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PALLADIUM MEDIATED ALLYLIC MITSUNOBU DISPLACEMENT: STEREOCONTROLLED SYNTHESIS OF HEPOXILIN A3 AND TRIOXILIN A3 METHYL ESTERS

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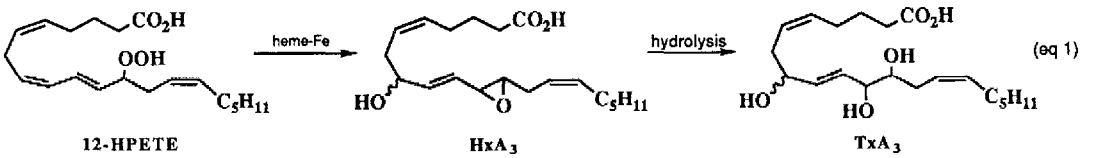
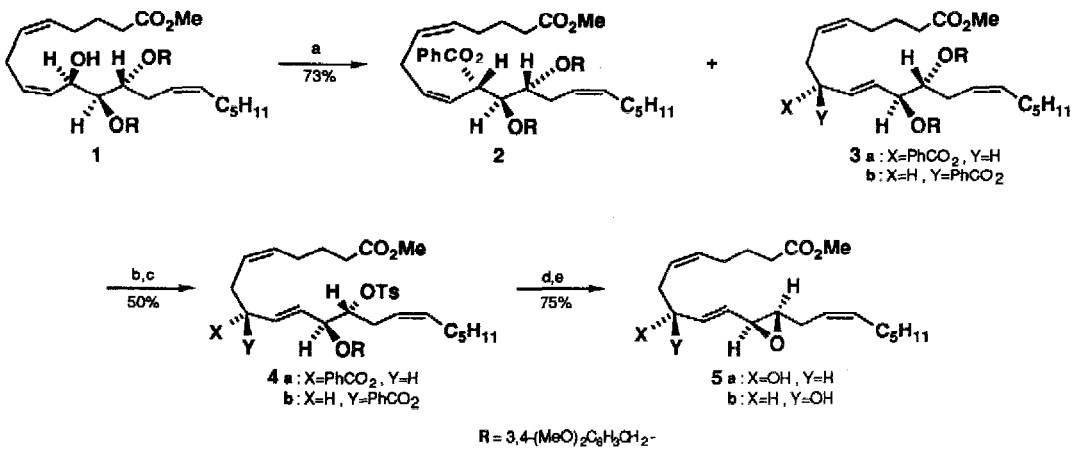
Summary: A regio- and stereoselective palladium mediated allylic displacement under Mitsunobu conditions was exploited for the preparation of several hepoxilin A3 and trioxilin A3 stereoisomers.

Hepoxilin A3 (HxA3) is generated as a pair of C(8)-diastereomers from 12-hydroperoxyeicosatetraenoic acid (12-HPETE) via an intramolecular rearrangement[1] catalyzed by naturally occurring heme-iron complexes[2] (eq 1). Enzymatic as well as non-enzymatic hydrolysis[3] of the labile *trans*-epoxide gives rise to the corresponding triols, trioxilin A3 (TxA3). Metabolites of the hepoxilin/trioxilin pathway have been identified in plants, marine organisms, and several mammalian species[4] wherein they have been proposed, *inter alia*, to modulate neural signal transduction, stimulate hormone secretion, induced heat shock protein expression, and mobilize intracellular calcium[5].



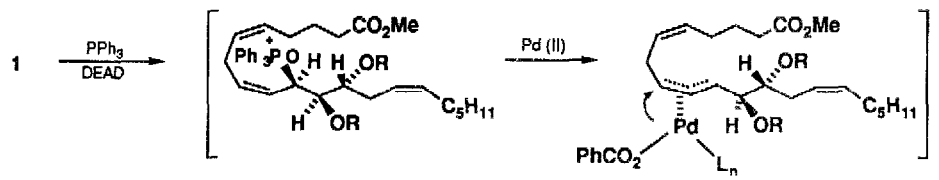
The constitution of HxA3 derived from 12(S)-HPETE was established by Corey and Su[6], who subsequently clarified the absolute configurations of the C(8)-alcohols[7]. As part of a comprehensive synthetic program to expedite the physiologic evaluation and structural elucidation of novel eicosanoids, we describe herein a stereocontrolled route to HxA3 and TxA3 stereoisomers based on a novel palladium mediated allylic displacement[8] of an acyclic, chiral alcohol[9] under Mitsunobu conditions.

Scheme



[a] DEAD/Ph_3P/$PhCO_2H$, $PdCl_2(CH_3CN)_2$, THF, 25 ° C, 30 min.[b] 2%HCl/MeOH, 24 ° C, 2h.[c] TsCl, C_5H_5N/CH_2Cl_2, 0 ° C,12h.
[d] DDQ, CH_2Cl_2/H_2O (20:1), 0° C, 4h.[e] NaOMe/MeOH, 0 ° C, 12h.

Previously, it was noted that Mitsunobu inversion of triol **1**, a key intermediate in the synthesis[10] of trioxilin B3, afforded approximately equal amounts of benzoate **2** and a chromatographically separable mixture of transposition products **3a,b** (**a/b**, 4:1). We now report similar treatment of **1** in the presence of freshly prepared $PdCl_2(CH_3CN)_2$ (0.1 equiv) rapidly resulted in the nearly exclusive production of **3a,b**[11] (73%; **a/b**, 10:1) (Scheme). A mechanistic rationale for this transformation involves palladium interception of the initially formed Mitsunobu oxyphosphonium intermediate[12] to give a π-allyl complex (eq 2). Subsequent *cis*-transfer of coordinated[13] benzoate to carbon generates the observed major diastereomer **3a**. Control experiments using **2** as well as the benzoate of **1** established that neither palladium promoted [3,3]-sigmatropic rearrangement[14] nor allylic displacement at C(8) are significant contributors to product formation under the above reaction conditions.

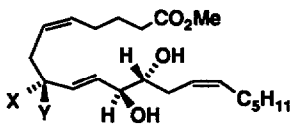


(eq 2)

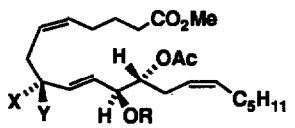
Access to the hepoxilin series from **3** exploited an unexpectedly specific hydrolysis of only the C(12)-benzyl ether. Thus, exposure of **3a** to 2% HCl/MeOH under carefully controlled conditions and tosylation of the resultant alcohol led to **4a** (TLC: SiO_2, 5% $MeOH/CH_2Cl_2$, $R_f \sim 0.36$). Cleavage of the remaining benzyl ether using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and NaOMe induced ring closure with concomitant

benzoate solvolysis gave HxA3 methyl ester **5a**[15], $[\alpha]^{24}_D$ = -26° (c 0.83, acetone). The 8(S)-isomer **5b**, $[\alpha]^{24}_D$ = -5.1° (c 0.41, acetone), was obtained analogously from **3b**.

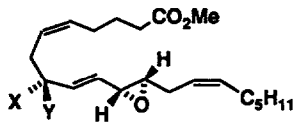
Alternatively, mild acidic hydrolysis of **3a** and **b** as above followed by acetylation (Ac_2O, py, O°C, 12h) evolved **7a** and **b**, respectively. Sequential DDQ deprotection (77%), tosylation (84%), and NaOMe ring closure/deacetylation (70%) culminated in **8a** and **b**. The enantiomeric pairs **5a/8b** and **5b/8a** were identical by HPLC and MS with the more polar methyl ester and less polar methyl ester, respectively, of HxA3 obtained by hematin catalyzed rearrangement of 12-HPETE.



6 a : X=OH, Y=H
b : X=H, Y=OH



7 a : X=$PhCO_2$, Y=H
b : X=H, Y=$PhCO_2$



8 a : X=OH, Y=H
b : X=H, Y=OH

Concurrent DDQ removal of both dimethoxybenzyl ethers from **3a** and benzoate solvolysis (NaOMe/MeOH, O°C, 10h) afforded TxA3 methyl ester **6a**, $[\alpha]^{24}D$ = -8.0° (c 0.65, CCl_4). Likewise, **3b** furnished **6b**, $[\alpha]^{24}_D$ = +2.8° (c 0.58, CCl_4).

Initial studies have demonstrated that other π-allyl palladium complexes can be generated from oxyphosphonium salts. Investigations into the scope and limitations of this methodology are in progress.

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15. Spectral data for **5a**: ^{1}H NMR (C_6D_6, 250 MHz) δ 0.87 (t, J~6.8 Hz, 3H), 1.14-1.40 (m, 6H), 1.55 (dt, J~7, 14Hz, 2H), 1.78-2.35 (complex m, 10H), 2.72 (dt, J~ 2, 5 Hz, 1H), 3.03 (dd, J~ 2, 7.5 Hz, 1H), 3.33 (s, 3H), 3.86-3.98 (m, 1H), 5.13-5.56 (m, 5H), 5.78 (dd, J~ 5, 16 Hz, 1H); mass spec (PICI, CH_4) of **5a** TMS ether: m/e (%) 451 (14, M+29), 423 (22, M+1), 407 (100), 333 (84, M-OSiMe$_3$), 315 (44). **5b**: ^{1}H NMR (C_6D_6, 250 MHz) δ 0.87 (t, J~6.5 Hz, 3H), 1.14-1.40 (m, 6H), 1.55 (dt, J~7, 14 Hz, 2H), 1.82-2.36 (complex m, 10H), 2.72 (dt, J~2, 5Hz, 1H), 3.03 (dd, J~2, 8 Hz, 1H), 3.32 (s, 3H), 3.90 (dd, J~5.5, 11 Hz, 1H), 5.25-5.57 (m, 5H), 5.78 (dd, J~5.4, 15.5 Hz, 1H). **6a**: ^{1}H NMR (C_6D_6, 250 MHz) δ 0.90 (t, J~6.5 Hz, 3H), 1.18-1.42 (m, 6H), 1.60(dt, J~7, 14 Hz, 2H), 1.93-2.20 (m, 6H), 2.25-2.52 (m, 4H), 3.37 (s, 3H), 3.82-3.95 (m, 1H), 4.15-4.30 (m, 2H), 5.35-5.68 (m, 4H), 5.91 (dd, J~5.5, 16 Hz, 1H), 6.03 (dd, J~5.5, 16 Hz, 1H).**6b**: ^{1}H NMR (C_6D_6, 250 MHz) δ 0.90 (t, J~6.5 Hz, 3H), 1.18-1.42 (m, 6H), 1.60(dt, J~7, 14 Hz, 2H), 1.92-2.22 (m,6H), 2.26-2.52 (m, 4H), 3.36 (s, 3H), 3.77-3.88 (m, 1H), 4.15-4.30 (m, 2H), 5.35-5.68 (m, 4H), 5.87 (dd, J~4.8, 15.6 Hz, 1H), 6.02 (dd, J~6, 15.6 Hz, 1H).

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