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An Efficient Asymmetric Functionalization to Highly Substituted Pyrrolidines

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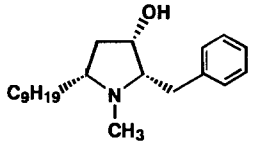
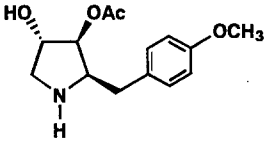
Abstract: *A stereoselective route to enantiomerically and diastereomerically pure pentasubstituted pyrrolidines has been developed by using reductive deoxygenation of quaternary α-hydroxy N-Boc pyrrolidine derivatives prepared from alkylation of the functionalized homochiral lactams. Stereochemistry of the new stereogenic center generated has been comfirmed unambiguously to be* ***R*** *by the formation of* C_2*-symmetrical compounds.*

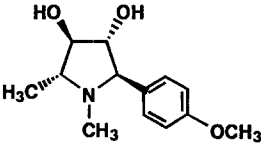
Structurally complex alkaloidal sugar mimics with a nitrogen in the ring have been isolated from plants and microorganisms and inhibit various glycosidases in a reversible and competitve manner.[1] Since such glycosidase inhibitors proved to have the potential to produce antiviral, insect antifeedant, antidiabetic, and anticancer effects, as well as immune modulatory properties, they have held considerable interest in the context of stereoselective heterocyclic synthesis. In particular, polysubstituted pyrrolidine alkaloids containing hydroxy functions such as preussin,[2] anisomycin,[3] and codonopsinine[4] have been the subject of extensive synthetic efforts which have culminated in numerous syntheses of racemic and homochiral forms.



Preussin



Anisomycin



Codonopsinine

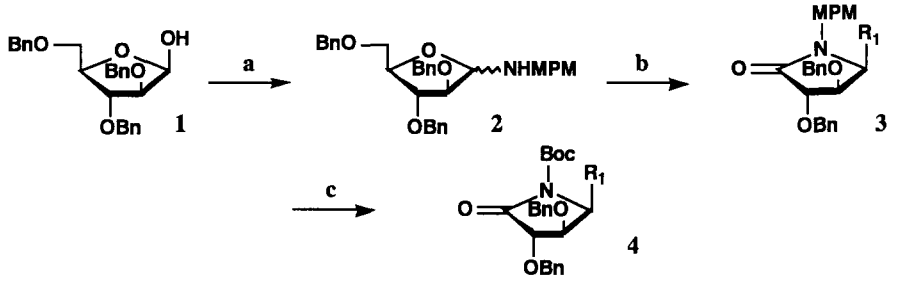
Although in the preparation of such nitrogen-containing natural products the synthetic utility of the *N*-acyliminium ion obtained from *N*-acyl pyrrolidines has been well documented,[5] little, if any, effort has been made for the utilization of the quaternary α-hydroxy carbon center present in such compounds.

In a recent continuation of our work designed to extend the employment of *N*-acyliminium ions for the synthesis of biologically active compounds, the *trans*-selective lactam formation protocol[6] and the application to

the first total synthesis of antibiotic, lentiginosine[7] have been developed in this laboratory.

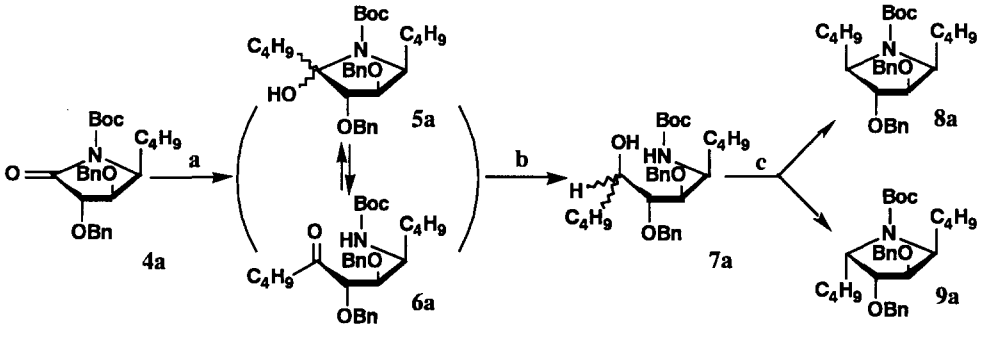
The central feature of this communication is to detail the results that the labile quaternary α-hydroxy *N*-Boc pyrrolidines underwent complete diastereospecific deoxygenation, leading to pentasubstituted sole products with ***R*** configuration.

Several homochiral lactams **3** were prepared from commercially available 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose **1** through successive amination and extremely stereoselective addition of Grignard reagents, followed by oxidative degradation with PCC (Scheme 1).[3c,8] The complete absence of the epimer of **3** at C-4 was ascertained unambiguously according to our reported double-check method.[3c] Thus, the compounds **3** were transformed into the desired N-Boc lactams **4** by 2 steps. As shown in Scheme 2, nucleophilic addition



Scheme 1. Reagents and conditions: (a) $MPMNH_2$, CH_2Cl_2, MS 4A; quant.; (b) 1 R_1MgX, -78--30 °C, THF; 2 PCC, MS 4A, CH_2Cl_2; [R_1=C_4H_9: 52% (**3a**), R_1=C_9H_{19}: 42% (**3b**), R_1=Bn: 51% (**3c**), based on **1**] (c) $Ce(NH_4)_2(NO_3)_6$, CH_3CN-H_2O; 2 $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2; [R_1=C_4H_9: 76% (**4a**), R_1=C_9H_{19}: 58% (**4b**), R_1=Bn: 76% (**4c**)] (2 steps).

of butylmagnesium bromide to **4a** at -78 °C interestingly afforded the labile quaternary α-hydroxy pyrrolidine **5a** which slowly tends to come to equilibrium with its open keto form **6a**.[9] The mixture of **5a** and **6a** was submitted to reduction with $NaBH_4$ to give **7a**[10] which was followed by mesylation and cyclization with *t*-BuOK[11], leading to the almost non-stereoselective diastereomer mixture of **8a** (41%) and **9a** (37%)[12] after separation on silica-gel chromatography. The newly created stereogenic centers of **8a** and **9a** were easily determined to be ***R*** and ***S*** respectively as indicated based on ^1H and ^{13}C NMR, since **9a** possesses a C_2-axis



Scheme 2. Reagents and conditions: (a) C_4H_9MgBr, -78 °C, THF; (b) $NaBH_4$, EtOH; 73%; (2 steps); (c) 1 MsCl, Et_3N, CH_2Cl_2; 2 *t*-BuOK, THF; 41% (**8a**); 37% (**9a**) (2 steps).

of symmetry.

Next, we investigated the utilization of the quaternary α-hydroxy pyrrolidine **5a** for Lewis acid-induced deoxygenation.[6] When the Grignard adduct to **4a** was treated with Et_3SiH in the presence of $BF_3 \cdot OEt_2$ at -78 °C, it afforded the corresponding deoxygenated pentasubstituted pyrrolidine **8a** (65%) exclusively. No other stereoisomer such as **9a** was observed in this reaction and accompanying formation of small amounts of ketone **6a** (7%) resulted from equilibrium of **5a** and *N*-Boc deprotected lactam of **4a** (8%) were isolated.

With the above results in hand, we examined further the reactions employing several types of substituted lactams under the same conditions. The results are summarized in Table 1.[13] The reaction proceeded with exclusive stereoselectivity to yield substituted pyrrolidine derivatives with ***R*** configuration in each case[14] irrespective of the types of R_1-alkylsubstituent. In this reaction *it is worth noting that no other diastereomeric compound was isolated and consequently it involves no separation of stereoisomers through the entire sequence until 1,2,3,4,5-pentasubstituted pyrrolidine 8 was synthesized from 1.*

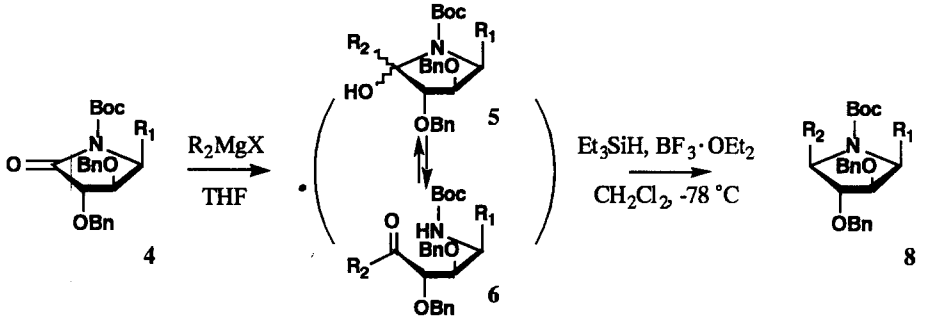


Table 1 Reductive Deoygenation of the Alkylated Products to **4**[a]

Entry	R_1	R_2	Yield[b] of **6** (%)	Yield[b] of **8** (%)	$[\alpha]_D$,deg[c] (Temp./°C, c)
1	C_4H_9	C_4H_9	7 (**6a**)	65 (**8a**)	-20.0 (23, 1.24)
2	C_4H_9	C_9H_{19}	21[e] (**6b**)	52 (**8b**)	-17.2 (25, 1.70)
3	C_4H_9	$PhCH_2$	5 (**6c**)	52 (**8c**)	-2.40 (26, 0.99)
4	C_9H_{19}	C_4H_9	7 (**6d**)	72 (**8d**)	-16.7 (23, 2.10)
5	C_9H_{19}	C_9H_{19}	13[e] (**6e**)	62 (**8e**)	-16.6 (26, 1.82)
6	C_9H_{19}	$PhCH_2$	2 (**6f**)	59 (**8f**)	-5.70 (24, 1.21)
7	$PhCH_2$	C_4H_9	6 (**6g**)	63 (**8g**)	-24.2 (24, 1.38)
8	$PhCH_2$	C_4H_9[d]	-- [f] (**6g**)	74 (**8g**)	-24.5 (26, 0.56)
9	$PhCH_2$	C_9H_{19}	8 (**6h**)	44 (**8h**)	-22.5 (23, 1.25)
10	$PhCH_2$	$PhCH_2$	-- [f] (**6i**)	33 (**8i**)	-8.50 (26, 0.84)

a) 3 equiv. of Et_3SiH and 6 equiv. of $BF_3 \cdot OEt_2$ were used. b) Isolated yield. c) Measured in $CHCl_3$. d) BuLi was used. e) Yield after reduction to alcohol with $NaBH_4$. f) Ketone form was not observed.

Although the reasons why such a highly diastereofacially selective reaction was accomplished are not clarified accurately at present, it would proceed through the attack of Et_3SiH to the *N*-acyliminium ion intermediate.[5] Additional studies on the mechanistic origin of this asymmetric induction are in progress.

Further, this strategy provides a new synthetic opportunity for the synthesis of biologically active natural pyrrolidine alkaloids.

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12 ^1H and ^{13}C NMR data ($CDCl_3$) for **8a** and **9a**. **8a**: ^1H NMR δ 0.89 (6H, br t, J = 4.4 Hz), 1.07-2.00 (12H, m), 1.48 (9H, s), 3.61-4.20 (4H, m), 4.50 (2H, s), 4.62 (2H, d, J = 2.0 Hz), 7.29 (5H, s), 7.31 (5H, s). ^{13}C NMR δ 13.9, 22.4, 22.7, 28.1, 28.3, 28.4, 29.7, 34.0, 58.3, 61.2, 71.6, 72.2, 79.0, 83.6, 84.7, 127.5, 127.6, 127.9, 128.2, 128.3, 137.7, 138.1, 155.1. **9a**: ^1H NMR δ 0.86 (6H, br t, J = 5.6 Hz), 1.07-2.03 (12H, m), 1.46 (9H, s), 3.79-4.21 (2H, m), 4.07 (2H, dt, J = 1.5, 5.8 Hz), 4.65 (4H, s), 7.31 (10H, s). ^{13}C NMR δ 14.0, 23.1, 28.5, 28.9, 29.7, 55.8, 73.1, 79.3, 81.6, 127.4, 127.5, 127.7, 127.9, 128.3, 138.3, 154.2.
13. Observed chemical shifts (^1H and ^{13}C NMR) of the other deoxygenated products (**8b-8i**) were almost identical with those of **8a** as indicated in reference 12.
14. Corresponding other *S* isomers (**9b**, **9d**, **9e**, **9g**, and **9h**) were also elaborated from **4** through the successive reactions of reduction and mesylation, followed by cyclization according to Scheme 2.

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