Diastereoselection in an Aqueous Diels–Alder Reaction: a Formal Total Synthesis of the Inhoffen–Lythgoe Diol

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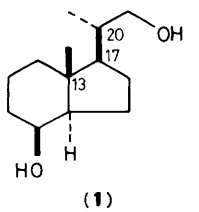
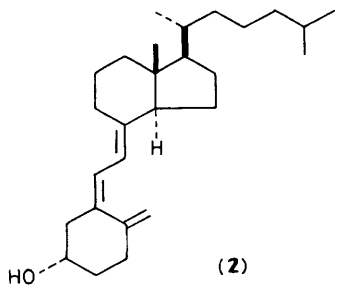
A formal synthesis of the Inhoffen–Lythgoe diol (**1**) featuring a novel intermolecular Diels–Alder strategy wherein an intact C(20) stereocentre as part of a diene unit is used to elaborate directly the stereocentres at C(13) and C(17) of the hydrindan ring system of (**1**), is reported.

Recent interest in vitamin D_3(**2**) and related metabolites has been responsible, in part, for a flurry of synthetic activity centred around construction of *C/D trans*-fused hydrindan ring systems possessing side chain stereochemistry at C(20) [*cf.* the Inhoffen–Lythgoe diol (**1**)].[1] Most of the approaches investigated to date feature elaboration of the C(20) stereocentre onto a partially or fully constructured *C/D trans*-fused ring system.[2] Herein we report a novel intermolecular Diels–Alder strategy in which an intact C(20) stereocentre is used to elaborate directly the stereocentres at C(13) and C(17) of a latent *C/D trans*-fused hydrindan ring system [*e.g.* (**3**) → (**4**) → (**5**), Scheme 1].[3] Manipulation of the Diels–Alder adduct (**4**) gives rise to the known hydrindan (**5**) which constitutes a formal total synthesis of the Inhoffen–Lythgoe diol (**1**),[4] as well as vitamin D_3 and related metabolites.[5]

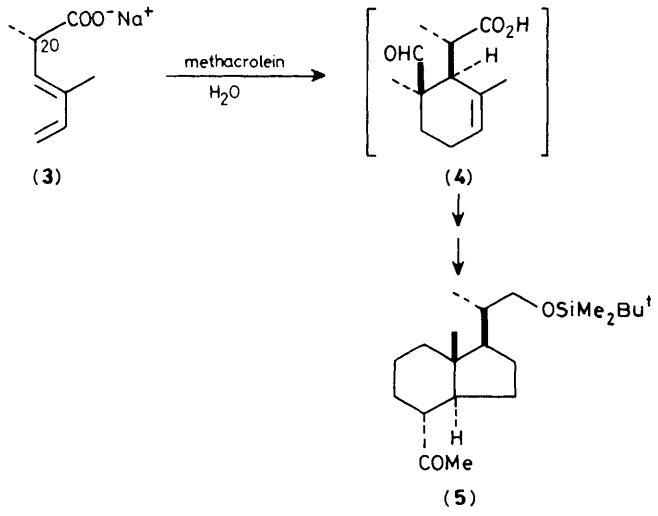
The chiral diene acid (**9**), which serves as the starting material for the preparation of hydrindan (**5**), is readily accessible in *ca.* 50% overall yield from commercially available material. Silylation [Bu^tPh_2SiCl, Et_3N, 4-*N*,*N*-dimeth-



(**1**)

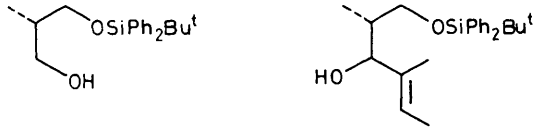


(**2**)



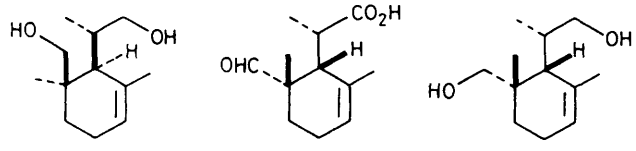
(3) (4) (5)

Scheme 1

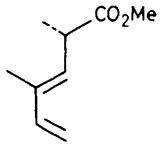


(6) (7)

(9) (8)



(10) (11) (12)



(13)

ylaminopyridine (DMAP), CH_2Cl_2] of (*R*)-(−)-methyl-3-hydroxy-2-methylpropionate and subsequent reduction [$LiBH_4$, tetrahydrofuran (THF)] of the ester unit generates alcohol (**6**). Oxidation [pyridinium chlorochromate (PCC), NaOAc, CH_2Cl_2, 0 °C] of (**6**) followed by treatment (THF, −30 °C) of the resulting aldehyde with the Grignard reagent

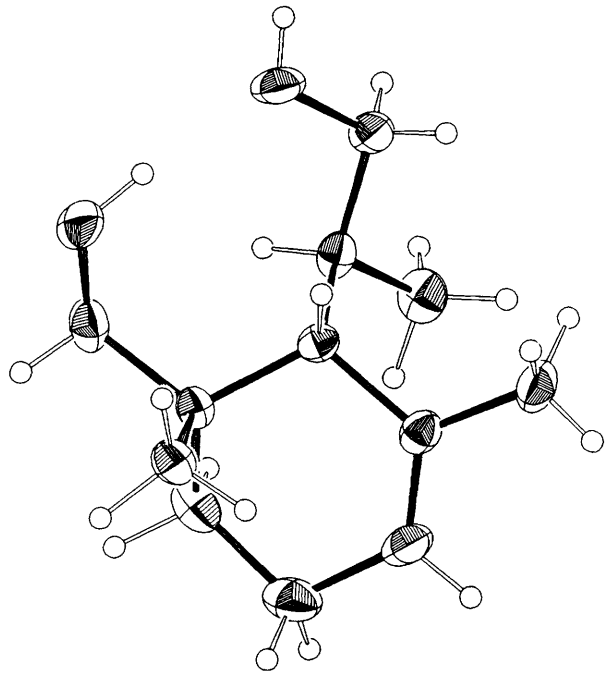
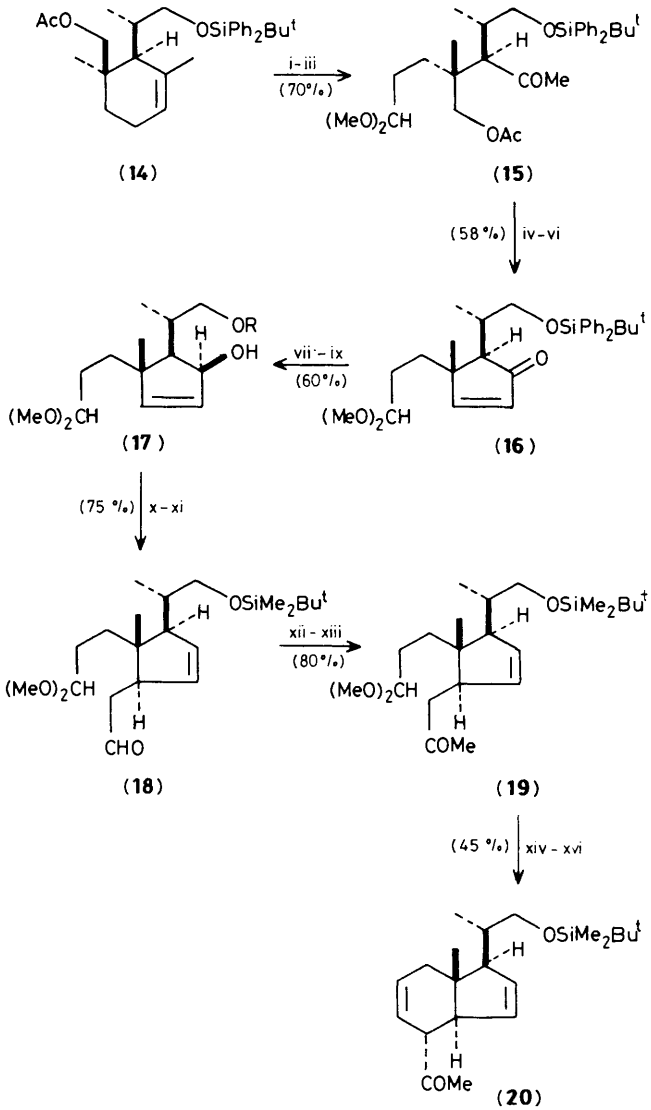


Figure 1. ORTEP drawing of the diol (**12**).

derived from 2-bromobut-2-ene provides allylic alcohol (**7**) as a mixture of diastereoisomers. Transformation of (**7**) into diene (**8**), $[\alpha]_D^{25}$ +34.8° (*c* 1.00, $CHCl_3$) was accomplished in 76% overall yield *via* a tandem sulphenate–sulphoxide [2,3] sigmatropic rearrangement/*syn* elimination sequence employing 2,4-dinitrobenzenesulphenyl chloride in ethylene dichloride containing triethylamine.[6] Desilylation [tetrabutylammonium fluoride (TBAF), THF, 2.5 h] and subsequent Jones oxidation affords diene carboxylic acid (**9**) $[\alpha]_D^{25}$ +177.6° (*c* 0.69, $CHCl_3$), in 72% overall yield. Remarkably, condensation[7] of methacrolein with the sodium salt of (**9**) (5 equiv., 2.0 M in water) at 55 °C for 16 h gives rise to carboxylic acid (**4**), (*ca.* 70% yield), which was directly treated at 0 °C with lithium aluminium hydride in THF, giving rise to crystalline diol (**10**), [90% yield, m.p. 107—108 °C, $[\alpha]_D^{25}$ +122.9° (*c* 1.00, $CHCl_3$)]. Approximately 15% of the diastereoisomeric adduct (**11**) could be isolated from the aqueous Diels–Alder reaction. Reduction of (**11**) under identical conditions affords diol (**12**) {m.p. 133—134 °C, $[\alpha]_D^{25}$ −149.8° (*c* 1.22, $CHCl_3$)}. The structures of diols (**10**) and (**12**) follow directly from a single crystal *X*-ray analysis of the minor diol (**12**) (Figure 1).† It is noteworthy that use of the methyl ester

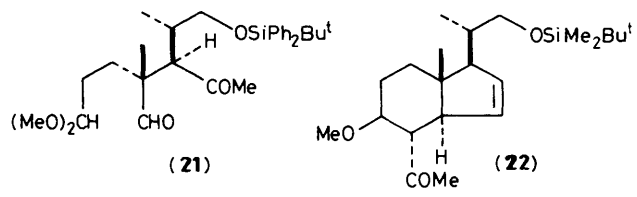
† *Crystal data* for (**12**): $C_{12}H_{22}O_2$, *M* = 198.30, monoclinic, space group $P2_1$, *a* = 5.963(2), *b* = 8.757(4), *c* = 11.376(5) Å, β = 101.17(3)°, *U* = 582.76 Å^3, D_c = 1.130 g cm^{-1}, *Z* = 2, Mo-K_α radiation, 1652 data collected, 824 unique, $6 < 2\theta < 45°$, *R* = 0.0257, R_w = 0.0281. The structure was solved by direct methods (MULTAN). All non-hydrogen atoms were readily located, and all hydrogen atoms were located following initial least-squares refinement. The full-matrix least-squares refinement was completed using anisotropic thermal parameters on all non-hydrogen atoms and individual isotropic thermal parameters on the hydrogen atoms. The final *R* value was 0.026. The final difference map was featureless, the largest peak was 0.104 eÅ^{-3}. The molecule has an internal hydrogen bond of 2.73 Å between O(9) and O(12), and an intermolecular hydrogen bond between O(9) and O(12) (54502) of 2.71 Å. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.



Scheme 2. Synthesis of the *trans*-hydrindan ring system (**20**). *Reagents and conditions*: i, OsO_4, pyridine, 13.5 h; ii, $NaIO_4$, MeOH, THF, 20 h; iii $CH(OMe)_3$, MeOH, $CeCl_3 \cdot xH_2O$, 10 h; iv, $LiBH_4$,THF, 3 h; v, $(COCl)_2$ dimethyl sulphoxide, Pr^i_2NEt, CH_2Cl_2, −78 °C; vi, KOH, EtOH, 30 min; vii, $NaBH_4$, $CeCl_3 \cdot xH_2O$, EtOH; viii, TBAF, THF, 30 min; ix Bu^tMe_2SiCl, Et_3N, DMAP, CH_2Cl_2, 2 h; x, ethyl vinyl ether, $Hg(OAc)_2$, 24 h; xi, decalin, 2 h, reflux; xii, MeLi, Et_2O, −78 °C; xiii, PCC, NaOAc, CH_2Cl_2, 1.5 h; xiv, hexamethyldisilazide, Me_3SiI, pentane, 3 h; xv, $ZnCl_2$, Et_2O, CH_2Cl_2, 12 h; xvi, $KOBu^t$, Et_2O, 2 h.

(**13**) in excess of neat methacrolein at 55 °C required 63 h to realize only a 10% yield of a 1:1 mixture of Diels–Alder adducts. Most surprising was the fact that no diastereoselectivity was observed.

With diol (**10**) available as a diastereoisomerically pure substance, our studies focused on elaboration of (**10**) into hydrindan (**5**) (Scheme 2). Selective protection of the less hindered alcohol in diol (**10**) employing t-butyldiphenylsilyl chloride in methylene chloride containing triethylamine and DMAP followed by acetylation (acetic anhydride, pyridine) readily provided (**14**), $[\alpha]_D$ +78.8° (*c* 0.99, $CHCl_3$), in 90% overall yield. Subsequent oxidative cleavage of the olefinic bond in (**14**) afforded the corresponding keto aldehyde which was directly transformed into keto acetal (**15**).[8] Treatment of



(**15**) with lithium borohydride in THF provided the corresponding diol (88%) which was oxidized to the corresponding ketoaldehyde (**21**). This was directly subjected to aldol condensation providing cyclopentenone (**16**), $[\alpha]_D^{25}$ +37.1° (*c* 1.15, $CHCl_3$). Reduction[9] of cyclopentenone (**16**) afforded the desired alcohol (**17**; R = $SiPh_2Bu^t$).

Chirality transfer from C(16) to C(14) was envisaged to proceed *via* a Claisen rearrangement which required replacing the t-butyldiphenylsilyl protecting group with a t-butyldimethylsilyl group. Aldehyde (**18**) was directly transformed into methyl ketone (**19**), $[\alpha]_D^{25}$ +8.2° (*c* 1.92, MeOH), which was converted into its corresponding thermodynamic silyl enol ether[10] and subjected to zinc chloride induced aldol condensation,[11] providing (**22**) in 75% yield. Elimination of the β-methoxy group afforded not the expected product, but instead the equilibrated product (**20**), $[\alpha]_D^{25}$ +40.4° (*c* 0.51, MeOH). Reduction (H_2–Pd, EtOAc) of diene (**20**) generated the known *trans*-fused hydrindan (**5**) 96% yield which has been transformed into the Inhoffen–Lythgoe diol (**1**).[2c]

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