Diastereoselective route to the tetrahydropyranoid core of the polyketide herbicide herboxidiene

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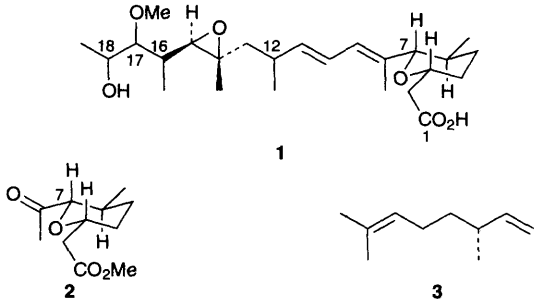
Nerol 15 is readily converted, *via* initial asymmetric epoxidation, into compound 2 which contains the tetrahydropyranoid core of herboxidiene 1, a potent phytotoxic compound isolated from *Streptomyces* sp. A7847.

As part of a screening program directed towards uncovering novel herbicides from microbial sources,[1] workers at Monsanto have recently reported[2] the isolation of a secondary metabolite produced by *Streptomyces* sp. A7847. This metabolite, which was named herboxidiene, displays potent phytotoxic properties and, at application rates of 35 g acre^{-1}, selectively controls (≥90%) various broadleaf annual weeds including oilseed rape, wild buckwheat and morning glory. Significantly, no phytotoxicity is observed for wheat. Through a combination of NMR spectroscopic, derivatisation and degradative studies the polyketide structure **1** was established for herboxidiene. However, the relative stereochemistries at C-7, C-12, C-16, C-17 and C-18 remain uncertain as does the absolute stereochemistry of **1**. Resolving all of these issues can probably be achieved through synthetic studies but, to the best of our knowledge, no relevant work has been reported to date. We are currently developing routes to compound **1** and now describe a short, efficient and selective synthesis of the tetrahydropyran **2**. Compound **2**, which was obtained by the Monsanto workers during chemical degradation of **1**, embodies the cyclic core of herboxidiene and could well serve as a synthetic precursor to the natural product.

Our initial efforts were focussed on addressing the issue of the (relative) stereochemistry at C-7 in **1** and **2**. To these ends a synthetic sequence was sought which would provide samples of both compound **2** and its C-7 epimer. This was achieved (Scheme 1) using cheap and commercially available (FLUKA) (−)-β-citronellene **3** as starting material. Thus, compound **3** was subjected to selective oxidative cleavage of the trisubstituted double-bond using a modification of literature procedures[3,4] and the known aldehyde **4** was thereby obtained in 50% yield. Subjection of compound **4** to a Wadsworth–Emmons reaction[5] with the anion derived from methyl diethylphosphonoacetate afforded a *ca.* 20:1 mixture of the conjugated ester **5**† and its (*Z*)-isomer (85% combined yield). Attempts to effect *cis*-dihydroxylation of the non-conjugated double bond within compound **5** using the Sharpless procedure (cat. OsO_4, Bu^tOOH)[6] failed because the conjugated double-bond reacted preferentially. In contrast, reaction of diene **5** with MCPBA resulted in regioselective epoxidation of the terminal double bond and a *ca.* 1:1 mixture of the diasteroisomeric epoxides **6** (96%) was obtained. Treatment of this mixture with aqueous perchloric acid[7] then gave the corresponding mixture of *vicinal*-diols **7** (64% combined yield). Reaction of these latter compounds with sodium hydride, under conditions established by Martín and coworkers,[8] resulted in intramolecular Michael-addition reaction and the formation of the hydroxmethyl-substituted tetrahydropyrans **8** and **9** (45% combined yield). These compounds were accompanied by small amounts (*ca.* 10%) of their respective C-3 epimers which could be removed by MPLC. However, compounds **8** and **9** could only be separated by HPLC so, for preparative purposes, it was more convenient to subject this mixture to reaction with pyridinium chlorochromate (PCC)/sodium acetate.[9] Under such conditions the corresponding mixture of aldehydes **10** and **11** was obtained (51% combined yield‡) and was immediately treated with methylmagnesium chloride. The diastereoisomeric 2°-alcohols **12** and **13** (79% combined yield) formed in this way were treated with PCC/sodium acetate to afford a mixture of *ent*-**2**



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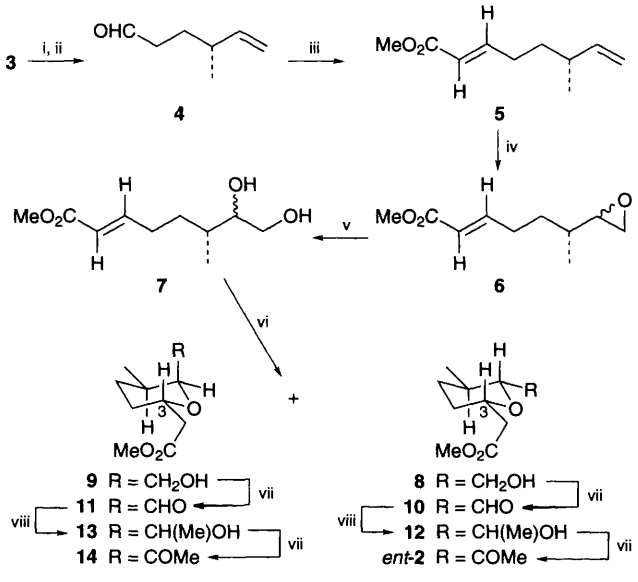

Scheme 1 *Reagents and conditions*: i, MCPBA (1.2 equiv), CH_2Cl_2, 0–5 °C, 1 h; ii, $HClO_4$, H_2O/THF, 18 °C, 4 h then $Pb(OAc)_4$ (1.1 equiv.), Et_2O, 18 °C, 2 h; iii, $MeO_2CCH_2P(O)(OEt)_2$ (1 equiv.), NaH (1 equiv.), $MeOCH_2CH_2OMe$, 0 °C, 2 h; iv, MCPBA (1.2 equiv.), CH_2Cl_2, 18 °C, 16 h; v, $HClO_4$, H_2O/THF, 18 °C, 4 h; vi, NaH (1.1 equiv.), THF, 0 °C, 1 h; vii, PCC (2 equiv.), NaOAc (0.5 equiv.), CH_2Cl_2, 18 °C, 3 h; viii, MeMgCl (1 equiv.), THF, 0 °C, 0.5 h then 18 °C, 3 h

and **14** (57% yield‡). These latter compounds were separated by HPLC and characterised spectroscopically.§ The NMR, IR and mass spectral data obtained for *ent*-**2** were in excellent agreement with those reported.[2] In the 300 MHz ^{1}H NMR spectrum of *ent*-**2** H-7 (δ 3.41) resonates as a doublet and the value of the coupling constant ($J_{7,6}$ = 10.2 Hz) is such as to imply a *trans*-diaxial relationship between H-7 and H-6.[10] In the analogous spectrum of compound **14**, H-7 (δ 3.90) also appears as a doublet but now the magnitude of the observed coupling ($J_{7,6}$ = 3.0 Hz) suggests this proton is equatorially orientated. In herboxidiene itself, H-7 appears as a doublet (at δ 3.34) with $J_{7,6}$ of 9.9 Hz. These data leave little doubt that the C-7 substituents in both **1** and **2** are in the equatorial arrangement as shown.

A completely diastereoselective synthesis of tetrahydropyran **2** is shown in Scheme 2. This began with the asymmetric epoxidation[11] of nerol **15** using diethyl (−)-tartrate as chiral ligand. The ensuing epoxide **16**[12] (75%)¶ was subjected to reductive-cleavage with $NaCNBH_3/BF_3.Et_2O$ and the resulting diol **17**[12] (73%) then converted into the corresponding diacetate **18** (72%) under standard conditions. Ozonyltic cleavage of this last compound furnished the aldehyde **19** (97%) which was immediately subjected to Still's modification[13] of the Wadsworth–Emmons olefination reaction and thereby ensuring almost exclusive formation of the (*Z*)-unsaturated ester **20** (78%). When compound **20** was treated with potassium carbonate in methanol sequential acetate hydrolysis/intramolecular Michael addition occurred leading to the tetrahydropyran *ent*-**8** (88%). The C-3 epimer of *ent*-**8** was not detected in the reaction mixture and it is believed, on the basis of model studies,[14] that the (*Z*)-geometry about the double bond in **20** exerts a controlling influence in ensuring a *cis*-relationship between the anomeric substituents in the primary cyclisation product. The conversion of *ent*-**8** into compound **2** was readily achieved by the pathway established earlier (Scheme 1). Thus, oxidation of the former compound gave *ent*-**10** (51%) which was immediately reacted with methylmagnesium chloride. Oxidation of the resulting mixture of diastereoisomeric diols *ent*-**12** (79%) then gave the target compound **2** {57%, $[\alpha]_D$ = −27.2¶,‖ (*c* 3.3, MeOH)} the NMR, IR and mass spectra of which were identical with *ent*-**2**.

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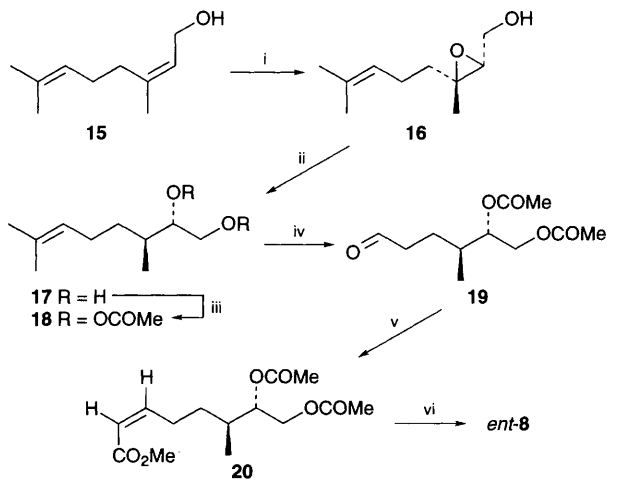

Scheme 2 *Reagents and conditions*: i, ref. 12; ii, ref. 12; iii, $(MeCO)_2O$ (2 equiv.), pyridine, DMAP (trace), 18 °C, 4 h; iv, O_3, CH_2Cl_2, PPh_3, −78 °C, 2 h; v, $MeO_2CCH_2P(O)(OCH_2CF_3)_2$ (1 equiv.), 18-C-6/MeCN complex (5 equiv.), $KN(TMS)_2$ (1 equiv.), THF, −78 °C, 0.5 h; vi, K_2CO_3 (5 equiv.), MeOH, 18 °C, 24 h then MeOH, H_2SO_4 (trace), 18 °C, 24 h

Footnotes

† All new compounds had spectroscopic data [IR, UV (where appropriate), NMR, mass spectrum] consistent with the assigned structure. Satisfactory combustion and/or high resolution mass spectral analytical data were obtained for new compounds and/or suitable derivatives.

‡ Attempts to improve upon this yield by using other oxidants (including Swern reagents) have been unsuccessful so far.

§ *Selected spectroscopic data* for *ent*-**2**/**2**: ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.8, 171.5, 89.0, 73.7, 51.7, 41.2, 32.2, 31.8, 31.1, 25.8 and 16.9; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (m, 1 H, H-3), 3.68 (s, 3 H, OMe), 3.41 (d, *J* 10.2 Hz, 1 H, H-7), 2.58 (dd, *J* 15.0 and 7.5 Hz, 1 H, H-2), 2.45 (dd, *J* 15.0 and 5.6 Hz, 1 H, H-2), 2.14 (s, 3 H, COMe), 1.88 (ddd, *J* 13.2, 7.2 and 3.6 Hz, 1 H), 1.70 (ddd, *J* 13.2, 6.0 and 3.6 Hz, 1 H), 1.53 (m, 1 H), 1.38 (m, 1 H), 1.27 (m, 1 H) and 0.85 (d, *J* 7.0 Hz, 3 H, Me); ν_{max}(NaCl)/cm^{-1} 2951, 2927, 1738, 1717, 1434, 1353, 1273, 1227, 1198, 1160, 1145, 1083 and 1021; MS *m/z* (Cl, methane) 215 (4%) M + H, 171 (88) M − MeCO, 139 (80) M − MeCO − MeOH and 97 (100); HRMS, M + H 215.1276. $C_{11}H_{18}O_4$ requires M + H 215.1283. For **14**: ^{13}C NMR (75 MHz) δ 210.2, 171.6, 85.5, 75.2, 51.7, 41.3, 30.1, 29.3, 27.3, 25.5 and 12.2; ^{1}H NMR (300 MHz) δ 3.90 (d, *J* 3.0 Hz, 1 H, H-7), 3.83 (m, 1 H, H-3), 3.70 (s, 3 H, OMe), 2.65 (dd, *J* 15.0 and 7.8 Hz, 1 H, H-2), 2.49 (dd, *J* 15.0 and 5.4 Hz, 1 H, H-2), 2.20 (m, 1 H), 2.12 (s, 3 H, COMe), 1.80 (m, 1 H), 1.69 (m, 1 H), 1.62–1.42 (cm, 2 H) and 0.87 (d, *J* 6.5 Hz, 3 H, Me); ν_{max}(NaCl)/cm^{-1} 2933, 1734, 1435, 1353, 1286, 1169 and 1068; MS *m/z* (Cl, methane) 215 (4%) M + H, 187 (68) and 171 (100) M − MeCO.

¶ Only modest ee's appear to be attainable in the standard asymmetric epoxidation of nerol [see (i) L. Van Hijfte and M. Kolb, *Tetrahedron*, 1992, **48**, 6393 and (ii) N. Mori and Y. Kuwahara, *Tetrahedron Lett.*, 1995, **36**, 1477). On the basis of $[\alpha]_D$ determinations, the epoxy alcohol **16** used for the present work is calculated to be in *ca.* 50% ee. It is assumed, therefore, that all the products derived from this compound, including target **2**, are of comparable ee. Highly enriched (>95% ee) **16** can be obtained by repeated recrystallisation of the derived 3,5-dinitrobenzoate [see (ii) above].

‖ The optical rotation of compound **2** derived from **1** has not been reported and we have been unable to obtain this information from the Monsanto group. Consequently, it has not been possible to draw any conclusions at this point about the absolute configuration of the tetrahydropyranyl residue associated with herboxidiene.

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