A Versatile Approach to Protected (4*S*,5*R*)-4-Hydroxy-5-(α-hydroxyalkyl)-2-pyrrolidinones

Xiang Zhou, 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, P. R. of China
Fax +86(592)2186400; E-mail: pqhuang@xmu.edu.cn

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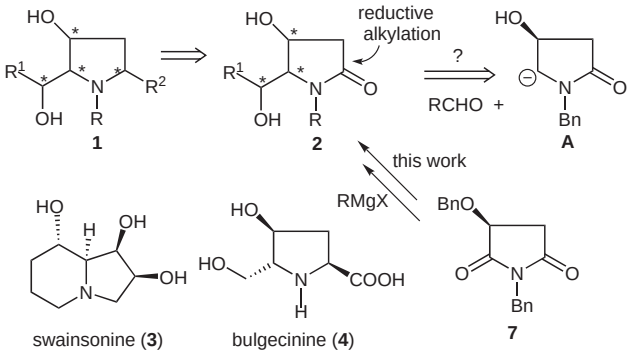
Dedicated to Professor Ben-Li Huang on the occasion of his 80th birthday

Abstract: Starting from (*S*)-*N*,*O*-dibenzylmalimide (**7**), a versatile four-step approach to (4*S*,5*R*)-*N*-benzyl-4-benzyloxy-5-(α-hydroxyalkyl)-2-pyrrolidinones **9** is reported. The method consists of Grignard reagent addition, *p*-toluenesulfonic acid monohydrate-mediated dehydration, one-pot epoxidation–methanol ring-opening reaction and reductive demethoxylation. 2-Pyrrolidinones **9** were obtained with excellent *trans*-diastereoselectivity in the pyrrolidinone ring and low diastereoselectivity at the carbinol center.

Key words: dehydration, enamide, 2-pyrrolidinones, epoxidation, asymmetric synthesis

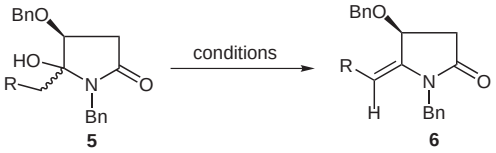
Carbanion-based C–C bond formation is a fundamental transformation in organic chemistry. While a huge number of methods have been developed for the carbanion generation and subsequent C–C bond formation,[1] there still exist many challenges in the classical carbanion chemistry.[2] The generation and C–C bond formation of chiral non-racemic *N*-α-carbanion of protected 4-hydroxy-2-pyrrolidinone **A** is one such challenge.[3] 4-Hydroxy-2-pyrrolidinone *N*-α-carbanion **A** represents a highly desirable synthon according to a conceptually attractive retrosynthetic analysis of 2-(α-hydroxyalkyl) 5-substituted 3-pyrrolidinols **1** (Scheme 1), the common structural motifs shared by a number of bioactive polyhydroxylated alkaloids[4] and azasugars[5] such as swainsonine[6] (**3**) and bulgecinine[7] (**4**).



Scheme 1

In recent years, we have been engaged[8] in the development of carbanion-based asymmetric approaches to 5-alkyl 4-hydroxy-2-pyrrolidinones (via tetramates),[9] 2-alkyl-3-pyrrolidinols,[3a,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, we now report a flexible approach to 5-(α-hydroxyalkyl) 4-hydroxy-2-pyrrolidinones **2**.

Our approach to **2** arose from some unexpected results in a related project.[12] When we attempted the α-amidoallylation (AllTMS, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C to r.t., 15 h) of *N*,*O*-acetals **5a**,**d**,**e**,**g** (a. R = H; d. R = *n*-Pr; e. R = *i*-Pr; g. R = *n*-C_6H_{13}),[12] only **5a** led to the desired α-amidoallylation product, the reaction of **5d**,**e**,**g** gave the dehydrated products **6d**,**e**,**g**, respectively, in 75–82% yields (Scheme 2). In view of the recent advances in the enamide chemistries,[13,14] it was realized that these findings would found a basis of a versatile approach to 5-(α-hydroxyalkyl)-4-hydroxy-2-pyrrolidinones **2**, and thus provided an alternative solution to the challenging problem.



Scheme 2

To this end, a further investigation on the acid-catalyzed dehydration[13] of *N*,*O*-acetals **5**[12] was undertaken (Scheme 2) and the results were summarized in Table 1. As can be seen from Table 1 (entries 1–5, 10), the dehydration of *N*,*O*-acetals **5** can be promoted by either Lewis acid or Brønsted acid. Comparable yields were obtained when using $BF_3{\cdot}OEt_2$ or $TsOH{\cdot}H_2O$ as an acid catalyst under optimized conditions (Table 1, entries 1, 2 vs. entry 3). The reaction can also be promoted by trifluoroacetic anhydride (TFAA)–pyridine system (Table 1, entry 6).[13e,g] However, this system was not adapted considering the complication in the work-up procedure, the cost and the safety of the chemicals used. Although the use of Lewis acid $BF_3{\cdot}OEt_2$ also led to satisfying results, the simplicity in using $TsOH{\cdot}H_2O$ as a catalyst led us to select it for further investigation.

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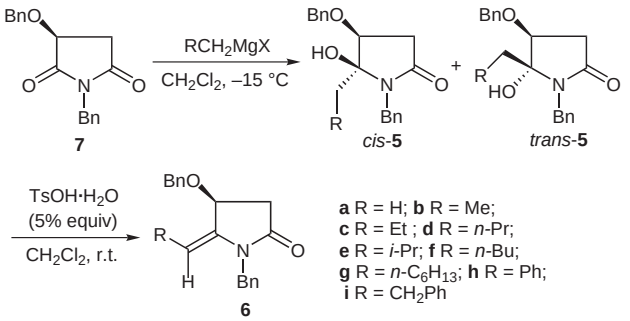
Table 1 Effects of the Reaction Condition on the Dehydration Reaction of **5c**,**d**,**e**,**h**

Entry	Starting material	Dehydration agent	Temperature	Time	Yield (%)
1	**5d**[a]	$BF_3{\cdot}OEt_2$, CH_2Cl_2	–78 °C, r.t.	12 h	75–77
2	**5e**[a]	$BF_3{\cdot}OEt_2$, CH_2Cl_2	–78 °C, r.t.	12 h	74–83
3	**5c**[b]	*p*-TsOH, CH_2Cl_2	r.t.	50 min	79
4	**5c**[b]	*p*-TsOH, CH_2Cl_2	0 °C	1.5 h	68
5	**5c**[b]	*p*-TsOH, CH_2Cl_2	–12 °C	2 h	58
6	**5c**[b]	TFAA/pyridine, THF	0 °C	1 h	78
7	**5c**[b]	Ac_2O, CH_2Cl_2	r.t.	48 h	ca. n.r.
8	**5c**[b]	Ac_2O/pyridine, CH_2Cl_2	r.t.	48 h	ca. n.r.
9	**5h**[a]	Ac_2O/pyridine, CH_2Cl_2	reflux	3 d	54
10	**5h**[b]	*p*-TsOH, CH_2Cl_2	r.t.	3 h	77

[a] Two diastereomers were used for the dehydration.
[b] Only *trans*-diastereomers were used for the dehydration.

The reaction was then extended to other *N*,*O*-acetals **5**, which were obtained by Grignard reaction with (*S*)-*N*,*O*-dibenzylmalimide (**7**) as described previously[12] (Scheme 3). Most of the *N*,*O*-acetals (**5a**–**g** and **5i**) were obtained with excellent C-2 regioselectivities (only one regioisomer was obtained in each case) and with diastereoselectivities ranged from 6:1 to 8:1 in favor of *trans*-diastereomer (*trans*-**5**). Only the reaction with benzyl magnesium bromide led to a 1:1 diastereomeric ratio. The results of the TsOH-promoted (5% molar equiv) dehydration reaction of the major diastereomers of **5** were displayed in Table 2. It is worth noting that the dehydration of **5a** was unsuccessful under several acidic conditions (TsOH, TFA, CSA, HCl, H_2SO_4).



Scheme 3

It is also important to note that all the dehydration reactions were incomplete, and partial epimerization of *trans*-diastereomers (*trans*-**5**) to *cis*-diastereomers (*cis*-**5**) was observed according TLC monitoring. The *cis*-diastereomers were poorly reactive towards the dehydration reaction and couldn't react completely. These results suggest that *cis*-**5** are thermodynamically more stable diastereomers. The low reactivity of the *cis*-*N*,*O*-acetals (*cis*-**5**) can be attributed to stereoelectronic effect.[16,17]

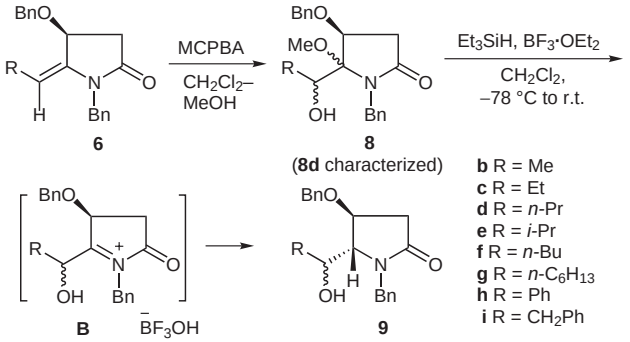
Table 2 Grignard Reagents Addition with **7** and the Subsequent TsOH-Mediated Dehydration Reaction[15]

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

[a] Diastereomeric ratios: 6:1 to 8: 1, only the major diastereomers were used for the dehydration.
[b] Diastereomeric ratio: ca. 1:1, only the *trans*-diastereomer was used for the dehydration.
[c] Isolated yield.
[d] Yield based on the recovered starting material (*cis*-diastereomer).

Another feature of the dehydration reaction is that the reaction is highly stereoselective, and only *E*-enamides (**6**) were obtained. The stereochemistry of **6d** was determined by NOESY experiences (^{1}H NMR).

Next, one-pot epoxidation–ring-opening of compounds **6** was investigated by using the method of Nagasaka and coworkers.[14] Thus, when **6d** was treated with MCPBA in absolute MeOH and CH_2Cl_2, the desired products **8d** were obtained as a mixture of four diastereomers with a combined yield of 83% (Scheme 4). To confirm the structure of the products, flash column chromatography separation



Scheme 4

of a sample of diastereomeric mixture of **8d** was undertaken, two pure diastereomers, and a mixture of the other two diastereomers were isolated and characterized.

The diastereomeric mixture of **8d** was then subjected to Lewis acid mediated ionic hydrogenation ($BF_3{\cdot}OEt_2$, Et_3SiH, CH_2Cl_2, –78 °C to r.t.),[18,12] which gave two separable diastereomers *trans*-**9d**[15] in 1:2 ratio with a combined yield of 78%. The fact that the reductive deoxygenation of a mixture of four diastereomers (**8d**) led to only two diastereomers (**9d**) might implicate that the transformation of **8d** to **9d** proceeded via the intermediacy of *N*-acyliminium ion[19] **B** (R = *n*-Pr), and the stereoselectivity in the 2-pyrrolidinone ring was higher than 95%. Both diastereomers **9d** were assigned to *trans* according to the observed vicinal coupling constant[20,12] (both $J_{4,5}$ = ca. 0 Hz). That oxidation of the diastereomeric mixture of **9d** (1:2; PCC, CH_2Cl_2, r.t., 4 h, yield 70%) afforded the corresponding ketone as the sole diastereomer ($J_{4,5}$ = ca. 0 Hz), confirmed the *trans*-stereochemistry in the 2-pyrrolidinone ring. The stereochemistries of the two diastereomers of **9d** at the C-1′ position were not determined.

With the MCPBA epoxidation–ring-opening of **6d** and the subsequent reductive deoxygenation reactions secured, the syntheses of other homologues or analogues of **9d** were investigated and the results were outlined in Table 3. The results displayed in Table 3 showed that the one-pot epoxidation–ring-opening of other enamides **6** worked similarly as **6d** did in terms of chemical yields and diastereoselectivities, which demonstrated the flexibility of the method.

In summary, stemmed from some unexpected findings in a related research project, a flexible four-step *trans*-diastereoselective approach to (4*S*,5*R*)-*N*-benzyl-4-benzyloxy-5-hydroxyalkyl-2-pyrrolidinones **9** was established starting from the known (*S*)-*N*,*O*-dibenzyl malimide (**7**). To the best of our knowledge, this represents the first flexible asymmetric approach to **9**, the protected form of **2**, and provides an alternative solution to the challenging problem showed retrosynthetically in Scheme 1. Application of the present method to the asymmetric synthesis of hydroxylated pyrrolidine-ring-containing alkaloids is under investigation and will be reported in due course.

Table 3 Results of MCPBA Epoxidation–Ring-Opening of **6** and the Subsequent Reductive Demethoxylation Reaction Leading to **9**

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

[a] Combined yield of four diastereomers.
[b] Combined yield of two diastereomers.
[c] Ratio determined by chromatography separation.
[d] Ratio determined by ^1H NMR.
[e] Ratio determined by HPLC.

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(15) All new compounds (**6** and **9**) gave satisfactory analytical and spectral data.

General Procedure for the Synthesis of 9.

To a solution of the more polar diastereomer of **5**[12] (1.0 mmol) in CH_2Cl_2 (10 mL) was added 0.05 mmol of *p*-TSA. The mixture was stirred at r.t. for 1 h. Then the reaction was quenched with sat. aq $NaHCO_3$ and extracted with CH_2Cl_2 (3×10 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 EtOAc–PE to give **6**. To a solution of **6** (1.0 mmol) in a mixture of 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 the mixture stirred for 1 h, it was allowed to reach r.t. and stirred overnight. Then, the reaction was quenched with a solution of aq $Na_2S_2O_3$ (10%) and sat. $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3×40 mL). The combined extracts were washed with brine, dried over anhyd Na_2SO_4, filtered and concentrated in vacuum. Filtration through a short pad of SiO_2 eluting with EtOAc–PE gave **8** as a mixture of diastereomers. The diastereomeric ratios were determined either by flash chromatographic separation or by analysis of ^{1}H NMR spectra of the crude mixture. To a cooled (–78 °C) solution of diastereomeric mixture of **8** (1.0 mmol) in dry CH_2Cl_2 (10 mL) were added dropwise triethylsilane (10 mmol) and $BF_3{\cdot}OEt_2$ (10.0 mmol) under nitrogen atmosphere. After stirred for 6 h at the same temperature, the reaction was allowed to warm up and stirred at r.t. overnight. The reaction was quenched with sat. aq $NaHCO_3$ and extracted with CH_2Cl_2 (3×20 mL). The combined extracts were washed with brine, dried over anhyd Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel eluting with EtOAc–PE to give **9**.

Selected physical and spectral data for **6d**: $[\alpha]_D^{20}$ +62.0 (*c* 0.4, $CHCl_3$). IR (film): 3060, 3023, 1719, 1674 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.22–1.38 (m, 2 H, $MeCH_2$), 1.94–2.12 (m, 2 H, $EtCH_2$), 2.68 (dd, *J* = 1.7, 17.8 Hz, 1 H, $COCH_2$), 2.78 (dd, *J* = 7.0, 17.8 Hz, 1 H, $COCH_2$), 4.42 (d, *J* = 11.2 Hz, 1 H, $PhCH_2O$), 4.53 (d, *J* = 11.2 Hz, 1 H, $PhCH_2O$), 4.70 (s, 2 H, $PhCH_2N$), 4.74 (dd, *J* = 1.7, 7.0 Hz, 1 H, BnOCH), 4.84 (t, *J* = 7.5 Hz, 1 H, =CH), 7.20–7.40 (m, 10 H, 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 (100) [M + H$^+$]. 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.

Selected physical and spectral data for **9d**: major diastereomer: colorless oil; $[\alpha]_D^{20}$ +44.2 (*c* 1.0, $CHCl_3$). IR (film): 3378, 3063, 3031, 1671 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.22–1.48 [m, 4 H, $Me(CH_2)_2$], 2.50 (dd, *J* = 1.3, 17.4 Hz, 1 H, $COCH_2$), 2.80 (dd, *J* = 6.9, 17.4 Hz, 1 H, $COCH_2$), 3.00 (br s, 1 H, OH), 3.40 (d, *J* = 4.9 Hz, 1 H, BnNCH), 3.78–3.84 (m, 1 H, C*H*OH), 4.18 (d, *J* = 15.0 Hz, 1 H, $PhCH_2N$), 4.19 (dd, *J* = 1.3, 6.9 Hz, 1 H, BnOCH), 4.40 (d, *J* = 11.7 Hz, 1 H, $PhCH_2O$), 4.48 (d, *J* = 11.7 Hz, 1 H, $PhCH_2O$), 5.00 (d, *J* = 15.0 Hz, 1 H, $PhCH_2N$), 7.20–7.40 (m, 10 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 19.3, 34.8, 38.6, 44.2, 68.0, 68.8, 70.4, 71.9, 127.7, 127.8, 128.4, 128.8, 136.2, 137.5, 174.2 ppm. MS (ESI): *m/z* (%) = 376 (100) [M + Na$^+$]; minor diastereomer: white crystals, mp 77–79 °C; $[\alpha]_D^{20}$ +13.9 (*c* 0.4, $CHCl_3$). IR (KBr, pellet): 3394, 3062, 3031, 1669 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.10–1.32 [m, 3 H, $Me(CH_2)_2$], 1.42–1.52 [m, 1 H, $Me(CH_2)_2$], 2.33 (br s, 1 H, OH), 2.51 (d, *J* = 17.7 Hz, 1 H, $COCH_2$), 2.75 (dd, *J* = 6.4, 17.7 Hz, 1 H, $COCH_2$), 3.58 (d, *J* = 4.6 Hz, 1 H, BnNCH), 3.61–3.65 (m, 1 H, C*H*OH), 4.02 (d, *J* = 6.4 Hz, 1 H, BnOCH), 4.18 (d, *J* = 15.2 Hz, 1 H, $PhCH_2N$), 4.42 (s, 2 H, $PhCH_2O$), 5.02 (d, *J* = 15.2 Hz, 1 H, $PhCH_2N$), 7.20–7.40 (m, 10 H, 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 (67) [M + H^+], 376 (100) [M + Na^+]. 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.

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