Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 1365–1368

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis of Simplified Herboxidiene Aromatic Hybrids

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Received 24 February 2000; accepted 17 April 2000

Abstract—The syntheses of simplified aromatic hybrids of the novel polyketide herboxidiene (**1**) are described. One of the hybrids prepared showed significant herbicidal activity against broad-leaved weeds in post-emergent application.

Herboxidiene (**1**) is a novel polyketide natural product isolated from *Streptomyces* sp. A 7847 by workers at Monsanto. This compound controls (>90%) several important biannual weeds at relatively low application rates (<250 g hectare^{-1}) without damaging wheat.[1] The relative and absolute configuration of **1** was deduced by a combination of X-ray analysis, asymmetric synthesis, and degradation studies,[2] and the first synthesis of the natural product has been reported.[3,4] The potent herbicidal activity of the molecule, as well as the recent discoveries that it up-regulates gene expression of low density lipoprotein receptors,[5] and shows anti-tumor activity,[6] suggest this natural product would be an ideal candidate for analogue synthesis.

Two features of herboxidiene are immediately striking: the *cis*-substituted tetrahydropyran acetic acid core, and the *E*,*E*-diene moiety situated between carbons 7–12.

We envisaged that incorporation of the *E*,*E*-diene moiety into a phenol ring, and subsequent attachment of various side chains would provide more stable, simplified analogues, that still retain the biological activity (Fig. 1). Such mimicking of a diene system has spectacular precedence with the *Strobilurin* class of fungicides.[7] In this paper we describe the syntheses of these compounds, and their herbicidal activity.

The central building block *cis*-[6-(3-hydroxy-phenyl)-tetrahydro-pyran-2-yl]- acetic acid methyl ester (**11**) was synthesised in racemic form as shown in Scheme 1, and involved intramolecular Michael addition of a hydroxyl functionality to a tethered acrylate system as the key step.[8] An advantage of this approach is that the reaction is thermodynamically controlled, so that the *cis*-substituted tetrahydropyran (with both bulky substituents equatorial) becomes almost the exclusive product when the reaction reaches equilibrium. Thus, Grignard reaction of *m*-bromoanisole **2** with cyclopentanone followed by in situ acid induced elimination of water yielded **3** in good overall yield. Protection group interconversion[9] was achieved in high yield by pyridinium hydrochloride dealkylation of **3**,[10] and subsequent protection of **4** with *tert*-butyldimethylsilylchloride (TBDMSCl). Standard dihydroxylation[11] of **5**, followed by sodium metaperiodate cleavage of the resultant racemic *cis*-diol **6**, led to the keto-aldehyde **7**. Wittig-Horner reaction of the latter gave the tethered acrylate system with excellent chemoselectivity as an 83:17 mixture of E:Z isomers. The isomers were separated by flash chromatography[12] and the *E*-isomer reduced with sodium borohydride to give the alcohol **9**, setting the stage for the intramolecular Michael addition. Under the conditions we previously reported for this type of addition,[8] smooth reaction occurred upon treatment of **9** with sodium hydride in THF at room temperature to give *cis*-substituted **10** as the sole product.[13] Removal of the TBDMS group was accomplished without problems using aqueous hydrofluoric acid in acetonitrile to yield pure racemic **11** as white crystals (melting point 89–90 °C, 32% from *m*-bromoanisole).[14] This synthesis has been carried out on a mole scale without difficulty.

The stereochemistry at C-2 in **10** is induced by the stereochemistry of the secondary alcohol moiety in **9**. It follows that an enantioselective synthesis of **11** can be achieved simply by reducing the ketone **8** with a chiral reagent. Thus, (−)-Ipc$_2$BCl (diisopinocampheyl-chloroborane) reduction of **8** at −25 °C in tetrahydrofuran gave the chiral alcohol **9** in reasonable yield after work

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PII: S0960-894X(00)00230-4

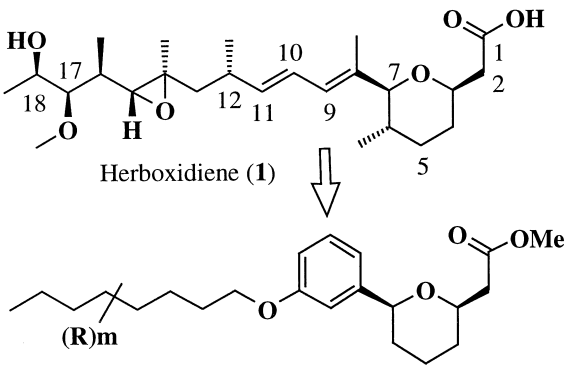


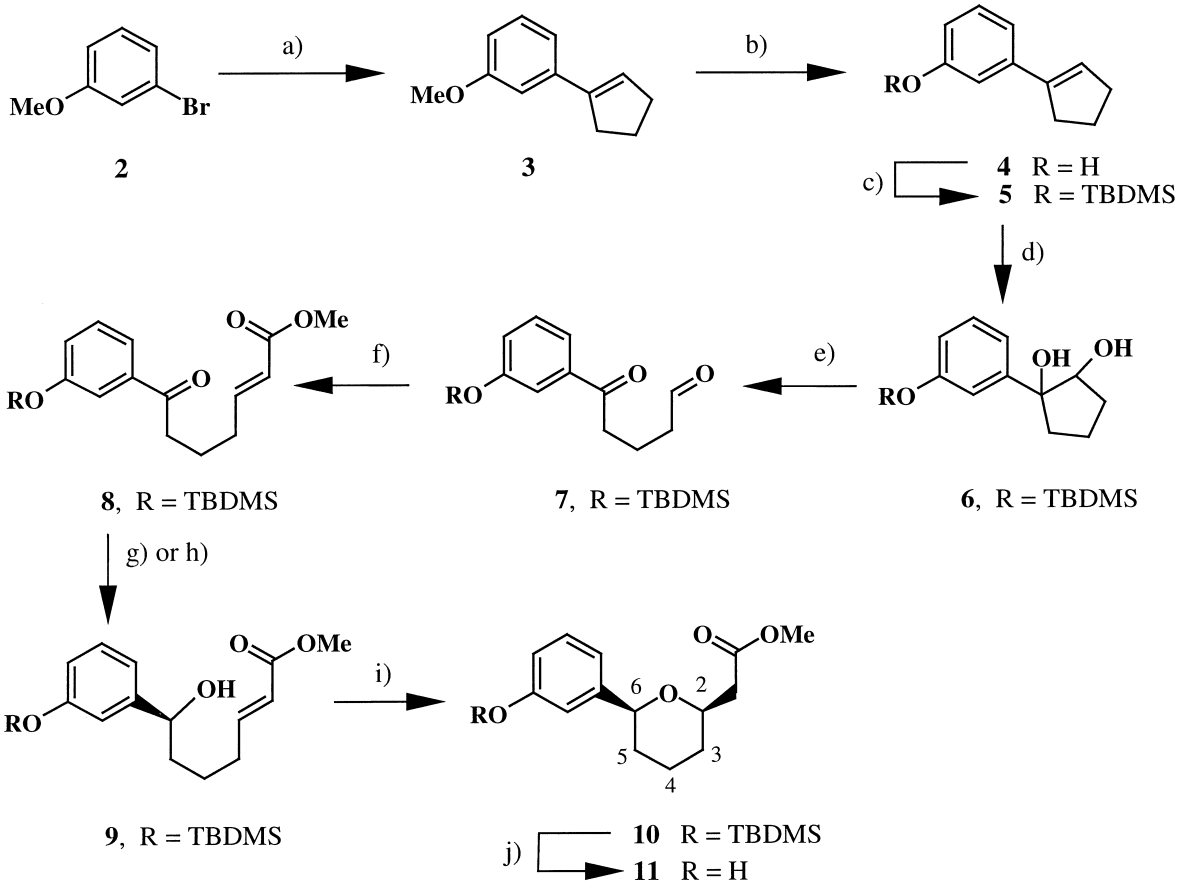
Figure 1. Aromatic hybrids of herboxidiene (**1**).

up and purification.[15a] Subsequent intramolecular ring closure and deprotection, as described in Scheme 1, led to (−)-**11** ($[\alpha]_D = -57.0°$ ($c = 1.0$, $CHCl_3$)) with 98% enantiomeric excess as determined by chiral HPLC analysis.[16] The mechanistic considerations of Brown[15a] and Marshall[15b] for this type of reduction enabled us to confidently predict that **9** was formed with the (*S*)-configuration.

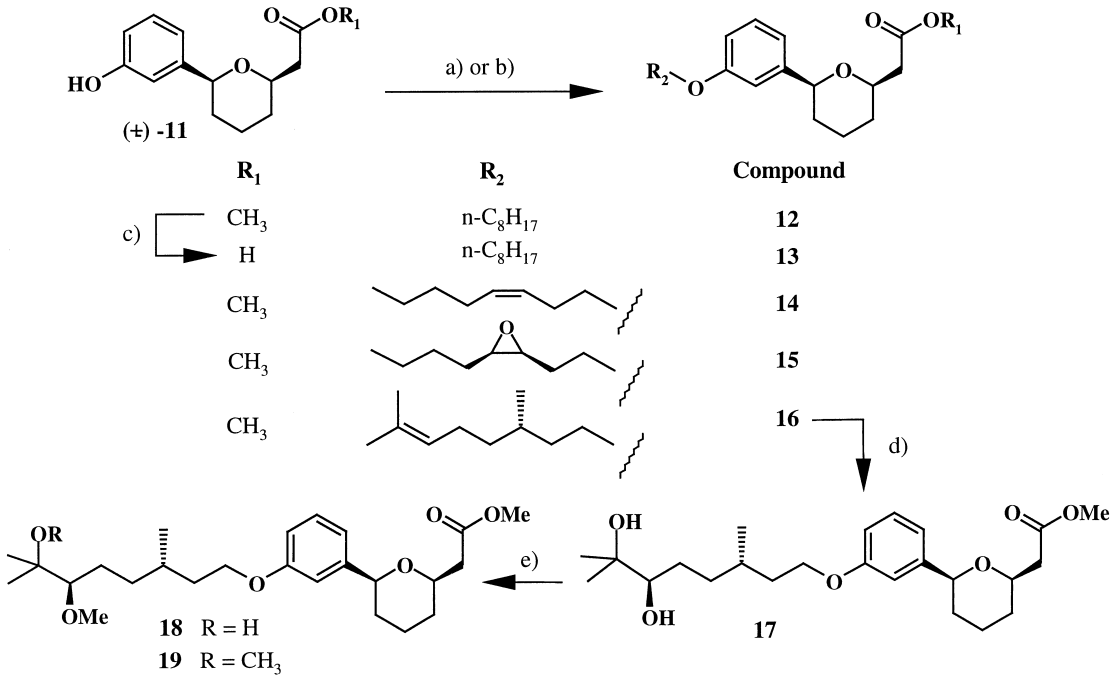
Several simple side chain mimics of herboxidiene were attached to racemic **11** by alkylation of the corresponding mesylates,[17] followed by straightforward manipulations of the products (Scheme 2). The asymmetric dihydroxylation of compound **16** was performed using AD-mix-β, and the stereochemical outcome is that predicted according to the mnemonic of Sharpless.[18] Alkylation of the resultant diol **17** gave dialkyl material **19**, and a monoalkyl derivative **18**. The position of the alkyl group in the latter was determined by $^1H/^{13}C$ HMBC spectroscopy.[19]

Of the derivatives shown in Scheme 2, we were pleased to find that **15** showed significant herbicidal activity, controlling the biannual weeds, *Abutilon*, *Amaranthus*, *Sinapis*, and *Solanum* to the extent of 10, 30, 40, and 90% respectively when applied post emergently at a rate of 1 Kg hectare^{-1}.[20] Although herboxidiene methyl ester is 100% effective at this application rate,[21] this would nevertheless indicate that the diene system can be mimicked by a phenol ring system of this type.

In conclusion, we have developed an efficient (asymmetric) synthesis of an aromatic tetrahydropyran acetic acid building block which can be used to prepare analogues of herboxidiene in which the *E,E*-diene moiety is replaced by a phenol ring. Significant herbicidal activity was found for one of the analogues prepared. Further studies on the synthesis of optically pure analogues of this type, with side chains more closely related to that of herboxidiene, will be reported elsewhere.



Scheme 1. Reagents and conditions: (i) Mg, THF, cyclopentanone, rt; (ii) Aqueous HCl (65% two steps); (b) Pyridinium.HCl, neat, 150 °C (100%); (c) TBDMSCl, Et_3N, DMAP(cat.), CH_2Cl_2, 0 °C to rt (94%); (d) *N*-Methylmorpholine oxide, OsO_4 (cat), Acetone:H_2O (3:1), rt (72%); (e) $NaIO_4$, THF:H_2O (4:1), rt (97%); (f) $Ph_3P{=}CHCO_2Me$, THF, rt (89%); (g) $NaBH_4$, THF, rt (98%) or (h) (−)-Ipc_2BCl, THF, −25 °C (56%); (i) NaH, THF, rt (92%); (j) HF (40% in H_2O):CH_3CN (95:5), (95%).



Scheme 2. Reagents and conditions: (a) R_2OSO_2Me, NaH, DMF, 0 °C to rt; (b) R_2OSO_2Me, K_2CO_3, DMF, 50 °C; (c) LiOH.H_2O, MeOH:H_2O (4:1); (d) AD-mix-β, *t*-BuOH:H_2O (1:1), 0 °C to rt; (e) Ag_2O, MeI, DMF, 50 °C.

References and Notes

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9. The *tert*-butyldimethylsilane (TBDMS) group was chosen as the protecting group to allow selective, mild deprotection at the final step in the syntheses. All attempts to directly add the TBDMS-protected Grignard to cyclopentanone failed, reduced Grignard being the only product obtained.
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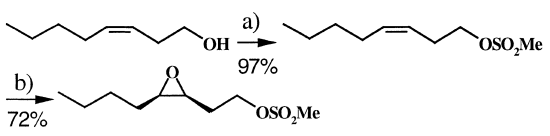
12. A mixture of the E and Z isomers can actually be used for the ring closure step but it was more convenient to separate isomers to simplify the GC analysis for this process. The effect of double bond geometry on kinetic intramolecular Michael addition reactions of this type has been reported. See; Banwell, M. G.; Bissett, B. D.; Bui, C. T.; Pham, Ha T. T.; Simpson, G. W. *Aust. J. Chem.* **1998**, *51*, 9.
13. As determined by gas chromatography analysis after thermodynamic equilibrium.
14. [(2*R*,6*S*)-6-(3-Hydroxy-phenyl)-tetrahydropyran-2-yl] acetic acid methyl ester (**11**): ^{1}H NMR (300 MHz, $CDCl_3$): 1.32.54, m, 2H; 1.63.75, m, 2H; 1.82, m, 1H; 1.91.97, m, 1H; 2.50, dd (J=15.3, 5.4 Hz), 1H; 2.68, dd (J=15.3, 7.5 Hz), 1 H; 3.68, s, 3H; 3.93.02, m, 1H; 4.45, dd (J=11.4, 2.1 Hz), 1H; 6.20, br s, 1H; 6.69, dd (J=8.1, 2.4 Hz), 1H; 6.81, d (J=2.4 Hz), 1H; 6.84, d (J=8.1 Hz), 1H; 7.13 ppm, t (J=8.1 Hz), 1H. ^{13}C NMR (75.4 MHz, $CDCl_3$): 23.4 (t); 30.7 (t); 32.6 (t); 41.3 (t); 51.7 (q); 74.5 (d); 79.4 (d); 112.9 (d); 114.1 (d); 117.5 (d); 129.1 (d); 144.2; 155.8; 172.5 ppm. Electron Spray MS (+Mode): 251 (MH^+, 100%); 207(18%): 131 (35%); 93 (15%).
15. (a) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539. (b) Midland, M. M.; McLoughlin, J. J. *J. Org. Chem.* **1984**, *49*, 1316.
16. Determined by HPLC analysis on a Chiracel OD-H column, eluting with 95:5 hexane:isopropyl alcohol.
17. The mesylates required for the preparation of compounds **12**, **14** and **16** were prepared by treatment of the commercially available alcohols with $MeSO_2Cl$, Et_3N, in CH_2Cl_2 according to standard procedures. The mesylate required for preparation of compound **15** was prepared as follows:



Reagents: (a) $MeSO_2Cl$, Et_3N, DMAP(cat.), CH_2Cl_2, 0 °C to rt (b) *meta*-Chlorperbenzoic acid, $NaHCO_3$, CH_2Cl_2, rt.
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19. ^{1}H NMR (300 MHz, $CDCl_3$) for **18**: 0.98, d (J=5.1 Hz), 3H; 1.18, s, 3H; 1.20, s, 3H; 1.10.05, m, 13H; 2.48, dd, (J=15.8, 5.9 Hz), 1H; 2.68, dd (J=15.8, 6.9 Hz), 1H; 2.90, dd,

(J = 6.9, 2.2 Hz), 1H; 3.50, s, 3H; 3.68, s, 3H; 3.88.90, m, 1H; 3.95, t (J = 6.9Hz), 2H; 4.38, d (J = 11.4 Hz), 1H; 6.75, br d (J = 7.2 Hz), 1H; 6.82.94, m, 2H; 7.21 ppm, t, (J = 7.2 Hz), 1H. ^{13}C NMR (75.4 MHz, $CDCl_3$): 20.7 (q); 24.6 (t); 25.2 (q); 27.2 (q); 29.0 (t); 31.2 (d); 32.3 (t); 33.8 (t); 35.0 (t); 36.8 (t); 42.1 (t); 52.6 (q); 61.9 (q); 66.8 (t); 74.0; 75.7 (d); 80.1 (d); 90.0 (d); 113.0 (d); 113.9 (d); 118.7 (d); 129.8 (d); 145.5; 159.9; 172.2: The position of the alkyl group was determined by ^{1}H/^{13}C HMBC spectroscopy; The dd at 2.90 ppm ($(CH_3)_2C(OH)\underline{C}\overline{H}(OCH_3)CH_{2-}$) correlated with the ^{13}C signals at 61.9 ppm ($O\overline{C}H_3$), 74.0 ppm ($(CH_3)_2\underline{C}(OH)CH(OCH_3)CH_{2-}$), and 24.6 ppm ($(CH_3)_2C(OH)CH(O\overline{C}H_3)\underline{C}H_{2-}$). ^{1}H NMR (300 MHz, $CDCl_3$) for **19** (inter alia); 3.78, dd (J = 7.9, 4.5Hz), 1H, $(CH_3)_2C(OCH_3)C\underline{H}(OCH_3)CH_2$-); 3.31, s, 3H ($OCH_3\underline{)}$; 3.37 ppm, s, 3H, ($OC\overline{H_3}$).

20. The dicotyledon test plants were cultivated under optimal greenhouse conditions with standard earth, and the test substances applied as 25% emulsion concentrates at the 4–6 leaf stage at the rates of active ingredient of 1 Kg hectare^{-1}. The plants were then further cultivated under optimal greenhouse conditions and after ca. 18 days the percentage plant damage rated by visual assessment.

21. The methyl ester of herboxidiene is actually more potent than the parent compound. See ref 1.