MHz, CD_3CN) δ 11.4, 27.4, 39.7, 44.6, 69.1, 71.0, 71.3, 74.0, 128.7, 129.0, 129.1, 129.2, 129.7, 130.0, 138.7, 139.8, 174.7 ppm; MS (ESI, *m/z*): 341 [$(M + 2H)^+$, 23], 340 ($M + H^+$, 100); Anal. calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.53; H, 7.57; N, 4.15. **2g** (minor diastereomer): R_f: 0.21 (AcOEt:PE = 1:1). White crystals, mp 93–94 °C (ethyl acetate/PE). $[\alpha]_D^{20}$ +25.8 (*c* 0.8, $CHCl_3$). IR (KBr pellet): 3381, 2924, 1667, 1448, 1355, 1067 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, $J = 7.4$ Hz, 3H, CH_3), 1.20–1.50 (m, 2H, $MeCH_2$), 2.30 (s, 1H, OH), 2.54 (d, $J = 17.7$ Hz, 1H, $COCH_2$), 2.78 (dd, $J = 6.3$, 17.7 Hz, 1H, $COCH_2$), 3.54–3.64 (m, 2H, C*H*OH, BnNCH), 4.04 (d, $J = 6.3$ Hz, 1H, BnOCH), 4.20 (d, $J = 15.5$ Hz, 1H, $PhCH_2N$), 4.42 (s, 2H, $PhCH_2O$), 5.04 (d, $J = 15.5$ Hz, 1H, $PhCH_2N$), 7.20–7.40 (m, 10H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.5, 25.8, 38.2, 46.0, 67.5, 70.2, 73.3, 74.0, 127.4, 127.6, 127.7, 127.8, 128.4, 128.6, 128.7, 136.3, 137.6, 174.3 ppm; MS (ESI, *m/z*): 340 ($M + H^+$, 50), 362 ($M + Na^+$, 100); Anal. calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 73.97; H, 7.76; N, 4.00.

*4.6.8. (4S,5R,1′R/S)-1-Benzyl-4-(benzyloxy)-5-(1-hydroxy-phenylethyl)pyrrolidin-2-one (**2h**)*

Combined yields of the diastereomers: 93% (**11h**); 98% (**2h**), separable diastereomeric mixture in 1.0:1.5 ratio. **2h** (major diastereomer): R_f: 0.31 (AcOEt:PE = 1:1). Colorless oil; $[\alpha]_D^{20}$ +38.0 (*c* 0.3, $CHCl_3$). IR (film): 3360, 3029, 2928, 2860, 1673, 1495, 1451, 1352, 1310, 1256, 1087 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.50 (br s, 1H, OH), 2.51 (d, $J = 17.4$ Hz, 1H, $COCH_2$), 2.62 (dd, $J = 5.2$, 13.8 Hz, 1H, $PhCH_2CH$), 2.72 (dd, $J = 8.5$, 13.8 Hz, 1H, $PhCH_2CH$), 2.81 (dd, $J = 6.8$, 17.4 Hz, 1H, $COCH_2$), 3.44 (s, 1H, BnNCH), 4.04–4.06 (m, 1H, C*H*OH), 4.06 (d, $J = 15.4$ Hz, 1H, $PhCH_2N$), 4.30 (d, $J = 6.8$ Hz, 1H, BnOCH), 4.38 (d, $J = 11.7$ Hz, 1H, $PhCH_2O$), 4.50 (d, $J = 11.7$ Hz, 1H, $PhCH_2O$), 4.98 (d, $J = 15.4$ Hz, 1H, $PhCH_2N$), 7.00–7.40 (m, 15H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.4, 39.5, 44.2, 67.7, 69.5, 70.4, 71.9, 126.6, 127.6, 127.7, 127.8, 128.5, 128.6, 128.7, 129.1, 136.0, 137.5, 137.7, 174.1 ppm; MS (ESI, *m/z*): 424 ($M + Na^+$, 15), 403 [$(M + 2H)^+$, 29], 402 ($M + H^+$, 100); Anal. calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.87; H, 6.80; N, 3.61; **2h** (minor diastereomer): R_f: 0.48 (AcOEt:PE = 1:1). Colorless oil; $[\alpha]_D^{20}$ −25.7 (*c* 0.3, $CHCl_3$). IR (film): 3382, 3030, 2925, 2868, 1672, 1495, 1449, 1356, 1259, 1173, 1084 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.80 (br s, 1H, OH), 2.39 (dd, $J = 10.7$, 13.2 Hz, 1H, $PhCH_2CH$), 2.57 (d, $J = 17.7$ Hz, 1H, $COCH_2$), 2.68 (dd, $J = 2.1$, 13.2 Hz,

1H, PhCH_2CH), 2.80 (dd, $J = 6.6$, 17.7 Hz, 1H, COCH_2), 3.74 (d, $J = 4.8$ Hz, 1H, BnNCH), 3.86 (ddd, $J = 2.1$, 4.8, 10.7 Hz, 1H, C*H*OH), 4.18 (d, $J = 6.6$ Hz, 1H, BnOCH), 4.42 (d, $J = 15.1$ Hz, 1H, PhCH_2N), 4.47 (d, $J = 12.0$ Hz, 1H, PhCH_2O), 4.50 (d, $J = 12.0$ Hz, 1H, PhCH_2O), 4.90 (d, $J = 15.1$ Hz, 1H, PhCH_2N), 6.90–7.40 (m, 15H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.2, 38.9, 46.3, 68.0, 70.3, 72.3, 73.3, 126.9, 127.5, 127.6, 127.7, 127.9, 128.1, 128.4, 128.7, 128.8, 129.1, 136.7, 137.3, 137.6, 174.1 ppm; MS (ESI, *m/z*): 403 [$(M + 2H)^+$, 24], 402 ($M + H^+$, 100); Anal. calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.69; H, 6.94; N, 3.48.

*4.6.9. (4S,5R,1′R/S)-1-Benzyl-4-(benzyloxy)-5-(1-hydroxyphenymethyl) pyrrolidin-2-one (**2i**)*

Combined yields of the diastereomers: 90% (**11i**); 98% (**2i**), inseparable diastereomeric mixture in 1.0:2.6 ratio. R_f: 0.31 (AcOEt:PE = 1:1). White crystals, mp 104–105 °C (ethyl acetate/PE). IR (KBr, Pellet): 3364, 3030, 2928, 1670, 1449, 1254, 1071 cm^{-1}. **2i** (major diastereomer): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.02 (s, 1H, OH), 2.46 (d, $J = 17.5$ Hz, 1H, COCH_2), 2.78 (dd, $J = 6.6$, 17.5 Hz, 1H, COCH_2), 3.66 (d, $J = 2.3$ Hz, 1H, BnNCH), 3.85 (d, $J = 12.0$ Hz, 1H, PhCH_2O), 3.92 (d, $J = 12.0$ Hz, 1H, PhCH_2O), 4.04 (d, $J = 6.6$ Hz, 1H, BnOCH), 4.14 (d, $J = 15.2$ Hz, 1H, PhCH_2N), 4.94 (d, $J = 2.3$ Hz, 1H, C*H*OH), 5.60 (d, $J = 15.2$ Hz, 1H, PhCH_2N), 7.20–7.40 (m, 15H, Ar) ppm; **2i** (minor diastereomer): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.00 (br s, 1H, OH), 2.22 (dd, $J = 5.8$, 17.4 Hz, 1H, COCH_2), 2.32 (d, $J = 17.4$ Hz, 1H, COCH_2), 3.81 (d, $J = 5.0$ Hz, 1H, BnNCH), 3.96 (d, $J = 5.8$ Hz, 1H, BnOCH), 4.12 (d, $J = 15.2$ Hz, 1H, PhCH_2N), 4.24 (d, $J = 11.8$ Hz, 1H, PhCH_2O), 4.29 (d, $J = 11.8$ Hz, 1H, PhCH_2O), 4.82 (d, $J = 5.0$ Hz, 1H, C*H*OH), 5.18 (d, $J = 15.2$ Hz, 1H, PhCH_2N), 7.20–7.40 (m, 15H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) for the mixture: δ 37.3, 38.6, 44.7, 45.6, 54.6, 64.6, 69.8 (2C), 70.1, 70.6, 71.5, 74.0, 125.6, 125.8, 127.4, 127.9, 128.1, 128.3, 128.8, 136.3, 137.4, 137.5, 139.9, 140.2, 174.5, 174.6 ppm; MS (ESI, *m/z*): 389 [$(M + 2H)^+$, 28], 388 ($M + H^+$, 100); Anal. calcd for $C_{25}H_{25}NO_3$: C, 77.49; H, 6.50; N, 3.61. Found: C, 77.61; H, 6.74; N, 3.83.

Acknowledgments

The authors are grateful to the NSF of China (20390050, 20572088, 20602028) for financial support. Partial support from the program for Innovative Research Team in Science and Technology in Fujian Province University is acknowledged.

References

[1] For reviews on the synthesis and biological activity of polyhydroxylated alkaloids, see: (a) H. Takahata, T. Momose, in: G.A. Cordell (Ed.), The Alkaloids, vol. 44, Academic, San Diego, 1993 Chapter 3;
(b) J.P. Michael, Nat. Prod. Rep. 14 (1997) 619;
(c) J.P. Michael, Nat. Prod. Rep. 15 (1998) 571;
(d) J.P. Michael, Nat. Prod. Rep. 16 (1999) 675;
(e) N. Asano, R.J. Nash, R.J. Molyneux, G.W.J. Fleet, Tetrahedron: Asymmetry 11 (2000) 1645.

[2] For comprehensive reviews on azasugars, see: (a) A.D. Elbein, R.J. Molyneux, in: A.E. Stutz (Ed.), Iminosugars as Glycosidase Inhibitors, Wiley-VCH, Weinheim, 1999, p. 216;
(b) P. Sears, C.-H. Wong, Angew. Chem., Int. Ed. 38 (1999) 2301;
(c) A.A. Watson, G.W.J. Fleet, N. Asano, R.J. Molyneux, R.J. Nash, Phytochemistry 56 (2001) 265;
(d) K. Afarinkia, A. Bahar, Tetrahedron: Asymmetry 16 (2005) 1239.

[3] R.J. Nash, E.A. Bell, G.W.J. Fleet, R.H. Jones, J.M. Williams, J. Chem. Soc., Chem. Commun. (1985) 738.

[4] For a recent synthesis of bulgecinine, see: S.P. Chavan, C. Praveen, P. Sharma, U.R. Kalkote, Tetrahedron Lett. 46 (2005) 439.

[5] For two recent reviews on the carbanion chemistry, see: (a) F. Alonso, M. Yus, Chem. Soc. Rev. 25 (1996) 155;
(b) M. Yus, Chem. Soc. Rev. 33 (2004) 284. For reviews involving the generation and application of α-lithioamines, see:
(c) T. Cohen, M. Bhupathy, Acc. Chem. Res. 22 (1989) 152;
(d) T.G. Gant, A.I. Meyers, Tetrahedron 50 (1994) 2297;
(e) P. Beak, A. Basu, D.J. Gallagher, Y.S. Park, S. Thayumanavan, Acc. Chem. Res. 29 (1996) 552;
(f) T. Cohen, Pure Appl. Chem. 68 (1996) 913;
(g) R.E. Gawley, Curr. Org. Chem. 1 (1997) 71;
(h) S.V. Kessar, P. Singh, Chem. Rev. 97 (1997) 721;
(i) A.R. Katritzky, M. Qi, Tetrahedron 54 (1998) 2647;
(j) H.P. Husson, J. Royer, Chem. Soc. Rev. 28 (1999) 383;
(k) G. Rassu, F. Zanardi, L. Battistini, G. Casiraghi, Chem. Soc. Rev. 29 (2000) 109;
(l) G. Casiraghi, F. Zanardi, G. Appendino, G. Rassu, Chem. Rev. 100 (2000) 1929.

[6] P.-Q. Huang, X. Zheng, S.-L. Wang, J.-L. Ye, L.-R. Jin, Z. Chen, Tetrahedron: Asymmetry 10 (1999) 3309.

[7] For a short discussion on challenges associated with the generation and C–C bond formation of chiral non-racemic *N*-α-carbanion of protected 4-hydroxy-2-pyrrolidinone B, see: (a) X. Zheng, C.-G. Feng, J.-L. Ye, P.-Q. Huang, Org. Lett. 7 (2005) 553. For a synthesis of a specific 2-pyrrolidinone derivative of type 2, see:
(b) J.F. Poisson, J.F. Normant, Org. Lett. 3 (2001) 1889. For a related work, see:
(c) D.M. Iula, R.E. Gawley, J. Org. Chem. 65 (2000) 6196.

[8] For a serials of papers on functionalised organolithium compounds, see: Tetrahedron Symposia-in-PrintC. Nájera, M. Yus (Eds.), Tetrahedron 61 (2005) 3125.

[9] (a) P.-Q. Huang, T.-J. Wu, Y.-P. Ruan, Org. Lett. 5 (2003) 4341;
(b) P.-Q. Huang, J. Deng, Synlett (2004) 247.

[10] For an achiral version, see: (a) T. Gallagher, M. Giles, R.S. Subramanian, M.S.J. Hadley, J. Chem. Soc., Chem. Commun. (1992) 166;
(b) S.H.J. Thompson, R.S. Subramanian, J.K. Roberts, M.S. Hadley, T. Gallagher, J. Chem. Soc., Chem. Commun. (1994) 933.
[11] T. Tang, Y.-P. Ruan, J.-L. Ye, P.-Q. Huang, Synlett (2005) 231.
[12] (a) P.-Q. Huang, S.-L. Wang, J.-L. Ye, Y.-P. Ruan, Y.-Q. Huang, H. Zheng, J.-X. Gao, Tetrahedron 54 (1998) 12547;
(b) B.-Y. He, T.-J. Wu, X.-Y. Yu, P.-Q. Huang, Tetrahedron: Asymmetry 14 (2003) 2101;
(c) L.-X. Liu, Y.-P. Ruan, Z.-Q. Guo, P.-Q. Huang, J. Org. Chem. 69 (2004) 6001. For an account, see: P.-Q. Huang, Synlett (2006) 1133.
[13] X. Zhou, P.-Q. Huang, Synlett (2006) 1235.
[14] (a) D.C. Ha, C.S. Yun, E. Yu, Tetrahedron Lett. 37 (1996) 2577;
(b) P.A. Jacobi, H.L. Brielmann, S.I. Hauck, J. Org. Chem. 61 (1996) 5013;
(c) S. Farcas, J.L. Namy, Tetrahedron Lett. 42 (2001) 879;
(d) S.-H. Kim, Y. Park, H. Choo, J.K. Cha, Tetrahedron Lett. 43 (2002) 6657;
(e) A. Padwa, P. Rashatasakhon, M. Rose, J. Org. Chem. 68 (2003) 5139;
(f) J.A. Mulder, K.C.M. Kurtz, R.P. Hsung, H. Coverdale, M.O. Frederick, L. Shen, C.A. Zificsak, Org. Lett. 5 (2003) 1547. For an approach to exo-glycals, see:
(g) W.B. Yang, Y.Y. Yang, Y.F. Gu, S.H. Wang, C.C. Chang, C.H. Lin, J. Org. Chem. 67 (2002) 3773.
[15] (a) Y. Koseki, S. Kusano, D. Ichi, K. Yoshida, T. Nagasaka, Tetrahedron 56 (2000) 8855;
(b) H. Xiong, R.P. Hsung, L. Shen, J.M. Hahn, Tetrahedron Lett. 43 (2002) 4449;
(c) Y. Koseki, H. Sato, Y. Watanabe, T. Nagasaka, Org. Lett. 4 (2002) 885;
(d) S.G. Davies, M.S. Key, H. Rodriguez-solla, H.J. Sanganee, E.D. Savory, A.D. Smith, Synlett (2003) 1659.
[16] J.-L. Ye, P.-Q. Huang, X. Lu, J. Org. Chem. 72 (2007) 35.
[17] (a) P. Deslongchamps (Ed.), Stereoelectronic Effetcs in Organic Chemistry, Pergamon, New York, 1983. See also:
(b) A.J. Kirby (Ed.), The Anomeric Effect and Related Stereoelectronic Effects at Oxygen, Springer, New York, 1983;
(c) G.R.J. Thatcher (Ed.), The Anomeric Effect and Associated Stereoelectronic Effect, ACS Symposium Series 593, American Chemical Society, Washington DC, 1993;
(d) E. Juaristi, G. Cuevas (Eds.), The Anomeric Effect, CRC, Boca Raton, FL, 1995.
[18] For a related stereoelectronic effect observed in another class of *N*,*O*-acetals, see: (a) M.-D. Chen, M.-Z. He, X. Zhou, L.-Q. Huang, Y.-P. Ruan, P.-Q. Huang, Tetrahedron 61 (2005) 1335. For an example of stereoelectronic control of oxazolidine ring-opening, see:
(b) J. Sélambarom, S. Monge, F. Carré, J.-P. Roque, A.A. Pavia, Tetrahedron 58 (2002) 9559.
[19] For reviews on Et_3SiH mediated ionic hydrogenation, see: (a) D.N. Kursanov, Z.N. Parnes, N.M. Loim, Synthesis (1974) 633;
(b) Y. Nagai, Org. Prep. Proc. Int. 12 (1980) 13.
[20] For recent reviews on the chemistry of *N*-acyliminium ions, see:
(a) W.N. Speckamp, M.J. Moolenaar, Tetrahedron 56 (2000) 3817;
(b) B.E. Maryanoff, H.-C. Zhang, J.H. Cohen, I.J. Turchi, C.A. Maryanoff, Chem. Rev. 104 (2004) 1431;
(c) J. Royer, Chem. Rev. 104 (2004) 2311.
[21] A. Bernardi, F. Micheli, D. Potenza, C. Scolastico, R. Villa, Tetrahedron Lett. 13 (1990) 4949.
[22] T.G. Back, O.E. Edwards, G.A. MacAlpine, Tetrahedron Lett. 18 (1977) 2651.
[23] R. Eckrich, B. Neumann, H.G. Stammler, D. Kuck, J. Org. Chem. 61 (1996) 3839.