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A facile synthesis of 5,6-dihydro-5-hydroxy-2(1*H*)-pyridone

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ABSTRACT

A short synthesis of 5,6-dihydro-5-hydroxy-2(1*H*)-pyridone was achieved from L-serine employing Horner–Emmons olefination as the key step.

The 2(1*H*)-pyridone ring system and the corresponding dihydro and tetrahydro derivatives are found abundantly in a wide variety of naturally occurring alkaloids and novel synthetic biologically active molecules.[1] Heterocycles incorporating a 2(1*H*)-pyridone framework constitute an extensively studied class of compounds owing to their diverse biological activities ranging from anti-HIV, antibacterial and antifungal to free radical scavengers. Several 3-amino-2-pyridinone acetamides act as thrombin inhibitors. Some non-nucleoside-3-aminopyridin-2(1*H*)-ones have been reported to exhibit HIV-1-specific reverse transcriptase inhibitory properties.[2] In addition, dihydro and tetrahydro derivatives of 2(1*H*)-pyridone have been applied as scaffold for the construction of constrained aminoacids,[3] quinoline[4a] and isoquinoline[4b] derivatives, indolizidine,[4c] quinolizidine alkaloids and polyhydroxylated piperidines[5,7] with important pharmaceutical activity.

5,6-Dihydro-5-hydroxy-2(1*H*)-pyridone alkaloid **1** has been isolated from the whole plant of *Piper sintenense* which exhibits cytotoxicity against P-388, H-T-29 or A-549 cell lines in vitro.[6] It is an important building block for the synthesis of (*R*)-pipermethystine[1b] and several other polyhydroxylated pyridones[7] such as (3*R*,4*R*,5*S*)-3,4,5-trihydroxy-piperidine-2-one and (3*R*,4*S*,5*S*)-3,4,5-trihydroxy-piperidine-2-one (Fig. 1). Despite its apparent simple structure, surprisingly there has been no report on the synthesis of N-unsubstituted pyridone **1** except for a sole publication of its *S*-enantiomer which has been synthesized by Herdeis et al. starting from D-ribonolactone.[6b]

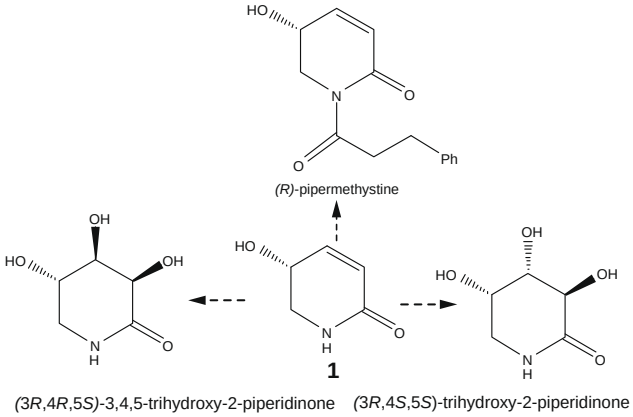

Figure 1. Structures of 2-pyridone-derived alkaloids.

Nevertheless, there are few methods available in the literature for preparing the chiral nonracemic N-substituted pyridone derivatives starting from either achiral or chiral pool starting materials and typically requiring a large number of synthetic steps.[1]

As a part of our research on the asymmetric synthesis of hydroxylated piperidines,[8] we became interested in developing a route to 2-pyridone derivatives. Herein we wish to report a new approach to 5,6-dihydro-5-hydroxy-2(1*H*)-pyridone from L-serine using Horner–Emmons olefination as the key step.

As illustrated in Scheme 1, the synthesis of **1** commenced with commercially available L-serine as a chiral pool starting material. Thus, L-serine **2** was initially transformed into the diol ester **3** by the reported procedure.[9] Selective primary hydroxyl protection of

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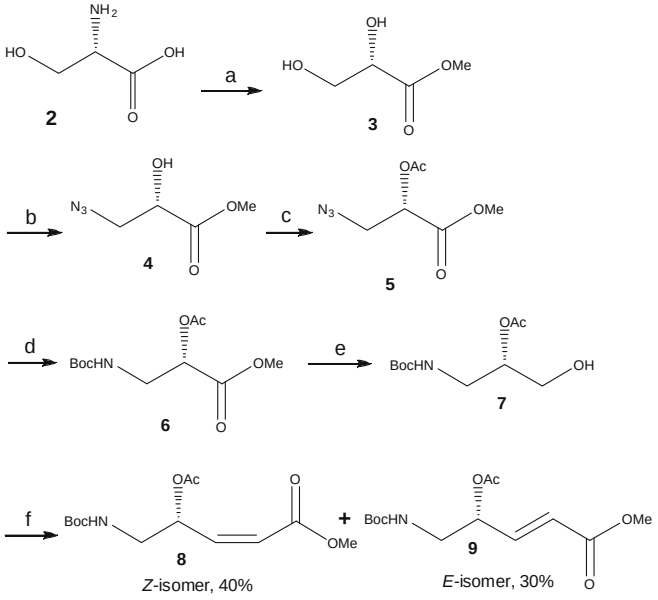
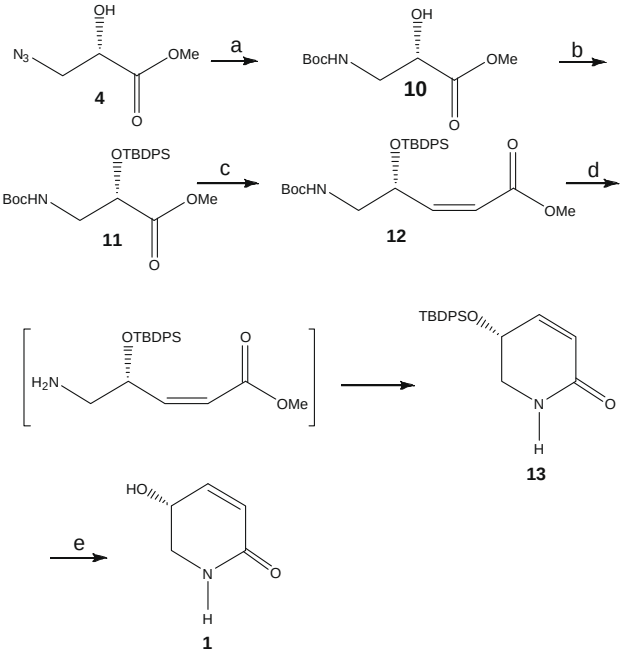


Scheme 1. Reagents and conditions: (a) $NaNO_2$, aq H_2SO_4, 3 days, 100%; (b) (i) TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, 0 °C, 2 h, 75%; (ii) NaN_3, DMF, 80 °C, 70%; (c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C-rt, 3 h, 70%; (d) H_2, $Pd(OH)_2/C$, Boc_2O, MeOH, 5 h, 75%; (e) DIBAL-H, CH_2Cl_2, −78 °C, 2 h, 70%; (f) (i) IBX, EtOAc, reflux, 2 h; (ii) $Ph_3P{=}CHCO_2Me$, MeOH, 0 °C, 24 h, 70%.



Scheme 2. Reagents and conditions: (a) H_2, $Pd(OH)_2/C$, Boc_2O, MeOH, 5 h, 75%; (b) TBDPS-Cl, imidazole, DMAP, CH_2Cl_2, 0 °C, 4 h, 80%; (c) (i) DIBAL-H, toluene, −78 °C, 2 h; (ii) $(CH_3{-}C_6H_4O)_2{-}P(O)CH_2CO_2Me$, NaH, −78 °C, THF, 5 h, 72%; (d) TMS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 5 h, then satd $NaHCO_3$, 24 h, 55%; (e) TBAF, THF, 0 °C-rt, 12 h, 40%.

diol was performed with tosyl chloride in the presence of catalytic amount of dibutyltin oxide[10] followed by the nucleophilic displacement of resulting tosylate with sodium azide to afford compound **4** in 70% yield. The acylation of hydroxyl group (**4**→**5**) followed by azide reduction in the presence of Boc_2O under hydrogenation conditions[11] using $Pd(OH)_2/C$ furnished the desired amino alcohol **6** in 75% yield. Subsequent reduction using 2 equiv of DIBAL-H at −78 °C produced alcohol **7** in 70% yield. It may be noted that we did not observe any cleavage of acetoxy group during DIBAL-H reduction. Oxidation of alcohol **7** with IBX followed by two carbon Wittig olefination in MeOH[12] at 0 °C resulted in a mixture of both cis- and trans-isomers in the ratio 4:3. The ratio of desired cis-isomer could not be improved even after performing the reaction at lower temperature (Scheme 1).

The poor yield obtained for cis-isomer could probably be attributed to the electron-withdrawing effect of acetoxy group. To circumvent the problem of low yield, we thought of masking the hydroxyl group preferably with a bulky protecting group. Towards this end, the azido compound was first reduced to amine in the presence of Boc_2O under hydrogenation conditions using ($Pd(OH)_2/C$) (**4**→**10**) followed by the hydroxyl group protection with *tert*-butyldiphenylsilyl chloride in the presence of imidazole to furnish compound **11** in 80% yield (Scheme 2). The ester group was reduced with 1.2 equiv of DIBAL-H at −78 °C to the corresponding aldehyde and subsequently subjected to two carbon Wittig olefination in MeOH at −78 °C. However, we could not observe much improvement in the ratio of cis-isomer. With an aim to prepare the required cis-compound, we then employed the new Horner–Emmons reagent, diarylphosphonoacetate for the highly selective synthesis of *Z*-unsaturated ester as reported by Ando.[13] Thus, the aldehyde obtained from **11** was treated with Horner–Emmons reagent, methyl (ditolylphosphono) acetate to produce the *cis*-olefin **12**[14] as the major isomer (98:2) as confirmed from the ^1H NMR spectroscopy of the crude product. The *Z*-selectivity of the (diarylphosphono) acetate reagent is a result of kinetic control and can be interpreted by the predominant formation of *erythro* adduct which irreversibly collapses to the *Z*-olefin. This could probably be attributed to the enhanced kinetic selectivity for the erythro adduct due to the steric hindrance of the aryl group and also silyloxy group at α-position rather than the electronic effect.[13] The Boc group was deprotected under standard conditions using TMS-OTf and 2,6-lutidine as base[15] and subsequently neutralized with saturated sodium bicarbonate solution to produce the pyridone derivative **13** in 55% yield.[6b,16] Finally, TBDPS group was deprotected with tetrabutyl ammonium fluoride to furnish the desired pyridone **1** as an oily compound in 40% yield, $[\alpha]^{25}$ +53.4 (*c* 0.23, MeOH); [lit.[6a] $[\alpha]^{26}$ +55.7 (*c* 0.2, MeOH)]. The spectral data of pyridone **1** were in accord with those described in the literature.[6a]

In conclusion, we have achieved a concise synthesis of 5, 6-dihydro-5-hydroxy-2(1*H*)-pyridone from L-serine in overall 5% yield using Horner–Emmons olefination as the key step. The generality of method shown has significant potential of its further extension to the other isomer and also to the construction of variety of materials derived from 2-pyridone derivatives. Currently studies are in progress towards this direction.

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14. *Spectral data of* **12**: $[\alpha]^{25}$ +1.4 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.09 (s, 9H), 1.42 (s, 9H), 3.30–3.47 (m, 2H), 3.55 (s, 3H), 4.81–4.91 (m, 1H), 5.59 (d, *J* = 10.4 Hz, 1H), 6.12 (dd, *J* = 11.8 Hz, *J* = 8.1 Hz, 1H), 7.34–7.46 (m, 6H), 7.60–7.71 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 26.8, 28.2, 45.9, 51.7, 71.7, 79.2, 119.3, 127.4, 127.5, 127.6, 127.7, 129.7, 129.8, 129.9, 132.6, 132.8, 133.3, 133.4, 135.6, 135.6, 135.7, 135.8, 149.5, 155.7, 165.7.
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16. *Spectral data of* **13**. $[\alpha]^{25}$ −62.4 (*c* 1.9, $CHCl_3$); IR. ν_{max}/cm^{-1} ($CHCl_3$): 3290, 1628, 1614; ^{1}H NMR (400 MHz $CDCl_3$) δ: 1.07 (s, 9H), 3.32 (dd, *J* = 12.5 Hz, *J* = 2.7 Hz, 1H), 3.42 (dd, *J* = 12.6 Hz, *J* = 2.2 Hz, 1H), 4.43–4.50 (m, 1H), 5.83 (d, *J* = 9.9 Hz, 1H), 6.43 (dd, *J* = 9.9 Hz, *J* = 3.2 Hz, 1H), 6.20 (s, 1H, NH), 7.38–7.48 (m, 6H), 7.64–7.67 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 19.0, 19.3, 26.8, 47.0, 124.2, 127.9, 130.1, 133.0, 133.1, 135.7, 144.2, 165.5; Mass (LCMS): $[M+Na]^+$ 374, 358, 306,280, 251, 221, 174.