A Synthetic Approach to Zoapatanol and Related Bicyclic Analogues

Richard Whitby,[a] Clive Yeates,[a] Philip Kocieński,*[a] and Gerard Costello[b]

[a] *Department of Chemistry, The University, Southampton, SO9 5NH, U.K.*
[b] *Imperial Chemical Industries PLC, Pharmaceuticals Division, Macclesfield, Cheshire, SK10 2NA, U.K.*

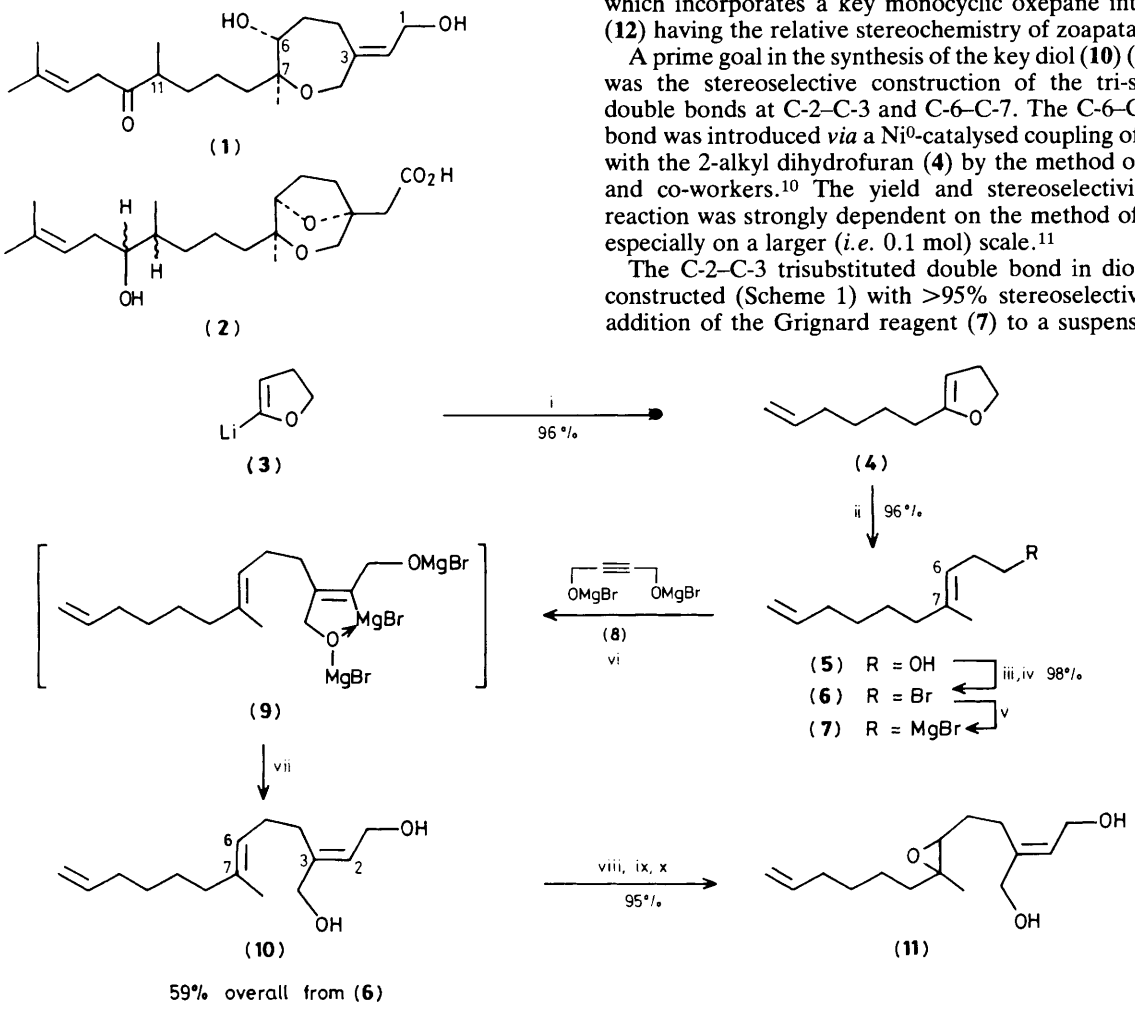
A Ni^0-catalysed coupling of MeMgBr with dihydrofuran (**4**) and addition of Grignard reagent (**7**) to a butyne-1,4-diol derivative (**8**) were key steps in the highly stereoselective construction of the trisubstituted double bonds in (**10**) which is a precursor to the oxepane ring system (**12**) of zoapatanol (**1**); subsequent elaboration of (**12**) gave (1*R**,4*S**,5*R**)-4-[5-oxo-8-methylnon-7-enyl]-3,8-dioxabicyclo[3.2.1]octane-1-acetic acid (**18**), a demethyl analogue of the potent antigestational agent ORF 13811 (**2**).

Zoapatanol (**1**) is an active constituent of the zoapatle plant *Montanoa tomentosa* which Mexican women have used for the past four centuries to induce menses and labour.[1,2] Several syntheses of zoapatanol have been reported[3—6] which corroborate the stereochemistry of the ring system but the diastereocontrolled introduction of the remote C-11 methyl group has not been attempted because the stereochemistry at C-11 has never been established; in fact, none of the structural evidence presented to date vouches for the stereochemical integrity of the side-chain methyl group in natural zoapatanol.[1]

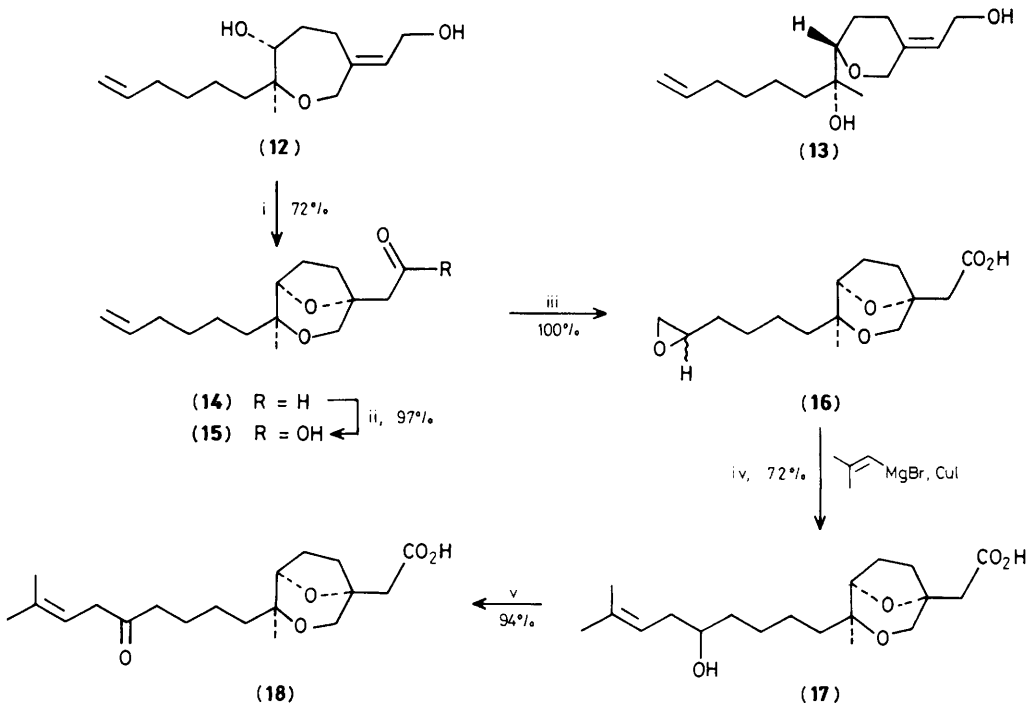
Recent interest in the use of zoapatanol in reproductive medicine has led to the development of a number of 3,8-dioxabicyclo[3.2.1]octane analogues which are much more active than zoapatanol itself and it has been suggested that *in vivo* transformations of the monocyclic oxepane to the bicyclic system, an easy transformation *in vitro*,[1,3] is a prerequisite for biological activity.[7] The 3,8-dioxabicyclo-[3.2.1]octane-1-acetic acid analogue ORF 13811 (**2**) has recently been extensively investigated[8,9] for use as a contragestational agent and is characterised by effects on uterine and vascular smooth muscle contractility similar to those induced by prostaglandin $F_{2\alpha}$. We now report a highly stereoselective synthesis of the C-11 demethyl analogue (**18**) of ORF 13811 which incorporates a key monocyclic oxepane intermediate (**12**) having the relative stereochemistry of zoapatanol.

A prime goal in the synthesis of the key diol (**10**) (Scheme 1) was the stereoselective construction of the tri-substituted double bonds at C-2–C-3 and C-6–C-7. The C-6–C-7 double bond was introduced *via* a Ni^0-catalysed coupling of MeMgBr with the 2-alkyl dihydrofuran (**4**) by the method of Wenkert and co-workers.[10] The yield and stereoselectivity of this reaction was strongly dependent on the method of work-up, especially on a larger (*i.e.* 0.1 mol) scale.[11]

The C-2–C-3 trisubstituted double bond in diol (**10**) was constructed (Scheme 1) with >95% stereoselectivity by the addition of the Grignard reagent (**7**) to a suspension of the



Scheme 1. *Reagents:* i, 1-iodohex-5-ene–tetrahydrofuran (THF), −20 → 50 °C; ii, MeMgBr (2 equiv.), $(PPh_3)_2NiCl_2$ (0.1 equiv.)–benzene, 60—78 °C, 45 min; iii, $MeSO_2Cl$, NEt_3–CH_2Cl_2, −10 °C; iv, LiBr–acetone, 20 °C, 22 h; v, Mg–Et_2O; vi, add (**7**) to (**8**) (1.1 equiv.), THF–Et_2O, reflux, 5 h; vii, saturated aqueous NH_4Cl; viii, AcCl, NEt_3–CH_2Cl_2, −5 °C; ix, *m*-$ClC_6H_4CO_3H$–CH_2Cl_2, −5 °C; x, K_2CO_3–MeOH, 0 °C, 40 min.



Scheme 2. *Reagents:* i, MnO_2–CH_2Cl_2, 5 min; ii, pyridinium dichromate–dimethylformamide (DMF), 20 °C, 20 h; iii, *m*-$ClC_6H_4CO_3H$–CH_2Cl_2, 20 °C, 4 h; iv, $Me_2C{=}CHMgBr$, 10 mol% CuI–THF, −40 °C, 1 h; v, pyridinium dichromate–DMF, 0 °C, 1 h.

acetylene (**8**) in ether followed by heating. On aqueous work-up a 58% yield of diol (**10**) [from bromide (**6**)] was obtained. The ease and high *trans*-stereoselectivity of this unusual addition[12] probably reflect the internal co-ordination of the alkenylmagnesium bromide intermediate (**9**). Trivial reactions were then used to convert (**10**) into the epoxy diol (**11**).

On treatment with 1.1 equiv. of $SnCl_4$ in tetrahydrofuran at −20—0 °C, epoxy-diol (**11**) cyclised in 72% yield to a 10:1 mixture of the desired oxepane (**12**) and the pyran (**13**) respectively. We have verified[13] the sensitivity of the ratio (**12**):(**13**) to Lewis acid-catalyst, as recently reported by Cookson and Liverton.[6] An analogous epoxy-diol has been isolated from *M. tomentosa* and it has suggested[14] that a similar acid-catalysed cyclisation accounts for the origin of the oxepane ring in zoapatanol *in vivo*. In five steps (Scheme 2), diol (**12**) was converted into the 3,8-dioxabicyclo[3.2.1]-octane-1-acetic acid derivative (**18**) (colourless oil) in 47% overall yield from (**12**): δ_H (360 MHz, $CDCl_3$) 1.15—1.40 (4H, m), 1.28 (3H, s), 1.52 (2H, m), 1.59 (3H, s), 1.71 (3H, s), 1.7—1.8 (3H, m), 2.09 (2H, m), 2.39 (2H, t, *J* 7 Hz), 2.58 (2H, ABq, *J* 12 Hz), 3.05 (1H, d, *J* 7 Hz), 3.43 (1H, d, *J* 11 Hz), 3.74 (1H, d, *J* 11 Hz), 3.84 (1H, d, *J* 11 Hz), 5.25 (1H, t, *J* 7 Hz), 9.2 (1H, br. s, CO_2H); δ_C (90 MHz, $CDCl_3$) 18.02 (q), 18.23 (q), 22.77 (t), 24.40 (t), 25.02 (t), 25.68 (q), 31.49 (t), 38.46 (t), 40.13 (t), 41.92 (t), 42.73 (t), 69.54 (t), 75.33 (s), 79.33 (s), 81.48 (d), 116.07 (d), 136.0 (s), 173.86 (s), 209.49 (s); *m/z* 338 (M^+, 20%), 269 (46), 251 (15), 226 (7), 205 (9), 161 (7), 157 (10), 143 (13), 139 (25), 127 (33), 111 (27), 109 (34), 97 (29), (25), 81 (100), 69 (57), 43 (84).

In conclusion, we have developed an efficient and flexible route to the zoapatanol ring system and bicyclic analogues which incorporates two highly stereoselective tri-substituted alkene syntheses. All of the reactions can be run on a substantial scale.

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