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Carboxy mediated stereoselective reduction of ketones with sodium triacetoxyborohydride: synthesis of novel 3,4-fused tetrahydropyran and tetrahydrofuran prolines ☆

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Abstract—In the presence of a carboxyl group positioned for participation, $NaBH(OAc)_3$ will reduce the usually unreactive ketones in a stereoselective manner. This reaction was applied in a key step to prepare precursors **7** and **15** toward the title compounds **1** and **2**. These results are consistent with the exchange of one of the acetoxy groups in the reducing agent with the carboxy group followed by intramolecular delivery of the hydride.

Due to their unique conformational properties, substituted prolines have been used extensively to influence the conformation of peptide backbones and to induce desired turns in host structures.[1] These nonproteinogenic amino acids are also incorporated into peptide molecules in an attempt to improve their pharmacological properties, and this methodology continues to be a powerful tool for identifying and elucidating structure–activity relationships.[2] In the course of our medicinal chemistry program, we desired to prepare and incorporate into a peptide molecule the substituted novel prolines **1** and **2** (Fig. 1).

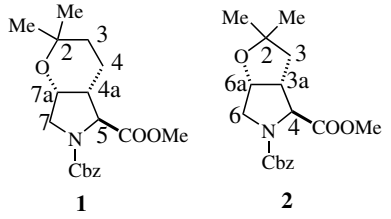
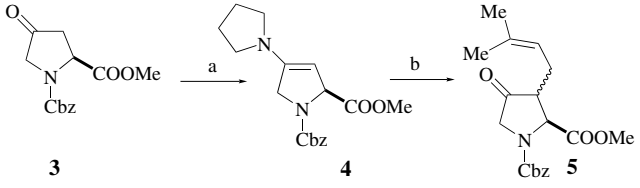


Figure 1.

Prenylation of enamine **4** derived from the ketone **3**[3] proceeded smoothly and the prenylated product **5** was isolated in ~50% yield in addition to unreacted starting material (Scheme 1).



Scheme 1. Reagents and conditions: (a) pyrrolidine, MS4A, toluene, Δ; (b) prenyl bromide, K_2CO_3, MeCN, then H_3O^+.

Reduction of **5** with $NaBH_4$ gave three products, **6**, **7**, and **8** in the increasing order of polarity and in a ratio of 11:18:24. Compound **6** has the stereochemistry as *cis*, *cis* across C-2, C-3, and C-4 because it is derived from the hydride attack solely from the α-side of the molecule. Compounds **7** and **8** are the corresponding α- and β-hydroxy isomers of the major 2,3-*trans* prenylation product (Scheme 2).

Keywords: Sodium triacetoxyborohydride; Stereoselective reduction; Tetrahydropyran and tetrahydrofuran proline.
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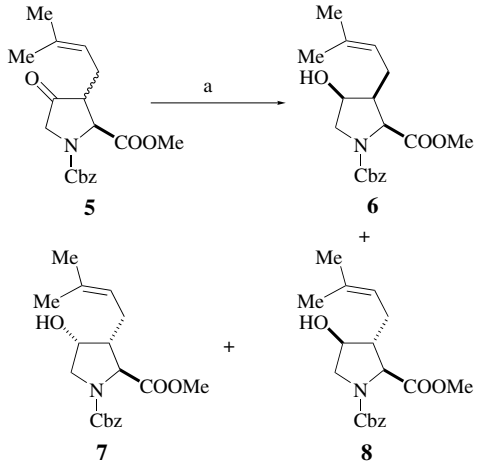
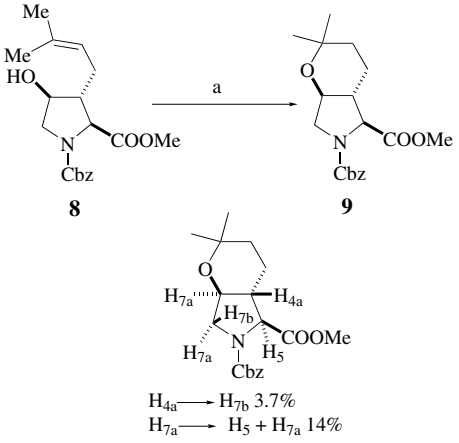


Scheme 2. Reagents and conditions: (a) $NaBH_4$, MeOH, THF.

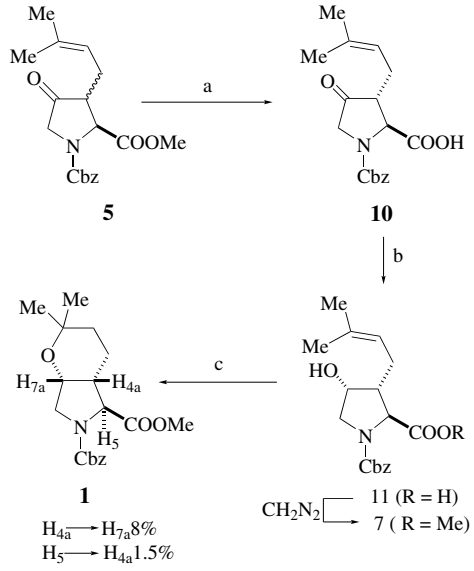


Scheme 3. Reagents and conditions: (a) $BF_3{\cdot}Me_2O$, CH_2Cl_2.

Upon treatment of **8** with $BF_3{\cdot}Me_2O$ the cyclization product **9** was obtained. PMR analysis through COSY and NOE experiments unambiguously established a *trans*, *trans* relationship between the substituents of C-2, C-3, and C-4 (Scheme 3).

In the meantime, saponification of esters **5** gave the acid **10**, a single product, in ~95% yield. It is reasoned that during ester hydrolysis, equilibration occurs at C-3 and the thermodynamically more preferred product **10** is obtained (Scheme 4).

Interestingly, reduction of the C-4 carbonyl group with $NaBH(OAc)_3$ gave **11** with an α-hydroxyl at C-4 as the sole product in 93% yield. This result is consistent with the exchange of one of the acetoxy groups of $NaBH(OAc)_3$ with the carboxyl group, which in turn donates hydride from the β-side of the molecule. This effect has been previously observed in the context of hydroxy ketones.[4] Some additional examples of this unprecedented stereoselective reduction of ketoacids with $NaBH(OAc)_3$ are described below. Treatment of **11** with CH_2N_2 gave the same C-2, C-3, C-4 *trans*, *cis* hydroxy ester **7** obtained above by direct reduction of the



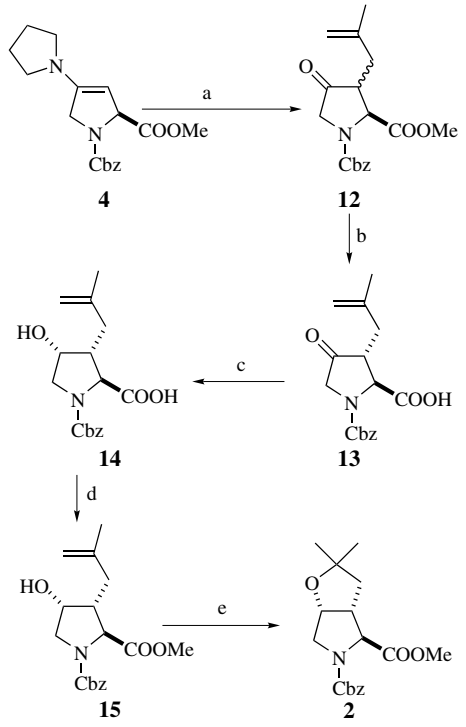
Scheme 4. Reagents and conditions: (a) 1 N LiOH, dioxane; (b) $NaBH(OAC)_3$, cat. AcOH then $TMSCHN_2$; (c) $BF_3{\cdot}Me_2O$, CH_2Cl_2.

keto ester **5** with $NaBH_4$. Cyclization of **7** by $BF_3{\cdot}Me_2O$ gave the title compound **1**, $[\alpha]_D^{21}$ −50.81 (*c* 1.0, $CHCl_3$) in 92% yield. The stereochemistry of **1** is clearly confirmed as *trans*, *cis* across C-2, C-3, and C-4 by PMR–NOE experiments.

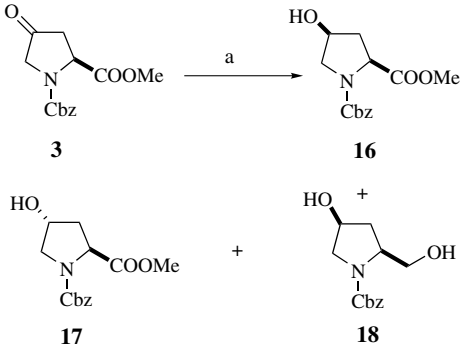
The same strategy was applied toward the synthesis of **2**. Thus, treatment of the enamine **4** with methallyl chloride in the presence of NaI and Na_2CO_3 followed by acidic work-up provided the alkylation product **12** in ~50% yield in addition to unchanged starting material. Basic hydrolysis of **12** then provided the thermodynamically more preferred 2,3-*trans* acid **13**, $[\alpha]_D^{21}$ −39.16 (*c* 1.0, $CHCl_3$) in 77% yield. Reduction of **13** with $NaBH(OAc)_3$ gave the C-2, C-3, C-4 *trans*, *cis* hydroxy acid **14**, $[\alpha]_D^{21}$ − 12.31 (*c* 1.0, $CHCl_3$) in 98% yield.[5] Treatment of **14** with CH_2N_2 followed by reaction of **15** with $BF_3{\cdot}Me_2O$ provided the title compound **2**, $[\alpha]_D^{21}$ − 40.32 (*c* 1.0, $CHCl_3$) in 84% yield (Scheme 5).

In order to understand the aforementioned processes, the reaction of $NaBH(OAc)_3$ with 4-ketoproline **19** was studied. Reaction of N-Cbz 4-ketoproline methyl ester **3** with $NaBH(OAc)_3$ failed to provide any product. Its reaction with $NaBH_4$ provided three products, the known 4-*cis* and 4-*trans* alcohols **16** and **17** as well as the over reduced 4-*cis* diol **18** in a 53:17:30 ratio (Scheme 6).

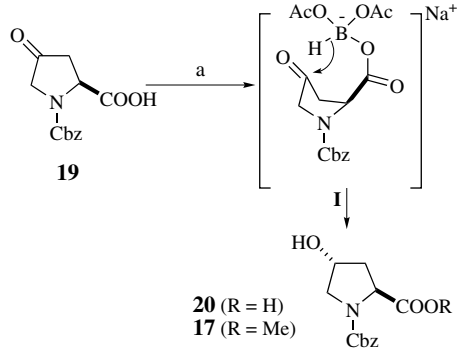
When the 4-ketoproline **19** was reacted with $NaBH(OAc)_3$ followed by treatment of **20** with CH_2N_2, the 4-*trans* hydroxy acid **17** was isolated in 95% yield (Scheme 7). As depicted in [I] this result is consistent with exchange of one of the acetoxy groups in $NaBH(OAc)_3$ with the carboxylic group in 4-ketoproline, which delivers the hydride from the β-face of the molecule. In a related example, reduction of pinonic acid methyl ester **21** with $NaBH_4$ gave as expected a mixture of *R* and *S* alcohols **22**[6] (Scheme 8).



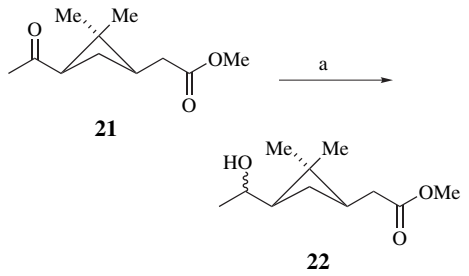
Scheme 5. Reagents and conditions: (a) methallyl chloride, NaI, K_2CO_3; (b) 1 N LiOH, dioxane; (c) $NaBH(OAc)_3$, cat. AcOH; (d) $TMSCHN_2$, Et_2O, MeOH; (e) $BF_3{\cdot}Me_2O$, CH_2Cl_2.



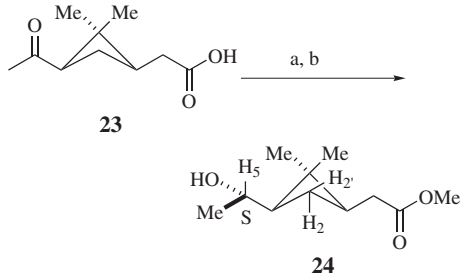
Scheme 6. Reagents and conditions: (a) $NaBH_4$, aq. THF.



Scheme 7. Reagents and conditions: (a) $NaBH(OAc)_3$.



Scheme 8. Reagents and conditions: (a) $NaBH_4$, aq. THF.



Scheme 9. Reagents and conditions: (a) $NaBH(OAc)_3$, cat. AcOH; (b) $TMSCHN_2$, Et_2O, MeOH.

In contrast, reaction of pinonic acid **23** with large excess of $NaBH(OAc)_3$ gave in modest (12%) yield a single 5*S* hydroxy compound **24**, $[\alpha]_D^{21}$ −21.86 (*c* 1.0, MeOH) (Scheme 9). The absolute configuration at C-5 was determined using *J*-coupling and NOE data, which revealed spatial proximity between Me (C-5) and H-2 and H-2′. The modest yield in this case suggests that a 6 carbon spatial distance between the participating carboxy group and the keto functionality is likely a limiting factor for the intramolecular hydride delivery. From the discussed examples it appears that a 4 carbon distance between the carboxy group and the site of hydride delivery, as in the rigid proline system, is optimal.[7]

Supplementary data

Information available: Experimental procedures and Characterization for **1**, **2**, and **24**.

References and notes

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5. Representative procedure to obtain **15**. To a stirred suspension of $NaBH(OAc)_3$ (125 g; 589 mmol) in of CH_2Cl_2 (1.4 L) was added with cooling (ice bath) a solution of **13** (66.6 g; 210 mmol) in CH_2Cl_2 (400 mL) over 40 min. Glacial acetic acid (67 mL) was then added and the reaction mixture stirred for ~20 h at room temperature. The reaction mixture was poured onto ice (2 L) and stirred for 1 h. CH_2Cl_2 (2 L) as added and the organic phase washed with brine (1 L × 2), dried over Na_2SO_4, and evaporated to dryness in vacuo to provide **14** as a syrupy liquid (70 g). It was dissolved in Et_2O/MeOH (930/270 mL), cooled to −5 °C and $TMSCHN_2$ (186 mL; 2 M in hexane) was added over 1 h. The reaction was kept at 0 °C for 1 h then stirred at room temperature for 3.5 h and evaporated to dryness in vacuo to provide almost pure **15** (71 g) as an oil. It was purified on a silica gel column using 10–30% ethyl acetate in hexane as eluent to provide pure **15** (65 g).
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7. All new compounds were characterized by ^1H, ^{13}C NMR, and high resolution mass spectra. When necessary 1D NOE and 2D NOESY NMR spectra were obtained to confirm relative stereochemistry. Elemental analyses were obtained for crystalline compounds only. Yields refer to isolated products and have not been optimized. Selective spectral data is given here.