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ASYMMETRIC SYNTHESIS OF (1*R*, 2*S*, 3*R*)-2-ACETYL-4(5)-(1,2,3,4-TETRAHYDROXYBUTYL)IMIDAZOLE

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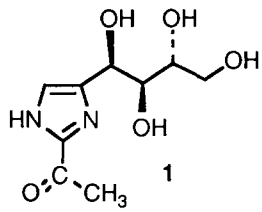
Abstract: A method for preparing the biologically active compound (1*R*, 2*S*, 3*R*)-2-acetyl-4(5)-(1,2,3,4-tetrahydroxybutyl)imidazole **1** using a palladium (0) catalysed coupling of 1-ethoxymethyl-4-iodoimidazole **2** to the functionalised vinylstannane **3** and the Sharpless catalytic asymmetric dihydroxylation is reported.

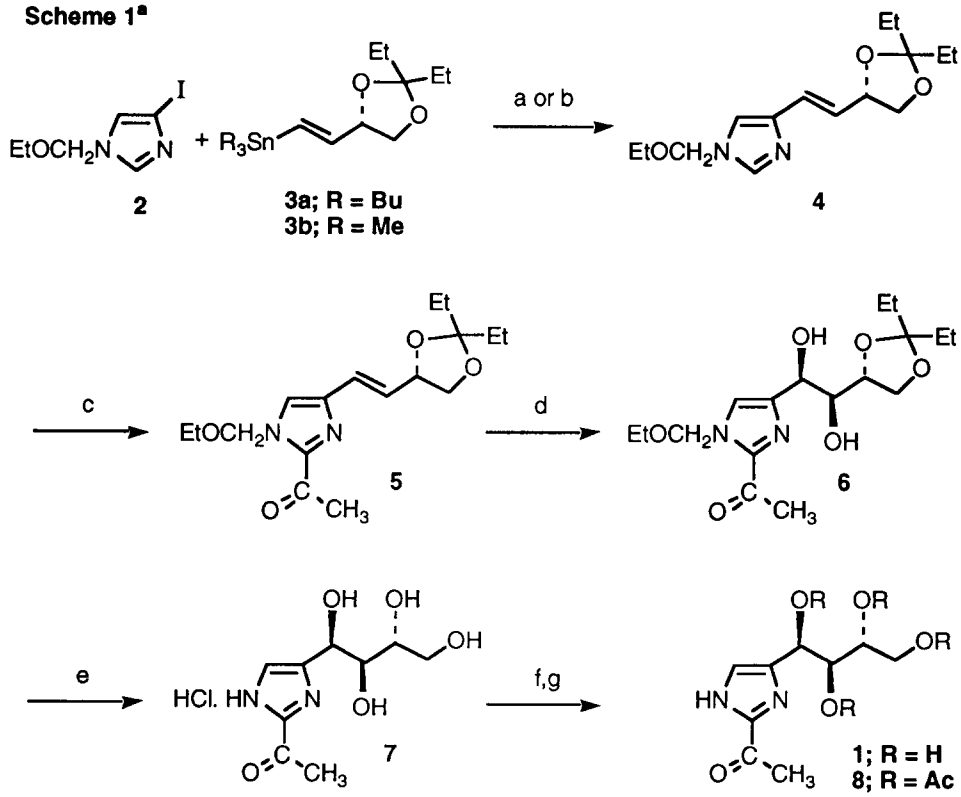
(1*R*, 2*S*, 3*R*)-2-Acetyl-4(5)-(1,2,3,4-tetrahydroxybutyl)imidazole (THI) **1**, a constituent of Caramel Colour III, has been found to depress blood lymphocyte counts in both mice and rats.[1] THI produces lymphopenia, apparently without toxic effects, in rats and mice and is able to affect the immune competence in the rat in quite small quantities (e.g. 1-50ppm in drinking water).[2] THI has also been reported to prevent spontaneous and cyclophosphamide-induced diabetes in non-obese diabetic mice.[3] To investigate the structure-activity relationships of this structurally simple but biologically intriguing molecule we desired a general and flexible synthesis of THI and its analogues. Three syntheses of THI have been reported and these all rely on the use of glucose derivatives to prepare the (1*R*, 2*S*, 3*R*)-1,2,3,4-tetrahydroxybutyl side chain.[4-6] These syntheses are either not sufficiently flexible for the synthesis of THI analogues[6] or suffer from poor overall yields.[4,5]



1

We report here a new synthetic protocol for the synthesis of THI as outlined in Scheme 1. This involves a palladium catalyzed coupling of the 1-protected-4-iodoimidazole **2** to the functionalized vinylstannane **3** to produce the (*E*)-alkene **4** and the Sharpless catalytic asymmetric dihydroxylation (AD) to introduce the (1*R*, 2*S*)-dihydroxy functionality into the butyl side chain of **1** (Scheme 1). We chose the ethoxymethyl ($EtOCH_2$-) protecting group for the imidazole nitrogen since this group would assist the introduction of the 2-acetyl group into the imidazole ring later in the synthesis. [7]

Scheme 1[a]



[a]Key: (a) 5 % $Pd_2(dba)_3$, 10 % $AsPh_3$, 10 % CuI, DMF, 80 °C, 24 h, 45 % from **3a**; (b) 5% $Pd(PPh_3)_4$, DMF,80 °C, 24 h, 83 % from **3b**; (c) (i) *n*-BuLi, THF, -78 °C, 1h, (ii) MeCONMe(OMe), -78 °C (1 h) to rt (1 h), 65 %; (d) AD mix-β, $(DHQD)_2$-PHAL (4 mol %) , methanesulfonamide (2 equiv.), t-BuOH / H_2O, 0 °C, 3 days, 80 %; (e) 10% HCl / ethanol (2 : 1), reflux 1 h; (f) $K_2CO_{3(aq)}$, 24 %; (g) Ac_2O / HOAc / $HClO_4$(cat), 60 °C, 1 h, 55 %.

Stille type coupling reactions[8-10] of 1-ethoxymethyl-4-iodoimidazole **2**[11] and vinylstannanes **3a** ((*E*) : (*Z*) = 81 : 19)[12] or **3b** ((*E*) : (*Z*) = 88 : 12)[12] using 5 % $Pd_2(dba)_3$, 10 % $AsPh_3$, 10 % CuI, DMF, 80 °C, 24 h[13], or 5 % $Pd(PPh_3)_4$, DMF, 80 °C, 24 h, respectively, gave the pure (*E*)-alkene **4** in 45 % and 83 % yields respectively.[14] The (*Z*)-geometric isomers of vinylstannes **3a** and **3b** underwent coupling at a much slower rate than their (*E*)-counterparts and none of the (*Z*)-isomer of **4** could be isolated from these reactions after purification by column chromatography on silica gel. Treatment of **4** with *n*-butyllithium (1.2 equiv.) in THF at -78 °C for 1 h, followed by quenching the resulting 2-lithio-imidazole derivative with *N*-methoxy-*N*-methyl acetamide[15] (1.4 equiv., -78 °C (1 h) to rt (1 h)) gave the 2-acetylimidazole **5** in 65 % yield. Catalytic asymmetric dihydroxylation (AD) of **5** at 0 °C for 3 days using commercially available AD mix-β,[16,17] additional chiral ligand ($(DHQD)_2$-PHAL (4 mol %) and methanesulfonamide (2 equiv.) in t-BuOH / H_2O gave the *syn* (1*R*, 2*S*)-diol **6**, in good yield (80 %) and high diastereoselectivity (d.e. 99 %) as determined by ^1H NMR analysis. In contrast, catalytic dihydroxylation of **5** in the absence of chiral ligand ($K_2OsO_4.H_2O$ (5 mol %)/ $K_3Fe(CN)_6$ (3 equiv.)/ K_2CO_3 (3 equiv.)/ $MeSO_2NH_2$ (2 equiv.) / t-BuOH, H_2O at 0 °C, 3 days) gave a mixture of **6** and its diastereomeric *syn*-(1*S*, 2*R*)-diol in a ratio of 3.5 : 1 respectively (^1H NMR (d^6-

acetone) (1*R*, 2*S*)-diol **6** : δ 4.84 (d, *J* = 2.0 Hz, H-1'); (1*S*, 2*R*-)-diol **6** : δ 4.72 (d, *J* = 4.4 Hz, H-1')). Hydrolysis of **6** with aqueous 10 % hydrochloric acid / ethanol (2 : 1) at reflux for 1 h gave the imidazole hydrochloride salt **7** plus several unidentified products. Neutralisation of this mixture with aqueous potassium carbonate solution and then cooling to 5 °C and collection of the precipitate gave THI (**1**) in 24 % yield from **6**. When this hydrolysis reaction was performed at 80 °C for 90 min then THI was obtained with fewer side products. The physical properties of our synthetic **1** (mp 240 - 244 °C (lit.[6] 234-236 °C), $[\alpha]_D^{23}$ -14.9 (c 1.4, HCl/H_2O) (lit.[5] $[\alpha]_D^{25}$ -12 (c 1.17, 1N HCl), ^1H NMR (DCl/D_2O)) were in agreement with those of **1** that was prepared according to the method of Buchi.[6] THI (**1**) prepared according to Scheme 1 and THI prepared via the method of Buchi were converted to the same tetraacetate **8** upon acetylation with acetic anhydride/acetic acid/perchloric acid (cat) at 60 °C.[18] The stereochemical outcome of the AD reaction of **5** was consistent with Sharpless's mnemonic.[17,19]

In summary, we have developed a new method for the synthesis of THI and a potential method for the synthesis of THI analogues from 1-ethoxymethyl-4-iodoimidazole **2** using palladium (0) catalysed coupling reactions with vinylstannanes to prepare 4-alkenyl imidazoles. The 1-ethoxymethyl protecting group allowed regioselective functionalisation of the C-2 imidazole position. The catalytic AD was employed to introduce the (1*R*, 2*S*)-dihydroxy functionality of THI. These methods should be generally useful for preparing other 4-substituted and 2,4-disubstituted imidazoles.[20]

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18. **8**: mp 153-154 °C, $[\alpha]_D^{24}$ -22.6 (c 0.58, CH_3CN) for **8** obtained from **1** that was prepared via the Buchi method;[6] $[\alpha]_D^{24}$ -20.0 (c 0.09, CH_3CN) for **8** obtained from **1** that was prepared according to Scheme 1. ^{1}H NMR (400 MHz, CD_3CN) δ 7.27 (1H, s), 6.05 (1H, d, J = 4.8 Hz), 5.56 (1H, dd, J = 5.2, 7.2 Hz), 5.18 (1H, ddd, J = 2.8, 5.6, 8.8 Hz), 4.25 (1H, dd, J = 3.2, 12.4 Hz), 4.11 (1H, dd, J = 6.0, 12.4 Hz), 2.51 (3H, s), 2.04, 2.02, 2.00, 1.98 (12H, 4 x s). ^{13}C NMR (100 MHz, CD_3CN) δ 188.7 (CO), 170.3 (CO), 169.7 (CO), 169.6 (CO), 169.5 (CO), 145.0 (C-2), 138.5 (C-4), 120.2 (C-5), 70.8 (CH), 68.7 (CH), 67.5 (CH), 61.5 (CH_2), 24.7 (Me), 20.0 (Me), 19.93 (Me), 19.88 (Me), 19.86 (Me). MS (ES +ve) *m/z* 399 ($M+H^+$, 100%), 339 (M-OAc, 71%). Anal. cald. for $C_{17}H_{22}N_2O_9$: C, 51.26; H, 5.57; N, 7.03. Found: C, 51.09; H, 5.66, N, 6.65.
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