Asymmetric total synthesis of PM-toxin A, a corn host-specific pathotoxin

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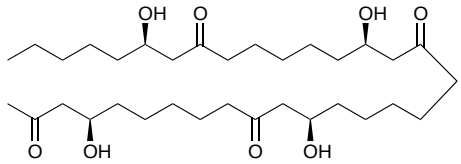
The first asymmetric total synthesis of PM-toxin A, a corn host-specific toxin produced by the fungal pathogen *Phyllosticta maydis*, starting from D-lactate is described.

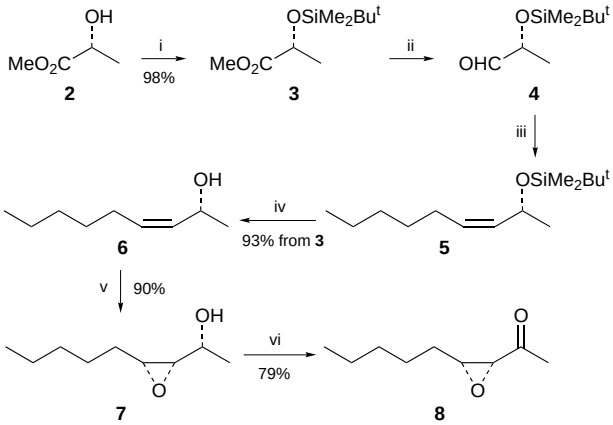
The fungal pathogen *Phyllosticta maydis* produces a corn host-specific pathotoxin, PM-toxin, which was revealed to be the cause of major epidemics of Northern T-corn leaf blight disease in the United States.[1] PM-toxin[2] and the HMT-toxin,[3] produced by the fungal pathogen *Helminthosporium maydis*, race T, are representative corn host-specific toxins.[4] PM-toxin consists of 10–15 components, of which the four major ones—PM-toxin A, B, C and D—have been isolated so far and determined to be linear C_{33} and C_{35} compounds containing a number of characteristic β-ketol (aldol) structures.[2] The unique structures of these corn pathotoxins as well as their marked host-specific toxicity have elicited much attention from biologists and synthetic chemists.[4,5]



PM-Toxin A **1**

We report here the first and highly stereoselective total synthesis of PM-toxin A **1** starting from D-lactate, in which three tandem aldol reactions and the regiospecific organoselenium-mediated reduction of four consecutive α,β-epoxy ketone units are involved as key steps.

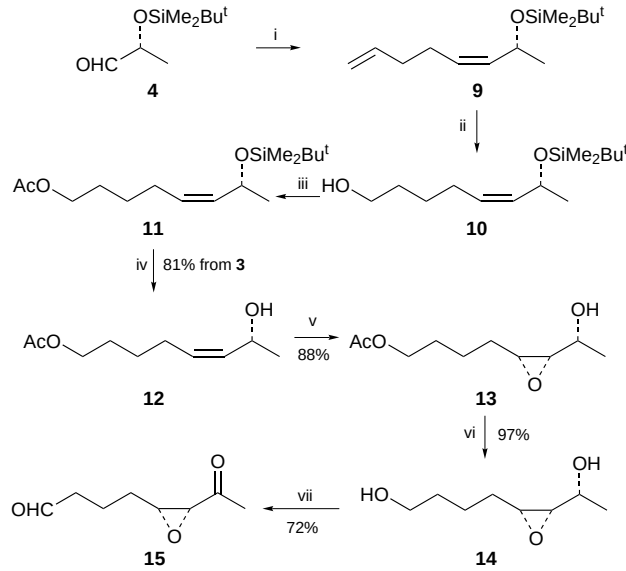
The starting methyl D-lactate **2** was treated with Bu^tMe_2SiCl and imidazole in DMF to give **3** in nearly quantitative yield (Scheme 1). Reduction of **3** with DIBAL-H cleanly produced the aldehyde **4** which was subjected to the Wittig reaction with hexyltriphenylphosphonium bromide to give the (*Z*)-alkene **5** along with a trace amount of the (*E*)-isomer. Subsequent treatment of **5** with Bu_4NF in THF afforded the (*Z*)-allylic alcohol **6** in 93% overall yield after purification by silica gel chromatography. Oxidation of the resulting alcohol **6** with MCPBA in CH_2Cl_2 gave rise to the α-epoxy alcohol **7** as the sole product in 90% yield, which was submitted to the Swern oxidation resulting in the formation of the desired epoxy ketone **8** in 79% yield. Thus a key compound for the synthesis of PM-toxin A **1** was synthesized in a stereoselective manner.



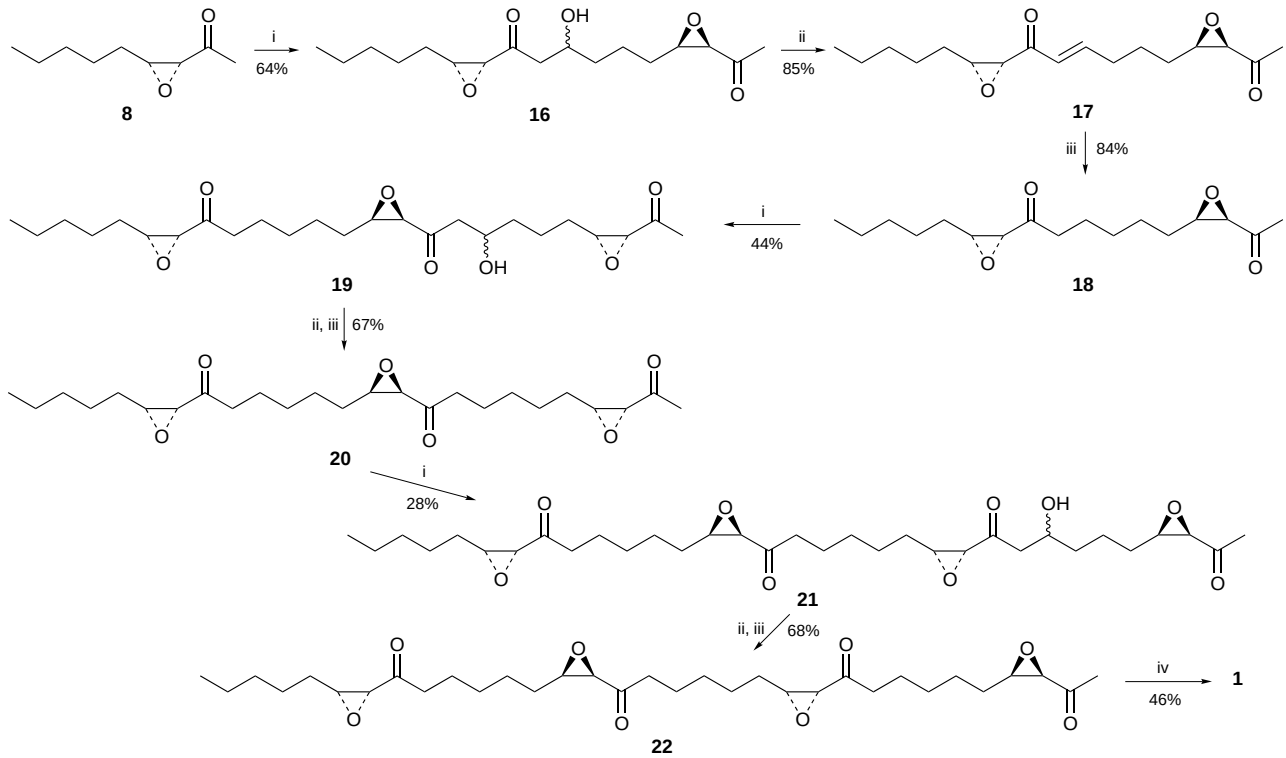
Scheme 1 *Reagents and conditions*: i, Bu^tMe_2SiCl, imidazole, DMF; ii, DIBAL-H, toluene, −78 °C; iii, hexyltriphenylphosphonium bromide, BuLi, toluene; iv, Bu_4NF, THF; v, MCPBA, CH_2Cl_2, 0 °C; vi, $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N

Another key component **15** was synthesized according to Scheme 2. The Wittig reaction of the aldehyde **4** with pent-4-enyltriphenylphosphonium bromide gave the (*Z*)-alkene **9** along with a minor amount of the (*E*)-isomer. Since the alkenes could not be separated at this stage, the mixture was treated with 9-borabicyclo[3.3.1]nonane (9-BBN) followed by treatment with alkaline H_2O_2 to furnish the alcohol **10** as an inseparable mixture of isomers. Subsequent acetylation of **10** with Ac_2O followed by treatment of the resulting acetate **11** with Bu_4NF in THF gave rise to the desired (*Z*)-allylic alcohol **12** in 81% overall yield from **3** after purification by silica gel column chromatography.† Upon epoxidation of the allylic alcohol **12** with MCPBA in CH_2Cl_2 the α-epoxy alcohol **13** was exclusively formed in 88% yield. The epoxy alcohol **13** thus obtained was converted to the keto aldehyde **15**, the second key intermediate, by the two step reaction sequence: (i) hydrolysis of the acetate (97%) and (ii) Swern oxidation (72%).

With the key compounds **8** and **15** in hand, we set about the crucial tandem aldol reaction toward the synthesis of tetrakis-epoxy ketone **22**. The first aldol reaction of **8** and **15** with lithium hexamethyldisilazide (LiHMDS) as base smoothly proceeded in THF at −78 °C giving rise to the hydroxy ketone **16** as a diastereoisomeric mixture in 64% isolated yield (Scheme 3). Subsequent treatment of **16** with methanesulfonyl chloride in CH_2Cl_2 in the presence of DMAP directly afforded



Scheme 2 *Reagents and conditions*: i, pent-4-enyltriphenylphosphonium bromide, BuLi, toluene; ii, 9-BBN, THF, 0 °C, then 8 M NaOH, H_2O_2; iii, Ac_2O, DMAP, pyridine; iv, Bu_4NF, THF; v, MCPBA, CH_2Cl_2, 0 °C; vi, NH_3, MeOH; vii, $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N



Scheme 3 *Reagents and conditions*: i, LiHMDS, THF, then **15**, −78 °C; ii, $MeSO_2Cl$, DMAP, CH_2Cl_2; iii, H_2, 10% Pd–C, EtOAc; iv, $Na[PhSeB(OEt)_3]$ (16 equiv.), AcOH (24 equiv.), EtOH, 0 °C

the enone **17** in 85% yield, which was then submitted to catalytic hydrogenation over 10% Pd–C in EtOAc, resulting in the formation of the bis-epoxy ketone **18** in 84% yield. Thus the bis-epoxy ketone **18** could be synthesized *via* a three step reaction sequence. The second aldol reaction of **18** and **15** was similarly performed using LiHMDS in THF at −78 °C giving the β-hydroxy ketone **19**‡ in 44% yield. Apparently, the yield of the second aldol reaction is lower than that of the first. The products **19** were similarly converted to the tris-epoxy ketone **20** by the two step reaction sequence of mesylation (80%) and subsequent hydrogenation (84%). The third aldol reaction of **20** and **15** was, as anticipated, reluctant to proceed under similar conditions, resulting in the formation of **21** in 28% yield. The products **21**‡ thus obtained were also converted to the tetrakis-epoxy ketone **22** by the two step reaction sequence of mesylation (90%) followed by catalytic hydrogenation (76%). Although the final aldol reaction suffered from low yield, the critical compound **22** for the synthesis of PM-toxin A **1** was secured in an optically pure form *via* the tandem aldol strategy. Finally, the organoselenium-mediated reduction[6] of the tetrakis-epoxy ketone **22**, the crucial reaction in the present synthesis, was performed by treatment of **22** with benzeneselenol (PhSeH, 16 equiv.) generated *in situ* from sodium (phenylseleno)triethylborate (16 equiv.)[7] and acetic acid (24 equiv.) in ethanol.[6,8] The reduction of four consecutive epoxy ketone moieties occurred regiospecifically at the α-position as expected,[7] and the crystalline PM-toxin A **1** was obtained in 46% isolated yield (68% based on the consumed substrate) after purification by silica gel chromatography. The physical properties of the synthetic compound§ were identical with those of an authentic specimen. Furthermore, ^1H and ^{13}C NMR spectra of the corresponding tetraacetate derived from the synthetic compound were also identical with those of authentic PM-toxin A tetraacetate. Thus the stereoselective asymmetric total synthesis of PM-toxin A **1** has been achieved by employing tandem aldol reactions and the regiospecific organoselenium-mediated reduction of α,β-epoxy ketone units as key steps.

We acknowledge Professor Y. Kono (Ibaragi University) for providing us with a ^1H NMR spectrum of authentic PM-toxin A tetraacetate. We are grateful to the Syourai Foundation and the Hoansya Foundation for their financial support.

Footnotes

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† At this stage, it was confirmed that no racemization of the aldehyde **4** had taken place *via* ^1H NMR analysis of the (*S*)-mandelate ester of **12**.

‡ A diastereoisomeric mixture.

§ *Selected data* for PM toxin A **1**: mp 117–119 °C (from acetone); $[\alpha]_D^{22}$ −45 (*c* 0.16, $CHCl_3$); UV λ_{max} 275.2 nm (MeOH); CD λ_{max} 281 nm (MeOH); FAB-MS *m*/*z* 583 ($M-H^-$); FD-MS *m*/*z* 607 ($M + Na^+$), 623 ($M + K^+$). The $[\alpha]_D$ was measured in $CHCl_3$ since the synthetic pure compound was almost insoluble in MeOH. Data for an authentic sample: mp 118–119 °C; $[\alpha]_D^{25}$ − 11 (MeOH); UV λ_{max} 276 nm (MeOH); CD λ_{max} 282 nm (MeOH); FAB-MS *m*/*z* 585 ($M + H^+$); FD-MS *m*/*z* 607 ($M + Na^+$) (ref. 2).

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