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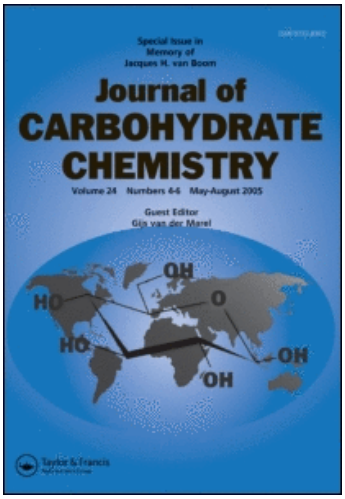

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A New Synthesis of 1-Deoxy-D-*threo*-2-pentulose, a Biosynthetic Precursor to the Thiazole Moiety of Thiamin

Allyson D. Backstrom[a]; R. Ausin[a]; S. McMordie[a]; Tadhg P. Begley[a]
[a] Department of Chemistry, Cornell University, Ithaca, New York

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COMMUNICATION

A NEW SYNTHESIS OF 1-DEOXY-D-*THREO*-2-PENTULOSE, A BIOSYNTHETIC PRECURSOR TO THE THIAZOLE MOIETY OF THIAMIN

Allyson D. Backstrom, R. Austin S. McMordie and Tadhg P. Begley*

Department of Chemistry, Cornell University,
Ithaca, New York 14853

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Thiamin pyrophosphate (vitamin B_1, **1**) is the cofactor involved in the stabilization of the acyl carbanion in biological systems.[1] It has been previously demonstrated that the thiazole moiety of thiamin is biosynthesized in *Escherichia coli* from cysteine (**3**), tyrosine (**4**) and 1-deoxy-D-*threo*-2-pentulose (**5, Scheme 1**).[2,3,4] We have cloned five of the *E. coli* thiazole biosynthetic genes and are currently studying the mechanistic enzymology of this pathway.[5] These studies require an efficient stereoselective synthesis of **5** by a route that will also facilitate the synthesis of putative biosynthetic intermediates on the thiazole pathway. While this sugar has been previously prepared in five steps from 2,3-*O*-isopropylidene-D-glyceraldehyde,[3] the published route is limited by lack of stereocontrol at C3 and a rather harsh final deprotection step. In this paper, we describe a new stereocontrolled synthesis of **5** from dimethyl-D-tartrate that overcomes these problems (**Scheme 2**).

Alcohol **6** was prepared in three steps from dimethyl-D-tartrate as previously described.[6] Oxidation of **6** with the Dess-Martin reagent,[7] followed by Grignard addition and reoxidation gave ketone **7**.[8,9] Removal of the isopropylidene group gave the mono protected pentulose **8**.[10] The ^1H NMR spectrum of **8** was complex indicating that **8** is in equilibrium with the corresponding hemiacetals **9, 9'** (**8:9:9'**=2:1:1 in $CDCl_3$). The synthesis was completed by hydrogenolysis of the benzyl ethers **8, 9, 9'** yielding the

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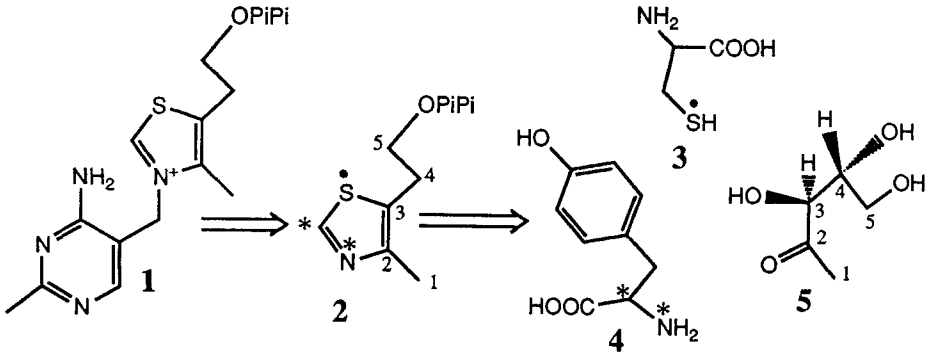
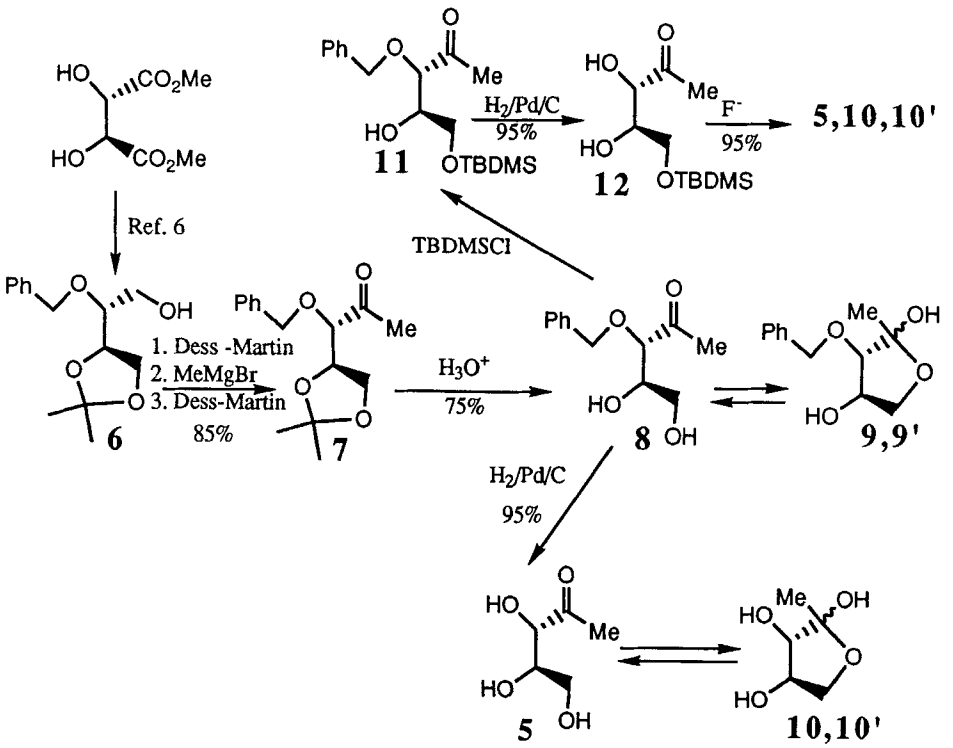


Scheme 1



Scheme 2

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pentulose **5** as a mixture of ketone **5** and hemiacetals **10, 10'** (**5:10:10'**=1:1:1 in CD_3OD).[11] The structure of **8** was confirmed by converting **8, 9, 9'** to the mono TBDMS ether **11**.[12] ^1H NMR analysis of the crude reaction mixture indicated the clean formation of **11**. Subsequent hydrogenolysis of **11** yielded **12** which was also shown by ^1H NMR to be a single compound.[13] Desilylation of **12** also yielded the pentulose as a mixture of isomers (**5, 10, 10'**), which was identical by ^1H NMR to that obtained by hydrogenolysis of **8, 9, 9'**.[14]

ACKNOWLEDGMENT

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8. Ketones **5, 7, 8** and **12** are all quite susceptible to base catalyzed elimination across the 3,4 CC bond.

9. Preparation of **7**. A solution of **6** (0.2 g, 0.6 mmol) in methylene chloride (2 ml) was added to a solution of the Dess-Martin reagent[7] (0.34 g, 0.8 mmol) in methylene chloride (5 ml) with stirring at room temperature. After 1 h the reaction mixture was diluted with ether (25 ml), and the resulting suspension was added to saturated $NaHCO_3$ (16 ml) containing a sevenfold excess of $Na_2S_2O_4$ (0.88 g, 5.6 mmol) and the layers were separated. The aqueous layer was extracted with ether (3 x 25 ml). The combined ether layers were dried over $MgSO_4$ and concentrated to give the aldehyde in quantitative yield as a clear oil which was used in the next step

without purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.73 (d, $J_{1,2}$=1.6 Hz, 1H, -CHO), 7.36-7.38 (m, 5H, Ar), 4.79 (d, $J_{a,b}$=11.9 Hz, 1H, -CH_aCH_bPh), 4.66 (dd, $J_{b,a}$=11.9 Hz, 1H, -CH_aH_bPh), 4.38 (m, 1H, H-3), 4.06 (dd, $J_{4a,3}$=6.6 Hz, $J_{4a,4b}$=8.9 Hz, 1 H, H-4a), 3.96 (dd, $J_{4b,3}$=6.0 Hz, $J_{4b,4a}$=8.9 Hz, 1H, H-4b), 3.86 (dd, $J_{2,1}$=1.5 Hz, $J_{2,3}$=5.4 Hz, 1H, H-2), 1.43 (s, 3H, -CH_3a), 1.35 (s, 3H, -CH_3b). Methylmagnesium bromide (1.4 equivalents) was added to a solution of the aldehyde in THF (2 ml) at -70°C and allowed to come to room temperature overnight. Unreacted methylmagnesium bromide was quenched with ethanol and the reaction mixture concentrated. Flash column chromatographic purification (1:1 methylene chloride/ethyl acetate) yielded a 1:1 mixture of the two stereoisomeric secondary alcohols. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.38 (m, 5H, Ar(a) and Ar(b)), 4.68, 4.69, 4.78 and 4.89 (4 d, $J_{a,b}$=11.5 Hz, total of 2 H, -CH_2Ph(a) and -CH_2Ph(b)), 4.30-4.39 (m, 1H, H4(a) and H4(b)), 3.76-3.84, 4.00-4.09 (4 dd, total 2H, H-5(a), H-5(a)', H-5(b) and H-5(b)'), 3.73-3.78 and 3.84-3.91 (2 m, total 1H, H-2(a) and H-2(b)), 3.26-3.28 and 3.40-3.43 (2 dd, total 1H, H-3(a) and H-3(b)), 1.46 and 1.39 (2 s, total of 6H, 2xCH_3 (acetonide group)), 1.23 and 1.24 (2 d, $J_{1,2}$=5.1 Hz, total 3H, -CH_3(a) and -CH_3(b)); HRMS (CI) calcd for $C_{15}H_{23}O_4$ $(M+H)^+$ 267.1596, found 267.1593. Dess-Martin oxidation (*vide supra*) of the secondary alcohols gave **7** in quantitative yield as a clear oil which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.38 (m, 5H, ArH), 4.73 (d, $J_{a,b}$=11.8 Hz, 1H, -CHaHbPh), 4.58 (d, $J_{b,a}$=11.8 Hz, 1H, -CHaHbPh), 4.31 (m, 1 H, H-4), 4.02 (dd, $J_{5a,5b}$=8.6 Hz, $J_{5a,4}$=6.6 Hz, 1 H, H-5a), 3.87 (dd, $J_{5b,5a}$=8.6 Hz, $J_{5b,4}$=6.6 Hz, 1 H, H-5b), 3.79 (d, $J_{3,4}$=5.1 Hz, 1 H, H-3), 2.25 (s, 3 H, -$COCH_3$), 1.44 and 1.35 (2 s, total of 6H, 2xCH_3 (acetonide group)).

10. Preparation of **8, 9, 9'**. Ketone **7** (0.26 g, 1.2 mmol) was stirred in THF (40 ml) and 2N HCl (20 ml) at room temperature for 3 h. The solution was neutralized with saturated aqueous $NaHCO_3$ and concentrated to 20 ml under reduced pressure. The mixture was extracted with ether (3 x 25 ml) and the aqueous layer saturated with NaCl and further extracted with ether (3 x 25 ml). The combined ether layers were dried ($MgSO_4$) and concentrated to give a yellow oil which was a mixture of **8, 9, 9'**. Crystallization (ether/hexane) gave the product, presumably as a single isomer, as white crystals (0.17g, 75% yield); mp 67-68°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.45 (m, 5H, Ar), 3.68-4.78 (complex multiplets, total 4H, H-3, H-4, H-5a and H-5b of ketone **8** and hemiketals **9, 9'**), 2.27, 1.56 and 1.54 (3 s in ratio 2:1:1, total 3H, -CH_3 of **8, 9, 9'**); HRMS (CI) calcd for $C_{12}H_{17}O_4$ $(M+H)^+$ 225.1127, found 225.1129; $[\alpha]_D$ -24° ($CHCl_3$).

11. Preparation of **5, 10, 10'** from **8, 9, 9'**. The benzyl ether **8** (20 mg, 0.09 mmol) was stirred in absolute ethanol with 10% Pd/C (5 mg) under a hydrogen atmosphere (40 psi) for 36 h at room temperature. The catalyst was removed and the filtrate concentrated to give **5, 10, 10'** (12 mg, quantitative yield) as a syrup. ^{1}H NMR (CD_3OD, 400 MHz) δ 3.49-4.20 (m, 4H, H-3, H-4, H-5a and H-5b) , 2.24, 1.42 and 1.38 (3 s in ratio 1:1:1, total 3H -CH_3) of **5, 10, 10'**; HRMS (CI) calcd for $C_5H_{11}O_4$ $(M+H)^+$ 135.0675, found 135.0659; $[\alpha]_D$ +28° (H_2O).

12. Preparation of **11**. The benzyl ethers **8, 9, 9'** (11 mg, 0.05 mmol), TBDMSCl (15 mg, 0.1 mmol) and imidazole (16 mg, 0.2 mmol) were stirred in dry DMF (1 ml) under Ar for 3 h. The DMF was removed under vacuum and the residue was purified by silica-gel chromatography (15% acetone/hexane) to give **11** (14 mg, 84% yield) as a clear oil. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.34-7.40 (m, 5H, Ar), 4.70 (d, $J_{a,b}$=11.5 Hz, 1H, -CHaHbPh), 4.48 (d, $J_{b,a}$=11.5 Hz, 1H, -CHaHbPh), 4.03 (d, $J_{3,4}$=2.7 Hz, 1H, H-3), 3.88-3.91 (m, 1H, H-4), 3.79 (dd, $J_{5a,4}$=8.0 Hz,

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$J_{5a,5b}$=9.8 Hz, 1H, H-5a), 3.62 (dd, $J_{5b,4}$=5.7 Hz, $J_{5b,5a}$=9.8 Hz, 1H, H-5b), 2.22 (s, 3H, -C(O)C$\underline{H}_3$), 0.90 (s, 9H, -SiC(C$\underline{H}_3$)$_3$), 0.07 (s, 3H, -SiC$\underline{H}_3$a), 0.06 (s, 3H, -SiC$\underline{H}_3$b); HRMS (CI) calcd for $C_{18}H_{31}O_4Si$ $(M+H)^+$ 339.1987, found 339.1992.

13. Preparation of **12**. **12** was prepared by hydrogenolysis of **11** in a manner similar to that described for compound **5**.[11] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.20 (d, $J_{3,4}$=2.1 H, 1H, H-3), 3.96 (m, 1H, H-4), 3.74 (dd, $J_{5a,4}$=7.7 Hz, $J_{5a,5b}$=9.8 Hz, 1H, H-5a), 3.64 (dd, $J_{5b,4}$=5.7 Hz, $J_{5b,5a}$=9.8 Hz, 1H, H-5b), 2.23 (s, 3H, -C(O)C$\underline{H}_3$), 0.91 (s, 9H, -SiC(C$\underline{H}_3$)$_3$), 0.09 (s, 6H, -Si(C$\underline{H}_3$)$_2$).

14. Preparation of **5**, **10**, **10'** from **12**. A solution of 1M $Bu_4NF.H_2O$ in THF (32 ml, 0.032 mmol) was added to a cooled (0°C) solution of **12** (6 mg, 0.24 mmol) in THF (5 ml) under Ar. The resulting solution was stirred at 0°C for 20 minutes, filtered through a plug of silica and the solvent removed to yield a colorless oil. ^{1}H NMR analysis demonstrated that the product composition was identical to that obtained from the hydrogenolysis of **8**, **9**, **9'**.

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