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An efficient one-pot synthesis of (+)-deoxypyridinoline

Maciej Adamczyk,* Donald D. Johnson and Rajarathnam E. Reddy

Department of Chemistry (9NM), Building AP20, Diagnostics Division, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6016, USA

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Abstract

An efficient one-pot synthesis of (+)-deoxypyridinoline (Dpd, **1**), the cross-link of bone collagen, was achieved from *tert*-butyl-(*S*)-(−)-[(2-*tert*-butoxycarbonyl)amino]-6-aminohexanoate (**2**) and *tert*-butyl-(*S*)-(−)-6-bromo-2-[bis(*tert*-butoxycarbonyl)amino]-5-oxohexanoate (**3**) in 42% yield. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: bone collagen; deoxypyridinoline; osteoporosis; pyridinium compounds.

(+)-Deoxypyridinoline (Dpd, **1**), a degradation product of bone collagen, has attracted much attention due to its clinical utility as a marker for the diagnosis of osteoporosis and other metabolic bone diseases.[1] Thus, Dpd (**1**) is essential for applications in the studies of bone biology and for use in assay development.[1,2] Currently it is isolated in a very low yield from bones (e.g., sheep, ox, turkey) by 6–9 M HCl hydrolysis at 110°C, a process that could also affect the integrity of stereocenters.[3] Therefore, Dpd (**1**) is an attractive synthetic target due to its novel and interesting structural features, coupled with practical applications in the diagnosis and therapeutic management of bone diseases. Recently two different multi-step strategies have been reported for the syntheses of Dpd (**1**). The first strategy involves construction of a substituted pyridine ring from amino acid components utilizing aldol chemistry.[4] The second approach consists of a sequential building of amino acid chains from a pyridine derivative, vitamin B_6.[5] In this paper, we describe an efficient one-pot synthesis of (+)-Dpd (**1**) from *tert*-butyl-(*S*)-(−)-[(2-*tert*-butoxycarbonyl)amino]-6-aminohexanoate (**2**) and *tert*-butyl-(*S*)-(−)-6-bromo-2-[bis(*tert*-butoxycarbonyl)amino]-5-oxohexanoate (**3**), the derivatives L-lysine and L-glutamic acid respectively.

Thus, (*S*)-(−)-amine (**2**)[6] was treated (Scheme 1) with 2.0 equiv. of (*S*)-(−)-bromide (**3**)[7,8] in the presence of anhydrous potassium carbonate in MeCN to facilitate the *N*-alkylation, and the reaction progress was monitored by TLC, HPLC, and ESI-MS.[9] After the disappearance of (*S*)-(−)-**2**, the resulting diketone intermediate (**4**) was then induced to undergo aldol cyclization, and subsequent aromatization of **5** by addition of methanol and additional potassium carbonate, and stirring the mixture in open air for 24 h. Finally, unmasking the Boc and *tert*-butyl protective groups using TFA–water, followed by

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* Corresponding author. E-mail: maciej.adamczyk@abbott.com

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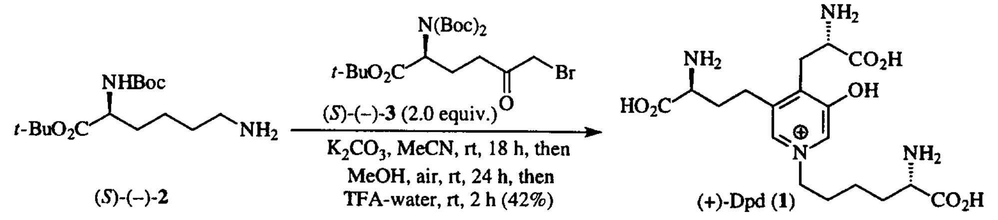
purification of the crude product by reversed phase HPLC afforded (+)-Dpd (**1**) as its TFA salt in 42% yield {$[\alpha]_D^{20}$ +37.6 (*c* 1.29, MeOH); lit.[4b] $[\alpha]_D^{20}$ +31.6 (*c* 0.25, MeOH)}.[10] In summary, an efficient one-pot synthesis of (+)-deoxypyridinoline (**1**), the cross-link of bone collagen, is described, which is amenable for combinatorial synthesis of a library of its analogs.



Scheme 1.

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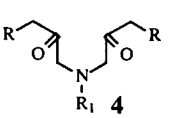
7. (*S*)-(–)-**3** was prepared from 1-*tert*-butyl-5-methyl-(*S*)-(–)-2-[bis(*tert*-butoxycarbonyl)amino]pentanedioate (Ref. 8) by hydrolysis, and according to Ref. 4b (LiOH, THF–H_2O, rt, 2 h; then isobutyl chloroformate, THF, 0°C, 40 min, then CH_2N_2, ether, 0–23°C, 3 h, then 48% HBr, ether, –20°C, 30 min, 54% yield).
8. Adamczyk, M.; Johnson, D. D.; Reddy, R. E. *Tetrahedron: Asymmetry* **1999**, *10*, 775.
9. Structure of the reaction intermediates, **4**, **5**, **6** and see also Ref. 4b.



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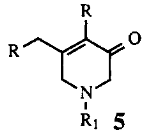

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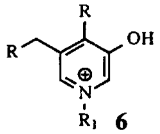

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R = CH_2-(*S*)-CHN$(Boc)_2$-CO_2t-Bu
R_1 = $CH_2(CH_2)_3$-(*S*)-CHNHBoc-CO_2t-Bu

10. Synthesis of (+)-Dpd (**1**): Anhydrous K_2CO_3 (0.137 g, 0.990 mmol, 5.0 equiv.) was added to the mixture of (*S*)-(–)-amine (**2**) (0.060 g, 0.198 mmol) and (*S*)-(–)-bromide (**3**) (0.190 g, 0.396 mmol, 2.0 equiv) which were dissolved in dry MeCN (2 mL) at room temperature under nitrogen. After stirring the mixture for 18 h, MeOH (2 mL) and an additional amount of anhydrous K_2CO_3 (0.274 g, 1.98 mmol, 10.0 equiv.) were added. The rubber septum was removed and the reaction mixture stirred at room temperature in open air for 24 h. The mixture was then concentrated on a rotary evaporator under vacuum, and the residue was treated with a mixture of trifluoroacetic acid:water (10 mL, 95:5 ratio) at room temperature. After stirring the mixture for 2 h, it was concentrated, and the residue was dissolved in MeCN:H_2O:TFA (20 mL, 1:99:0.1 ratio). The crude product was purified by preparative reversed phase HPLC (Waters, C18, RCM, μBondpak, 10.0 μ, 3×40 mm×100 mm, using MeCN:H_2O:TFA, 1:99:0.1, 20 mL/min at 215 nm). Concentration of the product to about 120 mL volume, and lyophilization afforded 0.072 g of (+)-Dpd (**1**) as its TFA salt in 42% yield. Analytical RP HPLC (Waters, C18, RCM, μBondpak, 10.0 μm, 8×100 mm): MeCN:H_2O:TFA, 1:99:0.1, 1.0 mL/min at 215 nm, R_t: 4.64 min, 99.7%, and the spectral properties were consistent with the reported data (Refs. 4b and 5).