Synthesis of the Trichothecene Mycotoxin, T-2 Tetraol

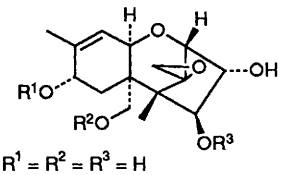
Ernest W. Colvin,* Mark J. Egan, and Fraser W. Kerr

Department of Chemistry, University of Glasgow, Glasgow G12 8QQ, UK

The synthesis, as its tetra-acetate (neosolaniol diacetate) (**21**), of T-2 tetraol (**1**), the parent member of a group of trichothecene mycotoxins including the highly toxic T-2 toxin (**2**) and HT-2 toxin (**3**), is described.

The trichothecene mycotoxins constitute a major group of complex fungal sesquiterpenoids.[1] They possess a wide range of largely adverse biological behaviour, including antibacterial, antiviral, cytostatic and phytotoxic activity. Despite some 80 non-macrocyclic trichothecenes being known, only a few have yielded to total synthesis;[2] these include trichodermin,[3] trichodermol,[4] verrucarol,[5] anguidine,[6] calonectrin,[7] and 12,13-epoxytrichothec-9-ene.[8]

Continuing our studies on the syntheses[3,9] and synthetic transformations[10] of the trichothecene mycotoxins, we communicate the first synthesis of the complex trichothecene, T-2 tetraol (**1**). The synthetic sequence is outlined in Scheme 1. Our synthetic strategy consisted of five key elements: (a) construction of the *cis*-fused *AB* ring system by a Diels–Alder cycloaddition, (b) formation of ring *C* by an intramolecular aldol reaction, (c) creation of the 3α,4β diol functionality of ring *C* by a stereoselective α-oxygenation/reduction protocol, (d) ring *A* enone formation *via* a regiospecific thermodynamically controlled α-selenylation, and (e) regio- and stereospecific reduction of this enone to the required α-alcohol.

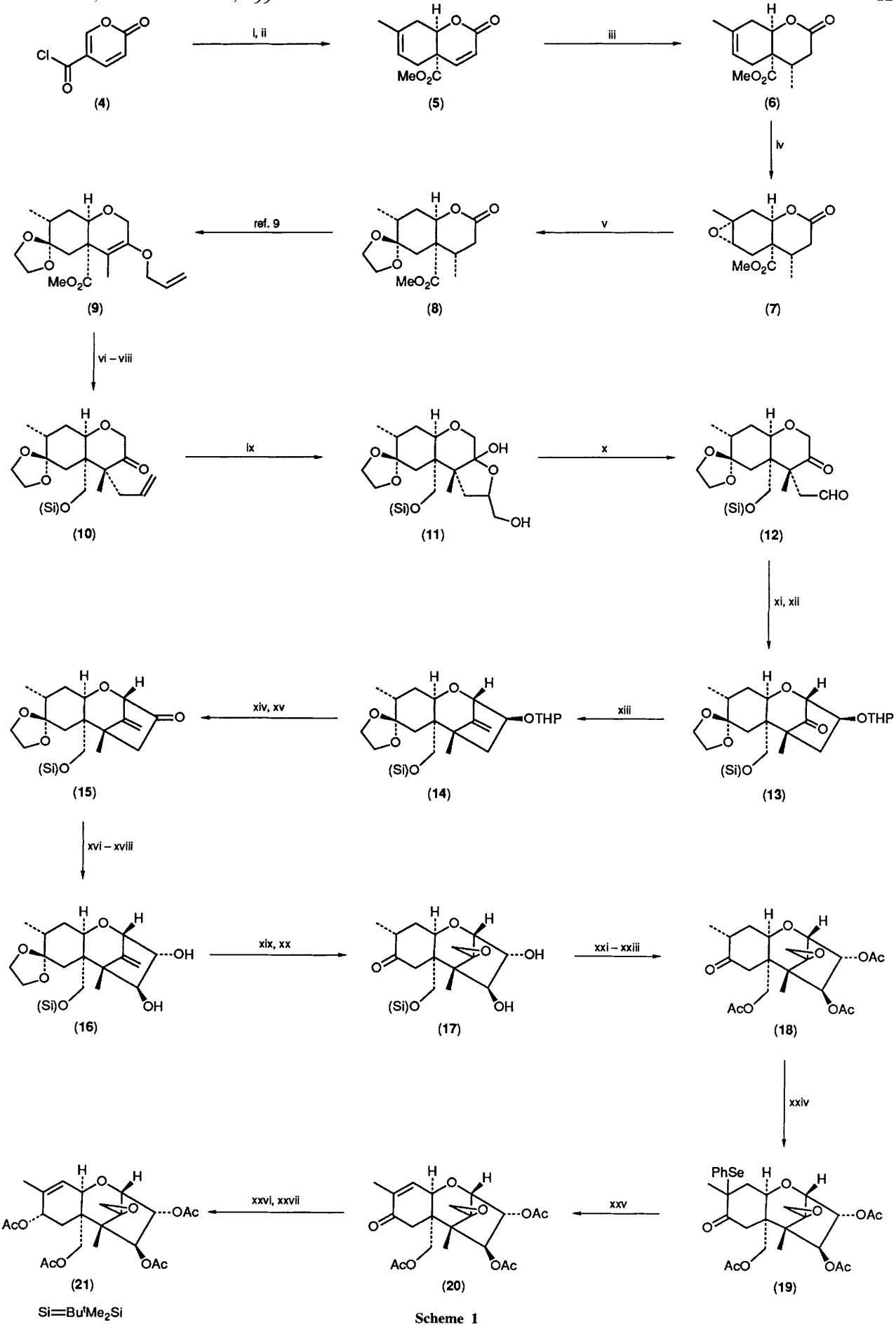


(**1**) $R^1 = R^2 = R^3 = H$

(**2**) $R^1 = (Me)_2CHCH_2CO$, $R^2 = R^3 = Ac$

(**3**) $R^1 = (Me)_2CHCH_2CO$, $R^2 = Ac$, $R^3 = H$

Scheme 1. *Reagents and conditions:* i, isoprene, toluene, 120 °C (sealed tube), 1 h; ii, MeOH, Et_3N, 0 °C, 41% overall; iii, $LiCuMe_2$, Me_3SiCl, Et_2O, −78 °C to room temp., 55%; iv, *m*-chloroperbenzoic acid (MCPBA), Na_2HPO_4, CH_2Cl_2, 0 °C, 2.5 h, 81%; v, ethane-1,2-diol, $BF_3{\cdot}Et_2O$, CH_2Cl_2, room temp., 18 h, 61%; vi, $LiAlH_4$, Et_2O, 0 °C, 0.5 h, 94%; vii, toluene, Et_3N (5%), 110 °C, 24 h, 89%; viii, $Bu^tMe_2SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, room temp., 0.5 h, 89%; ix, $NaIO_4$, OsO_4 (cat.), Et_2O, H_2O, room temp., 18 h, 88%; x, H_5IO_6, Et_2O, room temp., 5 min; xi, NaOMe, MeOH, reflux, 0.5 h, 62% overall; xii, dihydropyran, PPTS, room temp., 12 h; xiii, $Ph_3P{=}CH_2$, tetrahydrofuran (THF), hexane, reflux, 18 h; xiv, ethane-1,2-diol, PPTS, CH_2Cl_2, reflux, 18 h, 61% overall; xv, CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2, room temp., 1 h, 81%; xvi, $KN(SiMe_3)_2$, toluene, THF, 0 °C, 1 h; xvii, 2-*p*-tolylsulphonyl-3-(*p*-nitrophenyl)oxaziridine, THF, −78 °C to room temp.; xviii, $NaBH_4$, MeOH, 0 °C, 0.5 h, 37% overall; xix, MeOH, PPTS, room temp., 48 h, 90%; xx, MCPBA, Na_2HPO_4, CH_2Cl_2, room temp., 48 h, 50%; xxi, Ac_2O, pyridine (py), Et_2O; xxii, $Bu_4NF{\cdot}3H_2O$, THF, room temp., 48 h; xxiii, Ac_2O, py, 84% overall; xxiv, PhSeCl, PPTS, AcOEt, room temp., 48 h, 85%; xxv, O_3, CH_2Cl_2, −78 °C to room temp., 72%; xxvi, $LiBu^s_3BH$, THF, −78 °C[5] to room temp., 1 h; xxvii, Ac_2O, py, 88% overall.


i, ii
iii
iv
v
ref. 9
vi – viii
ix
x
xi, xii
xiii
xiv, xv
xvi – xviii
xix, xx
xxi – xxiii
xxiv
xxv
xxvi, xxvii
(4)
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(14)
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(16)
(17)
(18)
(19)
(20)
(21)
Si=BuᵗMe₂Si

Scheme 1

Cycloaddition[11] of coumalyl chloride (**4**) with isoprene followed by esterification of the product mixture gave the adduct (**5**)† and its regioisomer (isomeric ratio 4:1). Treatment of this mixture with lithium dimethyl cuprate gave, after purification,‡ the lactone (**6**) as a single methyl epimer. Epoxidation provided the epoxide (**7**), again as a single epimer, reaction of which with ethane-1,2-diol in the presence of $BF_3{\cdot}Et_2O$ provided the ketal (**8**).

Following established methodology,[9] two-step oxidation of the lactone enolate to the α-ketolactone, followed by allylation of this in its enol form and reductive deoxygenation gave the allyl enol ether (**9**). Hydride reduction of the ester function, followed by Claisen rearrangement and alcohol protection using t-butyldimethylsilyl trifluoromethanesulphonate[12] provided the α-allyl ketone (**10**) and its epimer (epimeric ratio 3.2:1). Attempted ozonolysis, to generate the required aldehyde moiety, proved unsuccessful. Remarkably, catalytic osmylation in the presence of sodium metaperiodate stopped at the diol stage, with isolation of the tetrahydrofuran (**11**). However, treatment of this with ethereal periodic acid[13] resulted in clean cleavage to the desired aldehyde (**12**).

Aldol cyclisation followed by pyridinium toluene-*p*-sulphonate (PPTS) catalysed[14] tetrahydropyranylation gave the full tricyclic system, as a mixture of 3β (**13**) and 3α epimers (epimeric ratio 4.2:1). The more abundant 3β epimer was subjected to the Wittig reaction to give the alkene (**14**). Selective tetrahydropyran (THP) ether deprotection, using ethane-1-2-diol in the presence of PPTS, followed by chromium trioxide–3,5-dimethylpyrazole[15] oxidation led to the ketone (**15**).

Oxaziridine-mediated α-hydroxylation[16] of the enolate of this ketone, followed by hydride reduction gave the desired 3α,4β diol (**16**), both reagents having attacked from the less hindered *exo* face of the oxabicyclo[3.2.1]octane sub-unit.[17] Selective acetal deprotection followed by epoxidation gave the keto-epoxide (**17**).

Fluoride-induced deprotection and per-acetylation gave the keto-triacetate (**18**). This ketone was identical in all respects, apart from being racemic, with the ketone obtained by catalytic hydrogenation of the naturally derived[10b] enone (**20**). This latter homochiral ketone (**18**) was used to complete the synthesis. PPTS-catalysed α-selenylation provided the selenide (**19**) as a mixture of epimers, but regioisomerically pure. Selenoxide formation and cycloelimination then provided the enone (**20**). Regio- and stereo-specific reduction of this enone using lithium tri-S-butylborohydride provided the 8α alcohol. Acetylation provided T-2 tetraol tetra-acetate (**21**), $[\alpha]_D^{25}$ +55.5° (*c* 0.128 in AcOEt), m.p. 182–183 °C (lit.,[18] 178—179 °C), with spectral properties identical in all respects with literature data.[18,19]

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† Compounds (**5**)—(**18**) are racemic; all other stereochemically defined compounds are homochiral.

‡ All reported compounds were fully characterised by elemental analysis and/or high resolution mass spectrometry, and IR and ^1H and ^{13}C NMR spectroscopy.

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