COMMUNICATION

Highly stereoselective total synthesis of PM-Toxin B, a corn host-specific pathotoxin

Mitsuru Hosaka, Hiroyuki Hayakawa and Masaaki Miyashita *

Division of Chemistry, Graduate School of Science, Hokkaido University, Hokkaido 060-0810, Japan. E-mail: miyasita@sci.hokudai.ac.jp

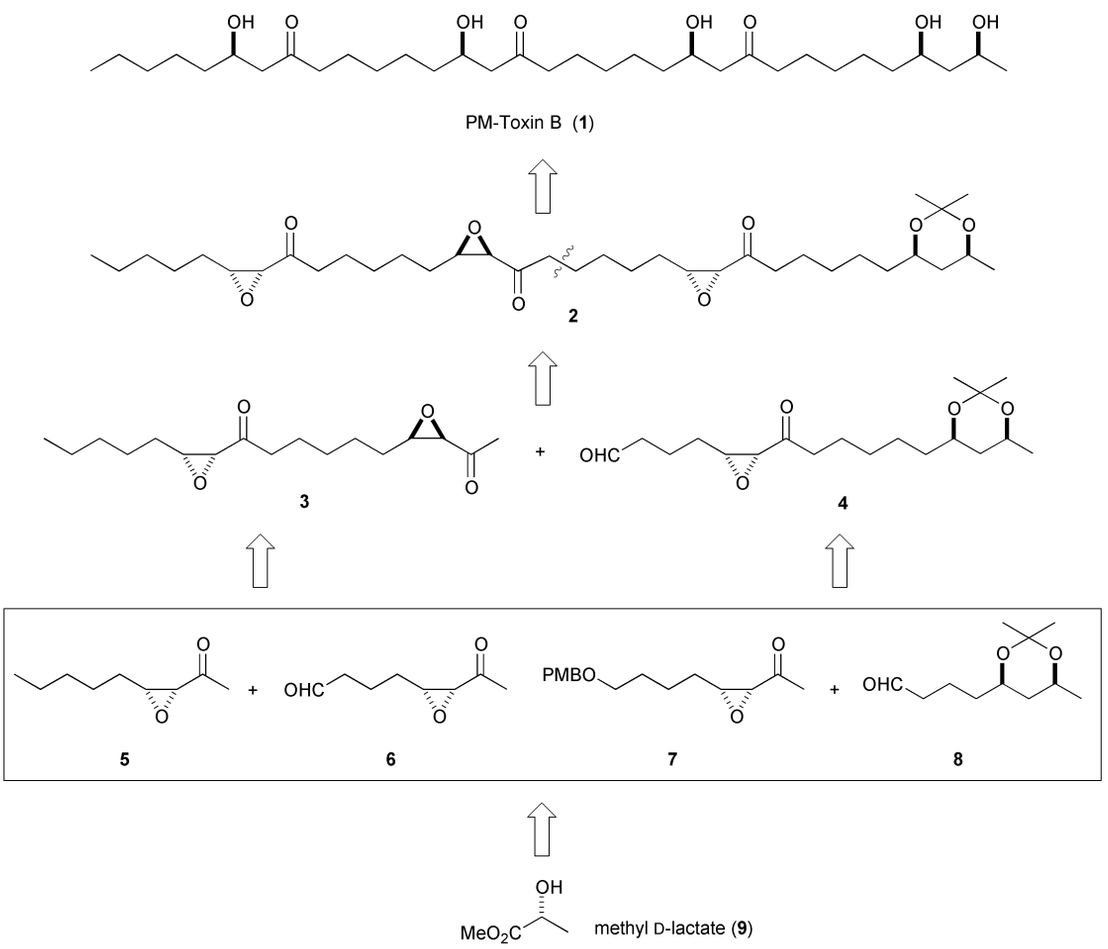
Received (in Cambridge, UK) 19th September 2000, Accepted 30th October 2000
First published as an Advance Article on the web 9th November 2000

The highly stereoselective total synthesis of PM-toxin B, a corn host-specific toxin produced by the fungal pathogen *Phyllosticta maydis*, has been achieved by a convergent synthetic strategy which involves cross-aldol coupling of four key segments and the regioselective reductive cleavage of three α,β-epoxy ketone functionalities by an organoselenium reagent as key steps.

The cause of major epidemics of Northern T-corn leaf blight disease in the United States in 1970 has been shown to be PM-toxin, a corn host-specific pathotoxin produced by the fungal pathogen *Phyllosticta maydis*.[1] PM-toxin[2] and HMT-toxin[3] produced by the fungal pathogen *Helminthosporium maydis*, race T, are representative corn host-specific toxins.[4] Among 10–15 PM-toxin components, the four major ones, PM-toxin A, B, C, and D, have been isolated so far and found 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] So far, only the synthesis of an isomeric mixture of PM-toxin B in a racemic form by Daly and co-workers has been reported.[6] Recently, we reported the first asymmetric total synthesis of PM-toxin A, containing a characteristic sequence of four aldol structures, by a linear synthetic strategy which involves four tandem aldol reactions as key steps;[7] however, the yield of the cross aldol reactions was greatly reduced as the carbon chain length of the substrate became longer.[7]

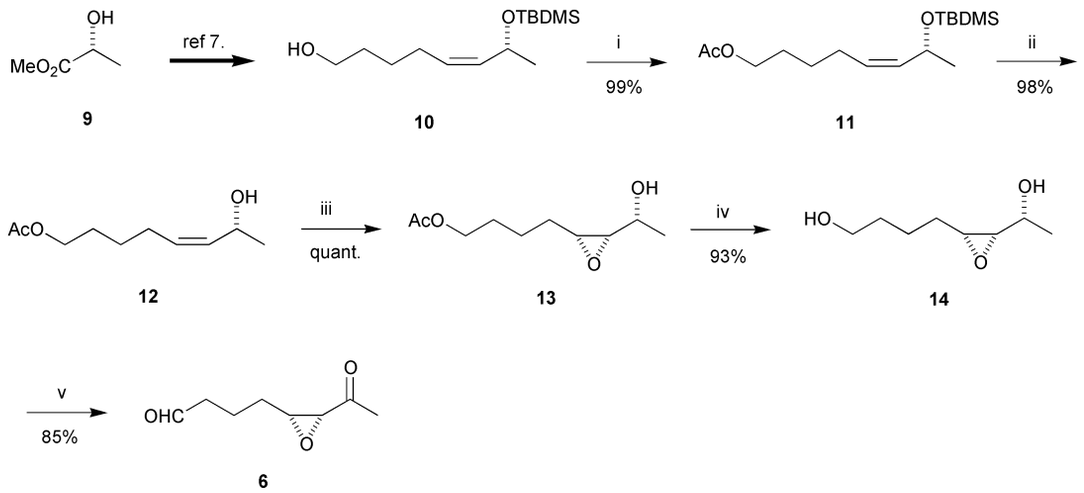
We describe herein the first and highly stereoselective total synthesis of PM-toxin B (**1**) by *a convergent synthetic strategy* which involves cross-aldol coupling of four key segments and the organoselenium-mediated regioselective reductive cleavage of three α,β-epoxy ketone units as key steps.

The retrosynthetic analysis for **1** is shown in Scheme 1. Taking into consideration chemically labile aldol structures, we designed a synthetic route which involves construction of

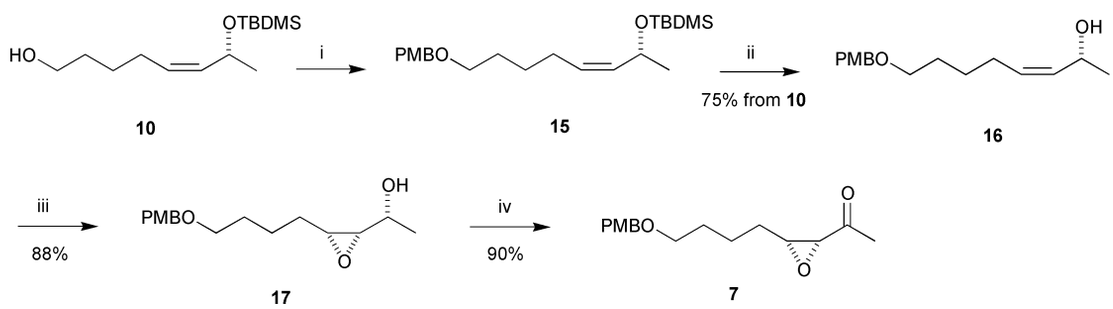


Scheme 1 The retrosynthetic analysis for the synthesis of **1**.

DOI: 10.1039/b007617l



Scheme 2 *Reagents*: i, Ac_2O, DMAP, pyridine; ii, Bu_4NF, THF; iii, MCPBA, CH_2Cl_2, 0 °C; iv, NH_3, MeOH; v, $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N.



Scheme 3 *Reagents*: i, $PMBOCH(=NH)CCl_3$, PPTS, CH_2Cl_2; ii, Bu_4NF, THF; iii, MCPBA, CH_2Cl_2, 0 °C; iv, $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N.

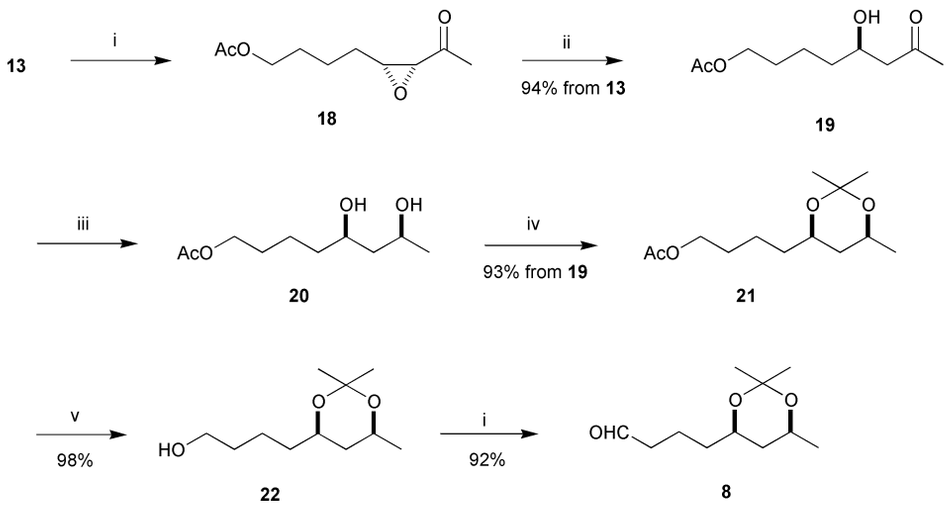
three aldol structures by regioselective reductive cleavage of tris-epoxy ketone **2** at the final stage of the synthesis. For the synthesis of the key tris-epoxy ketone **2**, **2** was divided into the left-half segment, bis-epoxy ketone **3**, and the right-half segment, epoxy aldehyde **4**, and both segments were designed to be assembled from the key fragments **5** and **6**, **7** and **8**, respectively. Furthermore, all these key fragments were designed to be synthesized from the same starting material, *i.e.*, methyl D-lactate (**9**), as shown in Scheme 1. The first epoxy ketone fragment **5** was efficiently and highly stereoselectively synthesized from **9** according to our previous route (63% overall yield for 6 steps).[7] Similarly, the second epoxy aldehyde **6** was also stereoselectively synthesized from **9** employing a modified procedure[7] as shown in Scheme 2. Thus, the (*Z*)-alkenyl alcohol **10** readily obtainable from **9** was converted to the acetate **11**, which was then treated with Bu_4NF in THF to give the (*Z*)-allylic alcohol **12** in 97% overall yield from **10**. Upon epoxidation of the allylic alcohol **12** with MCPBA in CH_2Cl_2 the α-epoxy alcohol **13** was produced exclusively and quantitatively. The epoxy alcohol **13** thus obtained was converted to the epoxy aldehyde **6** by the two-step reaction sequence: (1) hydrolysis of the acetate with NH_3 in MeOH (93%) and (2) Swern oxidation (85%).

On the other hand, the third key fragment **7** was prepared from the common intermediate **10** as shown in Scheme 3. Protection of the primary hydroxy group of **10** with 4-methoxybenzyl (PMB) trichloroacetimidate followed by treatment of the resulting TBDMS ether **15** with Bu_4NF in THF furnished the allyl alcohol **16** in 75% overall yield. Subsequent epoxidation of **16** with MCPBA in CH_2Cl_2 proceeded cleanly giving rise to the single α-epoxy alcohol **17** in 88% yield. The epoxy alcohol **17** thus obtained was converted to the epoxy ketone **7** by Swern oxidation (90%).

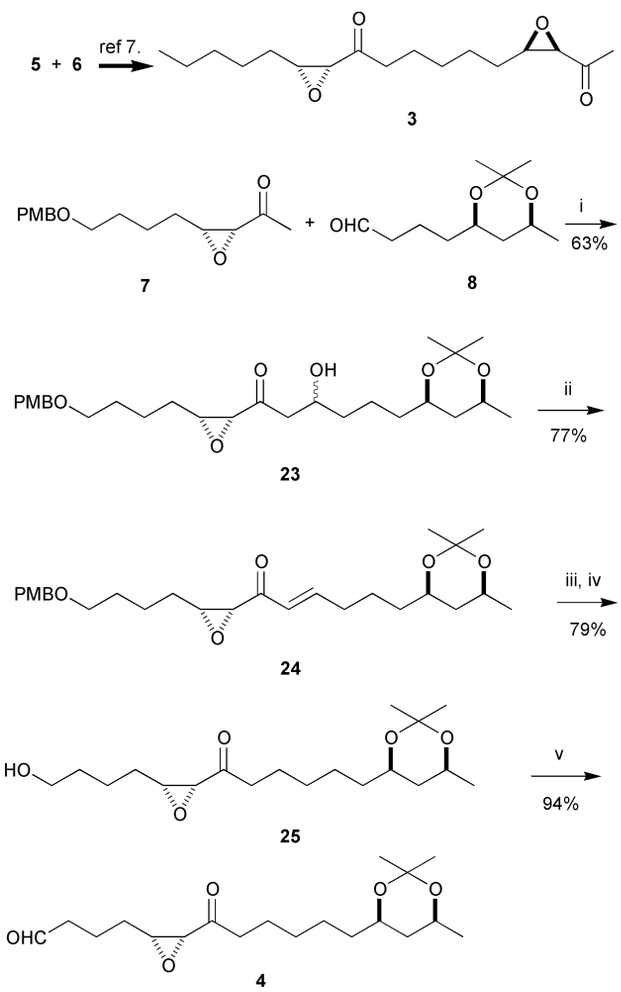
The fourth fragment **8** containing a *syn*-1,3-diol moiety was efficiently and highly stereoselectively synthesized according to Scheme 4. First, the epoxy alcohol **13** used in the synthesis of the fragment **6** was transformed into the epoxy ketone **18** by Swern oxidation, which was then subjected to the organoselenium reduction.[8] Thus, on treatment of **18** with sodium (phenylseleno)triethylborate ($Na[PhSeB(OEt)_3]$)[8] (2.5 equiv.) in ethanol in the presence of AcOH (3 equiv.) at 0 °C, the regioselective reductive cleavage of the epoxide moiety occurred to give the β-hydroxy ketone **19** as a single product in 94% isolated yield. It should be noted that the chemo- and regioselective reduction of an epoxy ketone moiety is possible by organoselenium reduction.[8] Construction of the requisite *syn*-1,3-diol **20** from the resulting β-hydroxy ketone **19** was successfully performed by diethylmethoxyborane–sodium borohydride reduction[9] in THF–MeOH (5 : 1) in excellent yield, and no diastereomer was detected, although other reducing agents inevitably formed a mixture of diastereomers in variable ratios. The 1,3-diol **20** thus obtained was converted to the fourth key segment **8** by the three-step reaction sequence: (1) protection of *syn*-1,3-diol with 2,2-dimethoxypropane (93%); (2) hydrolysis of the acetate with NH_3 in MeOH (98%); (3) Swern oxidation (92%).

With the four key fragments **5**–**8** in hand, we next focused on the cross-aldol reaction in the synthesis of the left segment **3** and the right segment **4**, respectively. Initially, the left segment **3** was synthesized by the aldol reaction of **5** and **6** as in the synthesis of PM-toxin A[7] (Scheme 5). On the other hand, the right segment **4** was successfully synthesized according to Scheme 5. Thus, the cross-aldol reaction of **7** (1.3 equiv.) and **8** (1 equiv.) by the use of lithium hexamethyldisilazide (LiHMDS, 1.3 equiv.) as base smoothly proceeded in THF at −78 °C giving rise to the hydroxy ketone **23** as a diastereomeric mixture in 63% yield. Subsequent treatment of **23** with methanesulfonyl chloride in CH_2Cl_2 in the presence of DMAP directly afforded the enone **24** in 77% yield, which was submitted to catalytic hydrogenation over 10% Pd-C in ethyl acetate followed by treatment with DDQ to give the epoxy alcohol **25** in 79% overall yield. Swern oxidation of the resulting alcohol **25** furnished the desired segment **4** in 94% yield.

With the left and right segments **3** and **4** in hand, we set out the final coupling reaction in the total synthesis of PM-toxin B

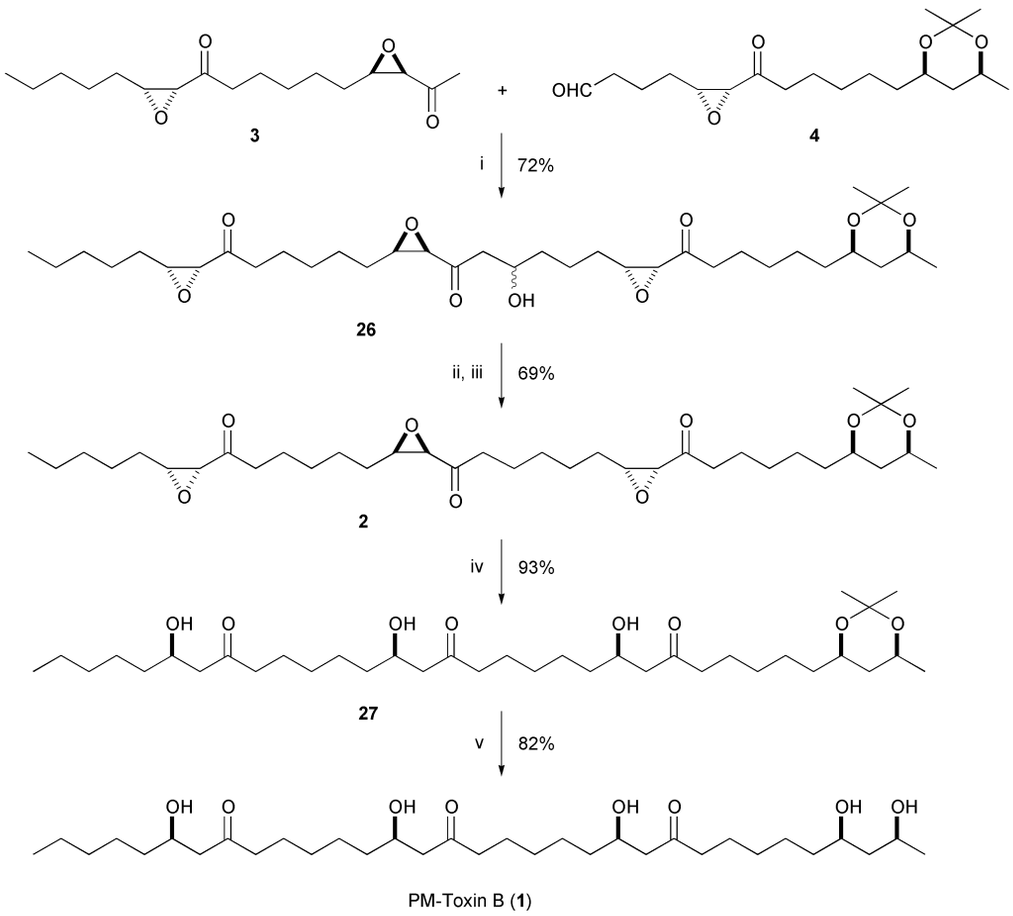


Scheme 4 *Reagents*: i, $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N; ii, Na[PhSeB(OEt)$_3$], AcOH, EtOH, 0 °C, 1 h; iii, $(CH_3CH_2)_2BOCH_3$, $NaBH_4$, THF–MeOH; iv, $(CH_3)_2C(OCH_3)_2$, PPTS, CH_2Cl_2; v, NH_3, MeOH.



Scheme 5 *Reagents*: i, LiHMDS (1.3 equiv.), THF, −78 °C, then **8**; ii, CH_3SO_2Cl, DMAP, CH_2Cl_2; iii, H_2, 10% Pd-C, AcOEt; iv, DDQ, CH_2Cl_2–H_2O (10 : 1); v, $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N.

(**1**) (Scheme 6). Fortunately, the key aldol reaction of **3** and **4** cleanly occurred with the use of LiHMDS in THF at −78 °C, giving rise to the β-hydroxy ketones **26** as a diastereomeric mixture in 72% isolated yield, although we were afraid that the yield of this cross-aldol reaction might decrease greatly as in the synthesis of PM-toxin A.[7] We were pleased, therefore, to obtain optimal results. The products **26** thus obtained were converted to the tris-epoxy ketone **2** by the two-step reaction sequence: (1) mesylation (79%) and (2) hydrogenation (87%). Thus, the key tris-epoxy ketone **2** for the synthesis of **1** was secured in an optically pure form based on the convergent aldol strategy. The critical organoselenium reduction of **2** was successfully performed by treatment with benzeneselenol (PhSeH) generated *in situ* from Na[PhSeB(OEt)$_3$] (15 equiv.)[8] and acetic acid (18 equiv.) in EtOH at 0 °C, whereupon the reductive cleavage of three epoxy ketone moieties occurred regioselectively at the α-position, giving rise to the crystalline tris-β-ketol **27** in 93% yield. Finally, on treatment of the resulting tris-β-hydroxy ketone **27** with 1 M HCl in THF at 0 °C, PM-toxin B (**1**) was obtained as crystals in 82% yield. Physical properties of the synthetic compound: mp 126–126.5 °C (from acetone); $[\alpha]_D^{24}$ −29.7 (*c* 0.38, $CHCl_3$), −6.8



Scheme 6 *Reagents*: i, LiHMDS (1.3 equiv.), THF, −78 °C, then **4**; ii, CH_3SO_2Cl, DMAP, CH_2Cl_2; iii, H_2, 10% Pd-C, AcOEt; iv, $Na[PhSeB(OEt)_3]$, AcOH, EtOH; v, 1 M HCl, THF, 0 °C.

(*c* 0.35, MeOH); UV λ_{max} 280 nm (ε 108, MeOH); CD λ_{max} 281 nm ($\Delta\varepsilon$ 0.36, MeOH); FD-MS *m*/*z* 587 (M + H^+), *m*/*z* 609 (M + Na^+), 625 (M + K^+). These results are in agreement with the reported data except melting point 97 °C, $[a]_D^{25}$ −10 (MeOH), UV λ_{max} 275 nm (ε 138, MeOH), CD λ_{max} 281 nm ($\Delta\varepsilon$ 0.36, MeOH)).[2b] ^{1}H NMR and ^{13}C NMR spectra of the synthetic compound were identical with those of natural PM-toxin B.[6,10]

In conclusion, the highly stereoselective total synthesis of PM-toxin B (**1**) has been achieved by a convergent strategy involving cross-aldol reactions and the regioselective reductive cleavage of α,β-epoxy ketone units as key steps.

This work was supported by a Grant-in-Aid for JSPS Fellows (No. 2709) and a Grant-in-Aid for Scientific Research on Priority Areas (No. 706: Dynamic Control of Stereochemistry) from the Ministry of Education, Science, Sports and Culture of Japan.

Notes and references

1 J. C. Comstock, C. A. Martinson and B. C. Gegenbach, *Phytopathology*, 1973, **63**, 1357; O. C. Yoder, *Phytopathology*, 1973, **63**, 1361.

2 (*a*) Y. Kono, S. J. Danko, Y. Suzuki, S. Takeuchi and J. M. Daly, *Tetrahedron Lett.*, 1983, **24**, 3803; (*b*) S. J. Danko, Y. Kono, J. M. Daly, Y. Suzuki, S. Takeuchi and D. A. McCrery, *Biochemistry*, 1984, **23**, 759; (*c*) Y. Kono, Y. Suzuki, S. Takeuchi, H. W. Knoche and J. M. Daly, *Agric. Biol. Chem.*, 1985, **49**, 559.

3 Y. Kono, S. Takeuchi, A. Kawarada, J. M. Daly and H. W. Knoche, *Tetrahedron Lett.*, 1980, **21**, 1537; Y. Kono, S. Takeuchi, A. Kawarada, J. M. Daly and H. W. Knoche, *Agric. Biol. Chem.*, 1980, **44**, 2613; Y. Kono, S. Takeuchi, A. Kawarada, J. M. Daly and H. W. Knoche, *Bioorg. Chem.*, 1981, **10**, 206.

4 J. M. Daly, Y. Kono, Y. Suzuki and H. W. Knoche, in *Pesticide Chemistry*, ed. J. Miyamoto, Pergamon Press, Oxford, 1983, p. 11; Y. Kono, Y. Suzuki and S. Takeuchi, *J. Synth. Org. Chem. Jpn.*, 1985, **43**, 980.

5 Y. Suzuki, H. W. Knoche and J. M. Daly, *Bioorg. Chem.*, 1982, **11**, 300; Y. Suzuki, S. J. Danko, Y. Kono, S. Takeuchi, J. M. Daly and H. W. Knoche, *Agric. Biol. Chem.*, 1984, **48**, 2321.

6 Y. Suzuki, S. J. Danko, Y. Kono, J. M. Daly and S. Takeuchi, *Agric. Biol. Chem.*, 1985, **49**, 149.

7 H. Hayakawa, M. Ohmori, K. Takamichi, F. Matsuda and M. Miyashita, *Chem. Commun.*, 1997, 1219.

8 M. Miyashita, T. Suzuki, M. Hoshino and A. Yoshikoshi, *Tetrahedron*, 1997, **53**, 12469; T. Suzuki and M. Miyashita, *J. Synth. Org. Chem. Jpn.*, 1998, **56**, 736.

9 K.-M. Chen, G. E. Hardtmann, K. Prasad, O. Repic and M. J. Shapiro, *Tetrahedron Lett.*, 1987, **28**, 155.

10 ^{1}H NMR (500 MHz, C_5D_5N): 0.82 (t, J = 7.0 Hz, 3H), 1.12–1.78 (m, 38H), 1.37 (d, J = 6.2 Hz, 3H), 1.87 (dt, J = 13.8, 9.5 Hz, 1H), 2.54 (t, J = 7.2 Hz, 2H), 2.55 (t, J = 7.3 Hz, 4H), 2.61 (dd, J = 15.0, 4.1 Hz, 1H), 2.62 (dd, J = 15.0, 4.1 Hz, 1H), 2.63 (dd, J = 15.0, 4.1 Hz, 1H), 2.79 (dd, J = 15.0, 8.6 Hz, 2H), 2.81 (dd, J = 15.0, 8.6 Hz, 1H), 4.01–4.12 (m, 1H), 4.24–4.47 (m, 4H); ^{13}C NMR (125 MHz, C_5D_5N): 210.3, 210.3, 210.3, 71.3, 67.8, 67.7, 67.7, 67.6, 51.3, 51.3, 51.3, 46.5, 43.8, 43.8, 43.8, 38.6, 38.3, 38.1, 38.1, 32.0, 29.6, 29.5, 29.5, 25.9, 25.9, 25.8, 25.7, 24.6, 23.9, 23.9, 23.9, 22.9, 14.1.