Polyquinanes from (*R*)-(+)-Limonene. Enantioselective Total Synthesis of the Novel Tricyclic Sesquiterpene (−)-Ceratopicanol

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The first total synthesis of the biogenetically important and structurally novel triquinane sesquiterpene (−)-ceratopicanol has been accomplished.

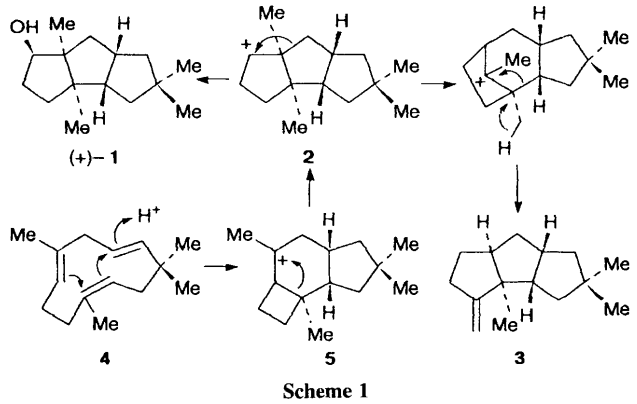
The Basidiomycotina provide a rich and varied source of structurally interesting and biologically active terpenoids, particularly sesquiterpenoids, biogenetically derived through the humulene cyclisation cascade.[1] In 1988, Hanssen and Abraham reported[2] the isolation and structure determination of a novel triquinane sesquiterpene (+)-ceratopicanol **1** from the fungus *Ceratocystis piceae* Ha 4/82 relying mainly on 2D NMR studies. The discovery of this new structural-type in nature provided the missing link (capture of cation **2**) in the biogenesis of hirsutene **3** and related sesquiterpenoids from humulene **4** *via* the protoilludane cation **5**, Scheme 1.[3] Besides these interesting biogenetic considerations, the uncommon presence of two vicinal, bridgehead quaternary carbons among the five continguous chiral centres, on a *cis,anti,cis*-triquinane framework, makes **1** an attractive synthetic proposition. In this communication, we report the first synthesis of (−)-ceratopicanol **1**, the enantiomer of the natural product, which also establishes the absolute configuration of the natural product.

Our approach to (−)-**1** from the cheap, abundantly available (*R*)-(+)-limonene **6** provides an economical and general entry into enantiomerically pure polyquinanes; the key element of which is the deployment of the isopropenyl group of **6** as an internal, disposable, chiral director.

Enantiomerically pure **7**, readily accessible from (+)-**6** as previously reported by us,[4] was isomerised to the tetrasubstituted alkene **8**† and the ester functionality was elaborated to the α-diazoketone moiety **9**. Brief exposure of **9** to BF_3–diethyl ether[5a] or trifluoroacetic acid[5b] resulted in a facile cyclisation to the bicyclic enone **10** in which the vicinal quaternary centres were duly installed. Oxidative disposal of the isopropylidene group in **10** was simply accomplished through catalytic Ru^{3+} oxidation to furnish the diquinane dione (−)-**11** in fair yield. A versatile building-block for assembling several sesquiterpenoids embodying this diquinane fragment, *e.g.* gymnomitrol[6] and ptychanolide,[7] was thus available in gram quantities in a short sequence.

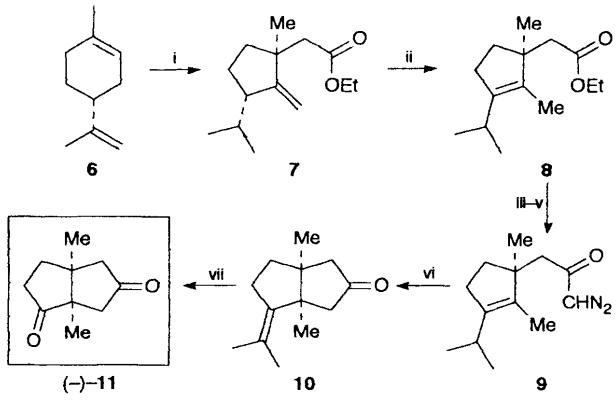
For the synthesis of ceratopicanol, however, **10** with a masked carbonyl group appeared to be more serviceable; and to append the third five-membered ring, a new 5,5-dimethylcyclopentenone annulation protocol was developed.[8] Barbier-type addition of 3-lithio-2,2-dimethylpropyl *tert*-butyldimethylsilyl ether[9] to **10** led to a 4 : 1 diastereoisomeric mixture **12**, which was directly subjected to ozonolysis and deprotection to furnish readily separable keto-diols **13** and **14**,‡ Scheme 3. Oxidation of the major diol **13** with tetra-n-propylammoniumperruthenate (TPAP)[10] furnished the γ-lactone **15** in excellent yield. Similarly, **14** led to **16** on TPAP oxidation. Both the γ-lactones **15** and **16** underwent smooth rearrangement with P_2O_5–methanesulphonic acid reagent[11] to furnish the cyclopentenone annulated C_{15}-triquinane regioisomers **17** and **18** (2 : 1), respectively.† The major ene-dione **17** was stereo- and chemo-selectively reduced to a single *endo*-hydroxyenone **19**. Lithium–liq. NH_3 reduction on **19** furnished the more stable *cis,anti,cis*-diol **20** in which the newly generated hydroxy group had the *exo*-configuration.† The diacetate **21** of **20** underwent preferential reductive deacetoxylation of the *exo*-acetoxy group with Na–HMPA (HMPA = hexamethylphosphoramide) in the presence of Bu^tOH[12] to furnish (−)-ceratopicanol **1**, $[\alpha]_D^{20}$ −5.8° (lit.[2] + 6.4°). The 400 MHz ^1H NMR spectrum ($CDCl_3$) and 100 MHz spectrum (C_6D_6) of our sample were identical with that reported in the literature.[2]§ The natural product, therefore, has the absolute configuration (+)-**1**.

In summary, we have outlined a homochiral synthesis of polyquinanes of general utility from (+)-limonene and as its first application accomplished the total synthesis of a novel triquinane sesquiterpenoid (−)-ceratopicanol **1**.



Scheme 1

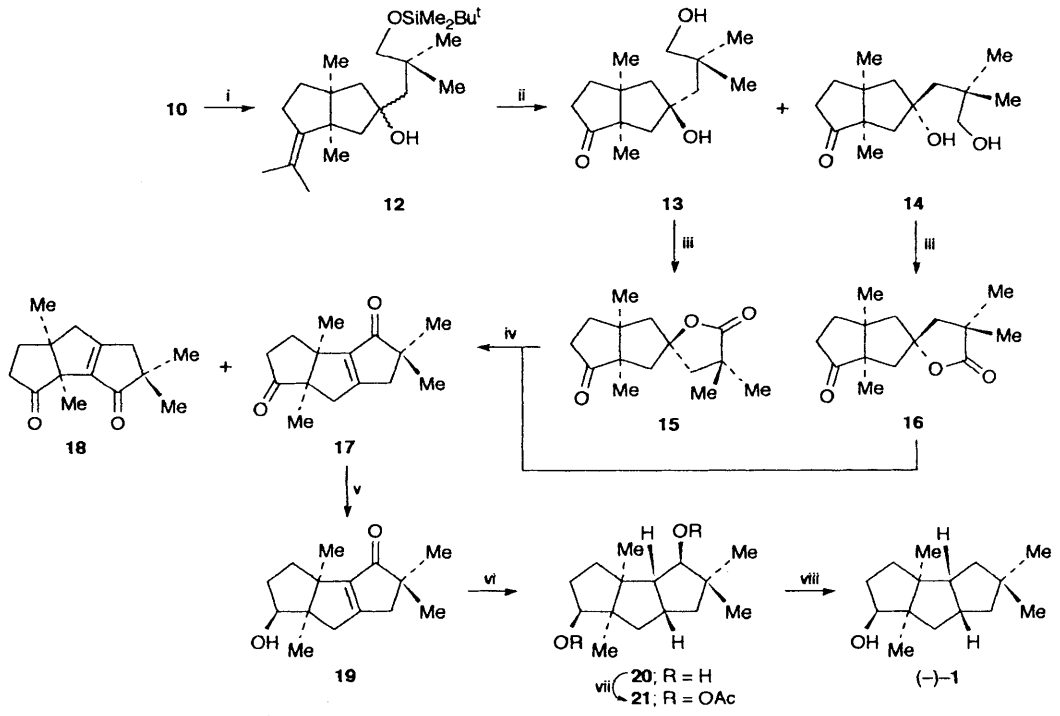
† All new compounds reported here were characterised on the basis of spectral and analytical data.



Scheme 2 *Reagents, conditions and yields*: i, ref. 4; ii, $BF_3{\cdot}Et_2O$, CH_2Cl_2 room temp., 16 h, 82%; iii, 5% aq. NaOH–MeOH, 80 °C, 3 h; iv, $(COCl)_2$-pyridine, CH_2Cl_2, room temp., 5 h; v, CH_2N_2, diethyl ether, 5 °C, 16 h (68% from **8**); vi, $BF_3{\cdot}Et_2O$, CH_2Cl_2 room temp., 5 min, 73%; vii, $RuCl_3$-$NaIO_4$, MeCN–CCl_4–H_2O, room temp., 1 h, 66%

‡ Separation of the diastereoisomers was not really necessary at any stage, as convergence was achieved at the stage of the formation of enones **17** and **18**. However, we separated diols **13** and **14** and carried them independently to characterise all the compounds.

§ ^{13}C NMR resonances for the natural ceratopicanol have not been reported in the literature.[2] Our synthetic sample had resonances at δ 82.7, 58.9, 55.0, 51.3, 48.8, 44.2, 42.0, 41.7, 40.9, 39.6, 31.6, 30.7, 28.6, 23.9 and 21.3.



Scheme 3 *Reagents, conditions and yields*: i, 3-bromo-2,2-dimethylpropyl *tert*-butyldimethylsilyl ether, Li, diethyl ether, 15 °C, 15 min, 57%; ii, O_3, MeOH, Me_2S, −78 °C and $Bu^n_4N^+F^-$, 73%; iii, TPAP–NMMO, 10% $MeCN–CH_2Cl_2$, room temp., 40 min, 91%; iv, $MeSO_3H–P_2O_5$, 80 °C, 65 min, 70%; v, $NaBH_4$, MeOH, −20 °C, 87%; vi, Li–liq. NH_3, Bu^tOH, NH_4Cl, 66%; vii, DMAP–Ac_2O, CH_2Cl_2, room temp., 30 min, 90%; viii, Na–HMPA, Bu^tOH–diethyl ether, 20%; (NMMO = 4-methylmorpholine *N*-oxide; DMAP = 4-dimethylaminopyridine)

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