COMMUNICATION

Constructing the side-chain of the polyketide herbicide herboxidiene: a protocol for the synthesis of enantiomerically enriched C-11 to C-19 fragments

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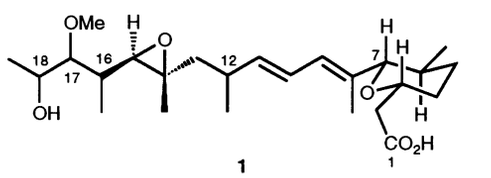
The aldehyde 5, corresponding to the C-11 to C-19 fragment of the polyketide herbicide herboxidiene 1, has been prepared in enantio-enriched form.

Herboxidiene **1**, a secondary metabolite produced by *Streptomyces* sp. A7847, displays potent phytotoxic properties and selectively controls various broadleaf annual weeds while being harmless to wheat.[1] As a result of its potentially useful herbicidal properties we have embarked on a programme aimed at developing syntheses of this polyketide and its congeners.[2] In this way we hope to resolve the ambiguities that remain regarding the relative stereochemistries at C-12, C-16, C-17 and C-18 as well as addressing the question of the absolute stereochemistry of **1**.[3] We have recently described[4] a short, efficient



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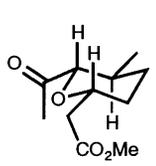

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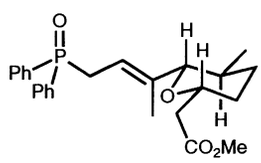

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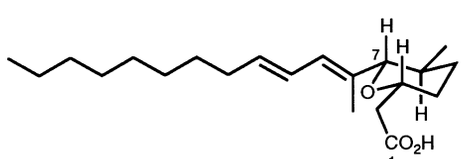

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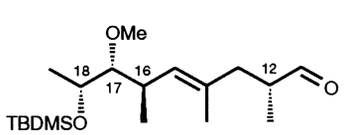

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and diastereoselective synthesis of the tetrahydropyranyl core, **2**, of herboxidiene and subsequently shown[5] that this material can be readily elaborated to the phosphine oxide **3** which engages in a Horner–Wittig reaction with nonanal to give, after *in situ* hydrolysis of the ester moiety, compound **4**. These results prompted us to seek methods for construction of C-11 to C-19 (side-chain) fragments of herboxidiene with an aldehyde group at the former carbon. We now report a synthesis of compound **5** in enantio-enriched form.† Of the four stereogenic centres associated with this fragment one (C-16) derives from the chiral pool while the remaining three have been formed by 1,2-asymmetric induction *via* nucleophilic additions to aldehydes. This approach has been used because of the well-recognised[6] capacity of such processes to allow installation, in a predictable but flexible manner, of vicinally related stereochemical arrays. The methods used should allow for ready construction, in enantiomerically enriched form, of the full set of diastereomers 'created' by the unassigned stereogenic centres associated with herboxidiene.

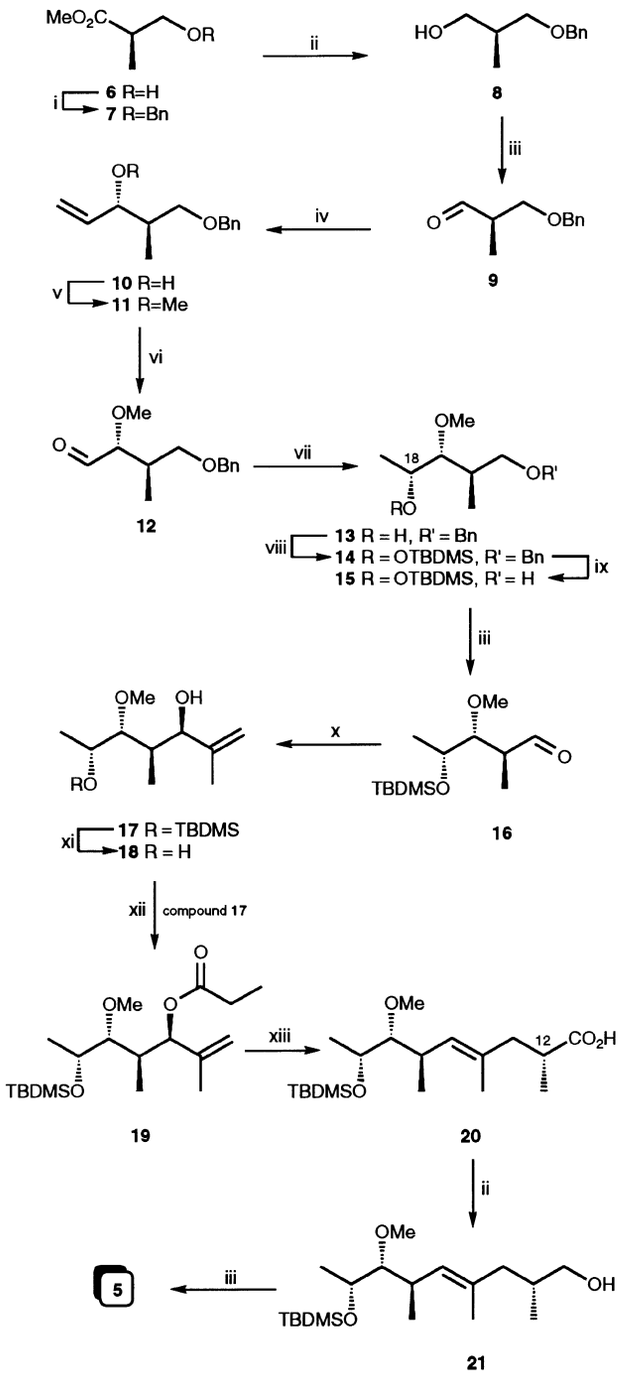
The synthesis (Scheme 1) of aldehyde **5** began with commercially available methyl (2*R*)-3-hydroxy-2-methylpropionate **6** (Aldrich, 99% ee)‡ which was converted into the corresponding benzyl ether **7** (73%)[7] under conditions which avoid racemisation.[8] Ester **7** was then reduced, by standard methods, to the corresponding alcohol **8** (85%)[7] and this was, in turn, converted into the aldehyde **9** (80%)[9] using the Swern reagent derived from oxalyl chloride and dimethyl sulfoxide. Nucleophilic addition of vinylmagnesium bromide to this last compound produced a 1:1 mixture of diastereoisomeric addition products§ (70% combined yield) which could be separated from one another by chromatography. The more polar material proved to be compound **10**[10] (as established by X-ray crystallographic analysis of a derivative—see below)¶ {$[\alpha]_D$ −22.9 (*c* 1.0 in $CHCl_3$)} which was subjected to *O*-methylation using potassium hydride and methyl iodide. In this manner the bis-ether **11** {94%, $[\alpha]_D$ +2.4 (*c* 1.0 in $CHCl_3$)} was obtained and immediately subjected to ozonolytic cleavage thereby affording aldehyde **12** {92%, $[\alpha]_D$ +37.8 (*c* 3.4 in $CHCl_3$)}. Reaction of compound

† We plan to introduce the epoxide ring associated with herboxidiene after Horner–Wittig chemistry has been used to connect the deoxy side-chain (*e.g.* **5**) to the tetrahydropyranoid core (*viz.* compound **3**). The validity of such an approach has recently been established by Kocienski *et al.*[2]

‡ The corresponding *S*-enantiomer is also available commercially.

§ The formation of a 1:1 mixture of diastereoisomers at this point is useful because it allows for the eventual generation of sets of diastereoisomers related to **5**.

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



Scheme 1 *Reagents and conditions:* i, $BnOC(NH)CCl_3$ (1.2 mol equiv.), CH_2Cl_2, CF_3SO_3H (cat.), *ca.* 18 °C, 16 h; ii, $LiAlH_4$ (0.5 mol equiv.), Et_2O, 0–5 °C, 1 h; iii, Me_2SO (2.4 mol equiv.), ClCOCOCl (1.2 mol equiv.), CH_2Cl_2, −60 °C, 1 h then Et_3N (13.5 mol equiv.) −60 °C, 1 h; iv, $H_2C{=}C(H)MgBr$ (1.2 mol equiv.), THF, −78 °C, 1 h then work-up at −78 °C; v, MeI (2.0 mol equiv.), KH (1.2 mol equiv.), THF, 0–18 °C, 2 h; vi, O_3 (excess), CH_2Cl_2, −78 °C, 1 h then PPh_3 (1.0 mol equiv.), −30–18 °C, 0.5 h; vii, MeMgCl (1.2 mol equiv .), THF, −78 °C, 1 h; viii, TBDMSCl (1.2 mol equiv.), imidazole (1.5 mol equiv.), DMF, 60 °C, 3 h; ix, H_2 (1 atm), 10% Pd on C, EtOH, 18 °C, 1 h; x, $H_2C{=}C(Me)Br$ (13.5 mol equiv.), Bu^{t}Li (27 mol equiv.), CuBr·DMS (6.7 mol equiv.), Et_2O, −78 °C, 0.5 h; xi, HF–pyridine (0.3 cm^3 per 0.3 g substrate), THF, 0–18 °C, 16 h; xii, $(EtCO)_2O$ (4.0 mol equiv.), DMAP (cat.), C_6H_5N, 18 °C, 16 h; xiii, $KN(TMS)_2$ (6.4 mol equiv.), HMPA–THF (25:80 *v*/*v*), −78 °C, 0.5 h then TMSCl (12 mol equiv.), Et_3N (4 mol equiv.) then heat at 45 °C, 3 h. DMAP = 4-(*N*,*N*-dimethylamino)pyridine; DMF = dimethylformamide; DMS = dimethyl sulfide; HMPA = hexamethylphosphoramide; TBDMSCl = *tert*-butyldimethylsilyl chloride; TMSCl = trimethylsilyl chloride.

12 with methylmagnesium chloride provided a 4:1 mixture of compound **13** {$[a]_D$ +0.88 (*c* 2.5 in $CHCl_3$)} and its C-18 epimer

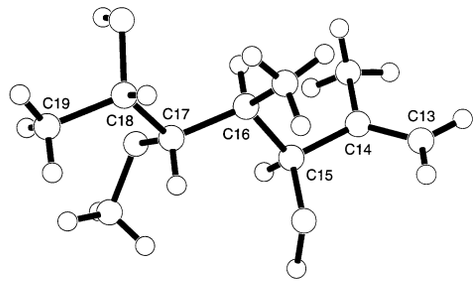


Fig. 1 ORTEP (herboxidiene numbering) of compound **18** derived from X-ray crystallaographic data

(herboxidiene numbering) (96% combined yield) which could only be separated from one another by HPLC techniques. It was more convenient, therefore, to convert this mixture into the corresponding *tert*-butyldimethylsilyl esters, **14** and 18-*epi*-**14** (93% combined yield) and these were then hydrogenolysed to give the corresponding mixture of alcohols **15** {77%, $[a]_D$ +3.5 (*c* 3.5 in $CHCl_3$)} and 18-*epi*-**15** {19%, $[a]_D$ −2.8 (*c* 0.5 in $CHCl_3$)} which could be readily separated by flash chromatography. Oxidation of alcohol **15** with the Swern reagent provided the corresponding aldehyde **16** {98%, $[a]_D$ +23.2 (*c* 2.5 in $CHCl_3$)} which was then reacted with isopropenyl cuprate[11a] to give allylic alcohol **17** {83%, $[a]_D$ −0.9 (*c* 1.5 in $CHCl_3$)} as the only detectable product of reaction. For the purpose of unequivocal characterisation, compound **17** was desilylated and the structure of the resulting crystalline diol **18** {75%, mp 90–91 °C, $[a]_D$ −3.7 (*c* 0.6 in $CHCl_3$)}‖ was determined by single-crystal X-ray analysis (Fig. 1)** which established the illustrated (relative) stereochemistries in all of the compounds described to this point. Completion of the synthesis of aldehyde **5** involved conversion of mono-ol **17** into the corresponding propionate **19** {82%, $[a]_D$ −7.3 (*c* 1.5 in $CHCl_3$)} which was, in turn, subjected to an Ireland–Claisen rearrangement[11] by sequential treatment with $KN(SiMe_3)$ and trimethylsilyl chloride–triethylamine then heating the intermediate (*Z*)-silyl ketene acetal at 45 °C. In this manner the unsaturated carboxylic acid **20** {80%, $[a]_D$ −2.3 (*c* 1.4 in $CHCl_3$)} was obtained. The (12*R*)-stereochemistry and (*E*)-geometry about the double bond in this compound are proposed on the basis of the well-defined outcomes[11] associated with Ireland–Claisen rearrangements of related substrates under the same reaction conditions. Reduction of acid **20** to the corresponding alcohol **21** {83%, $[a]_D$ −4.7 (*c* 0.4 in $CHCl_3$)} was readily accomplished with $LiAlH_4$ and the latter compound was then oxidised to the required alde-

‖ Chiral capillary GLC analysis of diol **18** (using a 25 m × 0.22 mm Cydex-B column as provided by SGE Pty Ltd, Melbourne) suggested this material was composed of a *ca.* 67:33 mixture of enantiomers (baseline resolution of the two peaks could not be achieved). The partial racemisation implied by this result most likely occurs during one or both of the reaction steps involving compound **9** since such aldehydes are notoriously prone to enolisation (see W. R. Roush, A. D. Palkowitz and M. A. J. Palmer, *J. Org. Chem.*, 1987, **52**, 316). On this basis, it is assumed that all of compounds **5** and **10**–**21** are of about 34% ee.

** *Crystal data* for compound **18**: $C_{10}H_{20}O_3$, M = 188.27, T = 296(1) K, orthorhombic, space group *Pbca*, a = 14.038(1), b = 17.344(1), c = 19.274(1) Å, U = 4692.9(5) $Å^3$, D_c (Z = 16) = 1.066 g cm^{-3}, $F(000)$ = 1664, μ(Cu-Kα) = 6.24 cm^{-1}, semi-empirical absorption correction; 3922 unique data ($2\theta_{max}$ = 120.1°), 1569 with $I > 3\sigma(I)$; R = 0.059, wR = 0.051, goodness-of-fit = 2.68. Data were measured on a Rigaku AFC6R rotating anode diffractometer (graphite crystal monochromator, λ = 1.541 80 Å). Refinement was by full-matrix least-squares analysis on F using the TEXSAN Structure analysis Software of Molecular Structure Corporation.[12] Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/104.

hyde **5**†† {94%, $[\alpha]_D$ −1.9 (*c* 1.75 in $CHCl_3$)} using the Swern reagent.

Note added in proof: the complete structure of herboxidiene has now been published (A. J. F. Edmunds, W. Trueb, W. Oppolzer and P. Cowley, *Tetrahedron*, 1997, **53**, 2785).

Acknowledgements

Dunlena Pty Ltd and the Australian Research Council are thanked for financial support. C. T. B. is the grateful recipient of an APRA (Industry) Scholarship which is being administered through the University of Melbourne. C. T. B. thanks both the Research School of Chemistry (ANU) and, more recently, the CSIRO Division of Chemicals and Polymers (Clayton) for the provision of laboratory facilities.

†† *Selected spectral data for* **5**: δ_C(50 MHz, $CDCl_3$) 205.1, 130.5, 129.4, 89.9, 70.7, 61.2, 44.4, 40.9, 34.2, 25.9, 20.0, 18.6, 18.1, 15.8, 12.9. −4.6, −4.7; δ_H(200 MHz, $CDCl_3$) 9.56 (m, 1 H, H-11), 5.20 (d, *J* 9.8 Hz, 1 H, H-15), 3.67 (m, 1 H), 3.41 (br s, 3 H, OCH_3), 2.74 (m, 1 H), 2.63–2.30 (complex m, 3 H), 1.93 (m, 1 H), 1.54 (broadened s, 3 H), 1.02–0.91 (complex m, 9 H), 0.83 (s, 9 H), 0.02 (s, 3 H), −0.01 (s, 3 H); ν_{max}(NaCl)/cm^{-1} 1731; *m*/*z* (EI, 70 eV) 342 (M^+, 0.5%), 285 [$(M - C_4H_9)^+$, 5], 203 [$(M - C_9H_{15}O)^+$, 86], 73 (100); (HRMS: M^+, 342.2582. $C_{19}H_{38}O_3Si$ requires *M*, 342.2590).

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Paper 7/01360D
Received 26*th February* 1997
Accepted 26*th February* 1997