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 reported² 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 reaction⁵ 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. OsO₄, Bu^tOOH)⁶ failed because the conjugated doublebond 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 diasteroisometric epoxides 6 (96%) was obtained. Treatment of this mixture with aqueous perchloric acid⁷ 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 Michaeladdition reaction and the formation of the hydroxmethylsubstituted 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



Scheme 1 Reagents and conditions: i, MCPBA (1.2 equiv), CH_2Cl_2 , 0–5 °C, 1 h; ii, HClO₄, H₂O/THF, 18 °C, 4 h then Pb(OAc)₄ (1.1 equiv.), Et₂O, 18 °C, 2 h; iii, MeO₂CCH₂P(O)(OEt)₂ (1 equiv.), NaH (1 equiv.), MeOCH₂CH₂OMe, 0 °C, 2 h; iv, MCPBA (1.2 equiv.), CH₂Cl₂, 18 °C, 16 h; v, HClO₄, H₂O/THF, 18 °C, 4 h; vi, NaH (1.1 equiv.), THF, 0 °C, 1 h; vii, PCC (2 equiv.), NaOAc (0.5 equiv.), CH₂Cl₂, 18 °C, 3 h; viii, MeMgCl (1 equiv.), THF, 0 °C, 0.5 h then 18 °C, 3 h

Chem. Commun., 1996 723

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 ¹H 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 (& 3.90) also appears as a doublet but now the magnitude of the observed coupling $(J_{7.6} = 3.0 \,\text{Hz})$ 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 epoxidation¹¹ of nerol 15 using diethyl (-)-tartrate as chiral ligand. The ensuing epoxide 16^{12} (75%) was subjected to reductive-cleavage with NaCNBH₃/BF₃.Et₂O and the resulting diol 17¹² (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 modification¹³ 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, O₃, CH₂Cl₂, PPh₃, -78 °C, 2 h; v, MeO₂CCH₂P(O)(OCH₂CF₃)₂ (1 equiv.), 18-C-6/MeCN complex (5 equiv.), KN(TMS)₂ (1 equiv.), THF, -78 °C, 0.5 h; vi, K₂CO₃ (5 equiv.), MeOH, 18 °C, 24 h then MeOH, H₂SO₄ (trace), 18 °C, 24 h

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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: ¹³C NMR (75 MHz, CDCl₃) δ 207.8, 171.5, 89.0, 73.7, 51.7, 41.2, 32.2, 31.8, 31.1, 25.8 and 16.9; ¹H NMR (300 MHz, CDCl₃) & 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); $v_{max}(NaCl)/(cm^{-1} 2951)$, 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. C11H18O4 requires M + H 215.1283. For 14: 13C 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; ¹H NMR (300 MHz) & 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); $v_{max}(NaCl)/cm^{-1}$ 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.

References

- 1 S. W. Ayer, B. G. Isaac, D. M. Krupa, K. E. Crosby, L. J. Letendre and R. J. Stonard, Pestic. Sci., 1989, 27, 221.
- 2 B. G. Isaac, S. W. Ayer, R. C. Elliott and R. J. Stonard, J. Org. Chem., 1992. 57, 7220.
- 3 L. A. Paquette and G. D. Maynard, J. Am. Chem. Soc., 1992, 114, 5018.
- G. J. Cernigliaso and P. J. Kocienski, J. Org. Chem., 1977, 42, 3622.
- 5 W. S. Wadsworth, Jr. and W. D. Emmons, J. Am. Chem. Soc., 1961, 83, 1733
- 6 K. Akashi, R. E. Palermo and K. B. Sharpless, J. Org. Chem., 1978, 43, 2063
- 7 I. Dyong and N. Jersch, Chem. Ber., 1976, 109, 896.
- 8 J. M. Palazón, M. A. Soler, M. A. Ramírez and V. S. Martín, Tetrahedron Lett., 1993, 34, 5467.
- E. J. Corey and J. W. Suggs, Tetrahedron Lett., 1975, 2647.
- 10 L. M. Jackman and S. Sternhell, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, Pergamon Press, London, 2nd edn., 1969, p. 288 and references cited therein.
- T. Katsuki and K. B. Sharpless, J. Am. Chem. Soc., 1980, 102, 5976; R. M. Hanson and K. B. Sharpless, J. Org. Chem., 1986, 51, 1922.
- 12 D. F. Taber and J. B. Houze, J. Org. Chem., 1994, 59, 4004.
- 13 W. C. Still and C. Gennari, *Tetrahedron Lett.*, 1983, 24, 4405.
 14 M. G. Banwell, C. T.Bui, H. T. T. Pham and G. W. Simpson, *J. Chem.* Soc., Perkin Trans. 1, in the press.

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