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Total synthesis of herboxidiene, a complex polyketide from *Streptomyces* species A7847*

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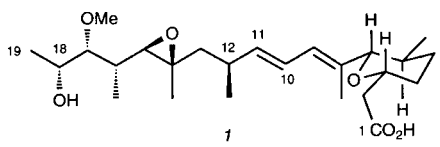
Abstract: A formal total synthesis of the polyketide herboxidiene (**1**) has been achieved by Horner–Wittig coupling of the side-chain fragment 12-*epi*-(**2**) with the tetrahydropyran-2-acetic acid derivative (**3**) followed by desilylation of the resulting triene (**19**) and hydroxyl-directed mono-epoxidation of the ensuing *bis*-homoallylic alcohol (**20**).

In 1992 a group at Monsanto (USA) detailed [1] the near complete structural elucidation of the polyketide herboxidiene (**1**, a.k.a. TAN-1609) which they had isolated from *Streptomyces chromofuscus* A7847. The same group also revealed [1] that the molecule displays potent and highly selective phytotoxic properties such that at application rates of 35 g/acre it selectively controls various crop pests such as oilseed rape, wild buckwheat, and morning glory while being harmless to wheat. Such properties, which are remarkable for a polyketide, prompted efforts by Edmund's group at Novartis AG [2] to re-isolate herboxidiene and then, through a combination of X-ray crystallographic, chemical degradation and chemical synthesis studies, to establish the full stereochemistry associated with compound (**1**). Such studies were accompanied by extensive SAR-work [3] as well as, thus far, unsuccessful efforts [2,3] to develop a total synthesis of the compound. At about the same time, three Japanese groups [4–6] reported isolating herboxidiene from various fermentation processes. One of these groups [4] reported that the compound up-regulates gene expression of low-density lipoprotein receptors (and thereby lowering cholesterol levels in blood plasma), while another has reported [6] that it blocks the cell cycle at the G2 phase in human and murine tumor cells by inducing apoptosis.



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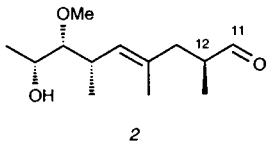

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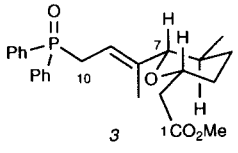

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The first total synthesis of herboxidiene was reported recently by Kocienski and coworkers [7] who adapted elegant earlier work [8] that had culminated in the preparation of herboxidiene A, a diastereoisomer of the natural product. We now report a (formal) total synthesis of the title compound that differs, in a number of respects, from that described by the Glasgow group [7]. The present work exploits the Katsuki–Sharpless epoxidation reaction, a chiral-pool starting material and substrate-directed transformations for establishing the correct stereochemistry associated with eight of the nine centers of chirality contained in the target molecule (**1**).

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As enunciated previously [9,10] an obvious disconnection of target (**1**) is between C10 and C11 so as to create substructures such as the side-chain molecule (**2**) and phosphine oxide core (**3**) that could be coupled to one another through a Horner–Wittig (HW) reaction. It was anticipated that the epoxide moiety associated with herboxidiene could be introduced via C18-hydroxyl-directed epoxidation after the HW-coupling step [7,11]. We have recently detailed [9] a synthesis of compound (**3**), that starts with the Katsuki–Sharpless asymmetric epoxidation of nerol, and shown that this phosphine oxide does couple in the appropriate fashion (i.e., with high *E*-selectivity) with model aldehydes. A highly diastereoselective synthesis of the herboxidiene side-chain is shown in Fig. 1 and starts with the commercially

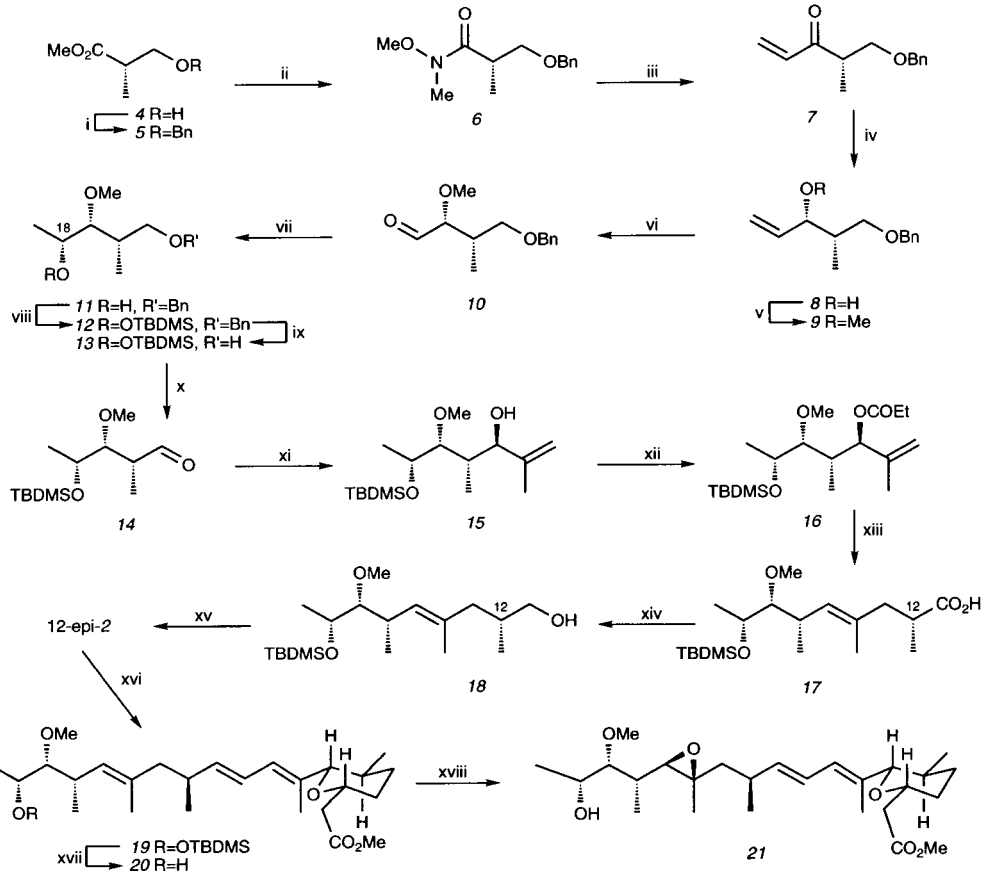

Fig. 1 *Reagents and conditions*: (i) $BnOC(NH)CCl_3$ (1.2 mole equiv.), CH_2Cl_2, CF_3SO_3H (cat.), *ca*. 0 to18 °C, 16 h; (ii) Me(MeO)NH.HCl (1.55 mole equiv.), *i*-PrMgCl (3.0 mole equiv.), THF, –15 °C, 0.5 h; (iii) $H_2C{=}C(H)MgBr$ (1.5 mole equiv.), THF, 0 °C, 0.5 h; (iv) $Zn(BH_4)_2$, CH_2Cl_2, –78 to 0 °C, 4.5 h; (v) MeI (2.5 mole equiv.), KH (2.5 mole equiv.), THF, 0–18 °C, 6 h; (vi) O_3 (excess), CH_2Cl_2, –78 °C, 1 h then DMS (1.0 mole equiv.), –30–18 °C, 0.5 h; (vii) Me_2Zn (1.0 mole equiv.), $TiCl_4$ (1.0 mole equiv.), THF, –78 °C, 0.5 h; (viii) TBDMSCl (2.0 mole equiv.), imidazole (3.0 mole equiv.), DMF, 60 °C, 3 h; (ix) H_2 (1 atm.), $Pd(OH)_2$, THF, 18 °C, 1 h; (x) SO_3/pyridine (3.0 mole equiv.), DMSO, CH_2Cl_2, 0 to 18 °C, 4 h then Et_3N, 0 °C, 1.0 h; (xi) $H_2C{=}C(Me)Br$ (13.5 mole equiv.), *t*-BuLi (27 mole equiv.), CuBr.DMS (6.9 mole equiv.), Et_2O, –78 °C, 3 h; (xii) $(EtCO)_2O$ (2.5 mole equiv.), DMAP (cat.), C_6H_5N, 18 °C, 16 h; (xiii) LDA (1.3 mole equiv.), HMPA/THF (1:2 v/v), –78 °C, 0.5 h then TBDMSCl (1.3 mole equiv) then heat at 50 °C, 6 h; (xiv) $LiAlH_4$ (1.0 mole equiv.), THF, 0 to 18 °C, 6 h; (xv) Dess–Martin periodinane (2.5 mole equiv.), CH_2Cl_2, 0 to 18 °C, 4 h; (xvi) Compound *3* (1.0 mole equiv.) NaH (10 mole equiv.), THF, 55 °C, 2 h then CH_2N_2 (excess), CH_2Cl_2, 18 °C, 16 h; (xvii) TBAF (1.5 mole equiv.), THF, 0–18 °C, 6 h; (xviii) *t*-BuOOH (3.0 mole equiv.), $VO(acac)_2$ (1.0 mole %), CH_2Cl_2, –8 °C, 72 h.

available methyl (2*S*)-3-hydroxy-2-methylpropionate (**4**) (Aldrich, 99% ee). Compound (**4**) was *O*-benzylated under conditions which avoid racemization [12] and the resulting ether (**5**) [13] (97%) converted into the corresponding Weinreb amide (**6**) (98%) {$[\alpha]_D$ = +4.6 (c = 2.0)} using *i*-propylmagnesium chloride as base. Treatment of the latter compound with vinylmagnesium bromide afforded, after acidic workup, the expected conjugated ketone (**7**) (92%) which underwent a chelation controlled 1,2-reduction with zinc borohydride [14] at –78°C to give a *ca*. 8:1 mixture of allylic alcohol (**8**) [15] (83%) {$[\alpha]_D$ = –9.6 (c = 2.8)} and the corresponding *anti*-isomer (*ca*. 10%) {$[\alpha]_D$ = +28.2 (c = 2.5)} which could be readily separated from one another by preparative HPLC. *O*-Methylation of compound (**8**), to give (**9**) (85%) {$[\alpha]_D$ = +12.2 (c = 1.3)}, followed by ozonolytic cleavage of the carbon–carbon double bond afforded the unstable aldehyde (**10**) (90%) {$[\alpha]_D$ = +22.5 (c = 2.2)} which was immediately reacted with dimethylzinc in the presence of $TiCl_4$ [16] to give alcohol (**11**) (70%) {$[\alpha]_D$ = +8.6 (c = 2.8)} as the only isolable reaction product. The readily derived TBDMS-ether (**12**) (80%) {$[\alpha]_D$ = +10.4 (c = 2.5)} was subjected to hydrogenolytic debenzylation and the ensuing 1°-alcohol (**13**) (80%) oxidized to the aldehyde (**14**) using the Parikh–Doering reagent [17]. Reaction of the last compound with the Gilman reagent obtained from 2-bromopropene then gave, via a chelation controlled process, the allylic alcohol (**15**) [70% from (*13*)] {$[\alpha]_D$ = +3.2 (c = 1.2)}. The derived propionate ester (**16**) (90%) {$[\alpha]_D$ = –22.0 (c = 1.6)} was subjected to an Ireland–Claisen rearrangement [10,18] involving sequential treatment with LDA then TBDMSCl in HMPA/THF from –78 to 50 °C. The (12*R*)-stereochemistry and the (*E*)-geometry about the double-bond in the ensuing γ,δ-unsaturated carboxylic acid (**17**) (75%) {$[\alpha]_D$ = + 5.8 (c = 2.2)} were initially proposed on the basis of the well-defined outcomes associated with the Ireland–Claisen rearrangements of related substrates under the same reaction conditions [7,10]. $LiAlH_4$-promoted reduction of compound (**17**) afforded the corresponding alcohol (*18*) (80%) {$[\alpha]_D$ = +6.4 (c = 1.6)} which was converted, using the Dess–Martin periodinane, into the unstable C12-epimer (80%) of the target aldehyde (**2**), *viz.* 12-*epi*-(**2**).

The stage was now set for the crucial HW-reaction involving phosphine oxide (**3**) [9] and, thence, the final stages of the total synthesis. In the event, coupling of aldehyde 12-*epi*-(**2**) and phosphine oxide (**3**) could be effected with sodium hydride. The reaction was accompanied by epimerization of the former compound with the result that a 3:2 mixture of triene (**19**) (39%) {$[\alpha]_D$ = +0.4 (c = 2.3)} and its C12-epimer (26%) {$[\alpha]_D$ = +18.4 (c = 1.5)} was obtained. These products could be separated from one another using semi-preparative HPLC techniques and desilylation of the chromatographically less-mobile compound (**19**) was accomplished using tetra-*n*-butylammonium fluoride (TBAF) in THF. The resulting alcohol (**20**) (68%) was then reacted with *tert*-butylhydroperoxide in the presence of $VO(acac)_2$, and in this way a *ca*. 4:1 mixture of herboxidiene methyl ester (**21**) (73%) {$[\alpha]_D$ = + 1.3 (c = 0.2), lit. [7] $[\alpha]_D$ = + 0.9 (c = 0.7)} and an isomer was obtained. These epoxides could also be separated from one another by semi-preparative HPLC, and the spectral data obtained on the former product matched, in all respects, those reported by Kocienski and coworkers [7].

The acquisition of herboxidiene methyl ester constitutes a formal total synthesis of herboxidiene because it has been shown that the former material can be converted into compound (**1**) by conventional hydrolysis [7]. In principle the problems of controlling C-12 stereochemistry could be addressed by effecting Ireland–Claisen rearrangement of the (*E*)-silylketene acetal derived from propionate ester (**16**) so as to give 12-*epi*-(**17**) and, thence, aldehyde (**2**) [7,18b]. Furthermore, there are indications in the literature [18b] that α-chiral aldehydes can participate in HW-reactions without epimerization/racemization when $NaN(SiMe_3)_2$ is used as base. Efforts to exploit such possibilities are currently underway in our laboratories.

REFERENCES

1. B. G. Isaac, S. W. Ayer, R. C. Elliott, R. J. Stonard. *J. Org. Chem*. **57**, 7220 (1992).
2. A. J. F. Edmunds, W. Trueb, W. Oppolzer, P. Cowley. *Tetrahedron* **53**, 2785 (1997).

3. A. J. F. Edmunds, G. Arnold, L. Hagmann, R. Schaffner, H. Furlenmeier. *Bioorg. Med. Chem. Lett.* **10**, 1365 (2000).
4. Y. Koguchi, M. Nishio, J. Kotera, K. Omori, T. Ohnuki, S. Komatsubara. *J. Antibiot*. **50**, 970 (1997).
5. T. Mizukami, Y. Sakai, T. Yoshida, Y. Uosaki, K. Ochiai, S. Akinaga. *Eur. Pat. Appl*. EP 781,772 [*Chem. Abstr*. **127**, 108054a, (1997)].
6. T. Horiguchi, M. Shirasaki, S. Tanida. *Takeda Kenkyushoho* **55**, 149 (1996) [*Chem. Abstr*. **125**, 185223r (1996)].
7. P. R. Blakemore, P. J. Kocienski, A. Morley, K. Muir. *J. Chem. Soc., Perkin Trans. 1*, 955 (1999).
8. N. D. Smith, P. J. Kocienski, S. D. A. Street. *Synthesis*, 652 (1996).
9. M. G. Banwell, C. T. Bui, G. W. Simpson. *J. Chem. Soc., Perkin Trans. 1*, 791 (1998).
10. M. G. Banwell, C. T. Bui, D. C. R. Hockless, G. W. Simpson. *J. Chem. Soc., Perkin Trans. 1*, 1261 (1997).
11. A. H. Hoveyda, D. A. Evans, G. C. Fu. *Chem. Rev*. **93**, 1307 (1993) and references cited therein.
12. U. Widmer. *Synthesis*, 568 (1987).
13. J. D. White, G. Nagabushana Reddy, G. O. Spessard. *J. Chem. Soc., Perkin Trans. 1*, 759 (1993).
14. S. Narasimhan and R. Balakumar. *Aldrichimica Acta* **31**, 19 (1998).
15. S. D. Burke, R. A. Ng, J. A. Morrison, M. J. Alberti. *J. Org. Chem*. **63**, 3160 (1998).
16. M. T. Reetz. *Acc. Chem. Res*. **26**, 462 (1993).
17. J. R. Parikh and W. von E. Doering. *J. Am. Chem. Soc*. **89**, 5505 (1967).
18. (a) R. E. Ireland and P. Maienfisch. *J. Org. Chem*. **53**, 640 (1988); (b) S. R. Schow, J. D. Bloom, A. S. Thompson, K. N. Winzenberg, A. B. Smith III. *J. Am. Chem. Soc*. **108**, 2662 (1986).

NOTE ADDED IN PROOF

An improved synthesis of phosphine oxide (**3**) has recently been reported [M. G. Banwell, M. D. McLeod, R. Premraj, G. W. Simpson. *Aust. J. Chem*. **53**, 659 (2000)].