Chiral Synthesis of (−)-Mesembranol Starting from D-Glucose

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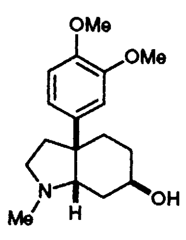
The chiral synthesis of the *Sceletium* alkaloid, (−)-mesembranol 1 is described; the cyclohexane ring in 1 is prepared in an optically active form from D-glucose using Ferrier's carbocyclisation reaction and the perhydroindole skeleton is effectively constructed by an intramolecular aminomercuration reaction.

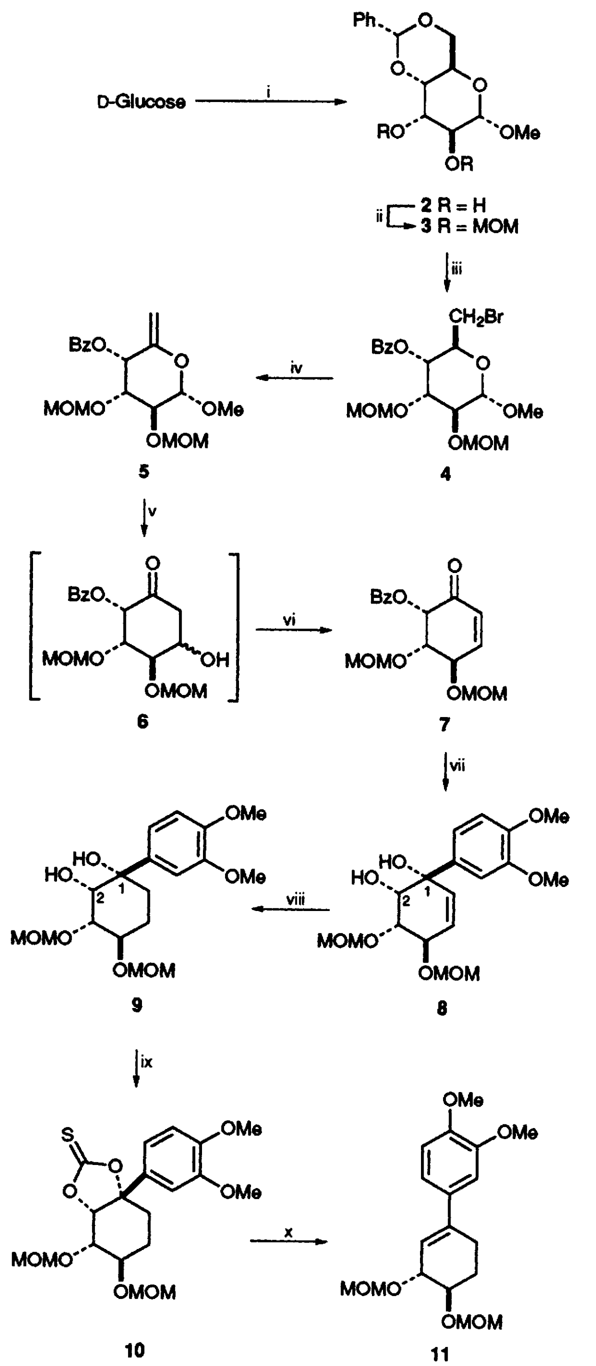
Ferrier's carbocyclisation reaction (Ferrier rearrangement) is one of the most efficient procedures for the construction of optically pure cyclohexanone derivatives from aldohexoses[1] and is frequently used in the synthesis of cyclitols and aminocyclitols.[2] Such chiral and highly oxygenated cyclohexanes derived from aldoses are potentially versatile chiral building blocks in natural product synthesis, however, applications of this reaction to the preparation of structurally more complex natural products are limited.[3] We report here a total synthesis of (−)-mesembranol,[4,5] a member of the *Sceletium* alkaloid family, utilising Ferrier's carbocyclisation reaction as the key reaction.

Methyl 4,6-*O*-benzylidene-α-D-altropyranoside **2**,[6] prepared from D-glucose in five steps, was protected as bismethoxymethyl ether to give **3**, which was treated with *N*-bromosuccinimide (NBS) in the presence of $BaCO_3$[7] to afford **4** (90% from **2**). Compound **4** was dehydrobrominated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give 5-enopyranoside derivative **5** in 96% yield. Catalytic Ferrier's carbocyclisation reaction of **5** using mercury(II) trifluoroacetate (0.5 mol%)[8] in acetone–water (2:1) at room temp. cleanly provided the cyclohexanone **6**, which, without purification, was transformed into the enone **7** by the action of methanesulfonyl chloride (MsCl) and triethylamine (88% yield from **5**). Reaction of **7** with 3,4-dimethoxyphenyllithium[9] in diethyl ether at −78 °C, followed by MeONa treatment gave the diol **8** as a single product in 56% yield.† Saturation of the double bond in **8** afforded **9** (100%), which was then transformed into thiocarbonate derivative **10** in 95% yield. Treatment of **10** with trimethyl phosphite[10] provided **11** in 74% yield (Scheme 1).

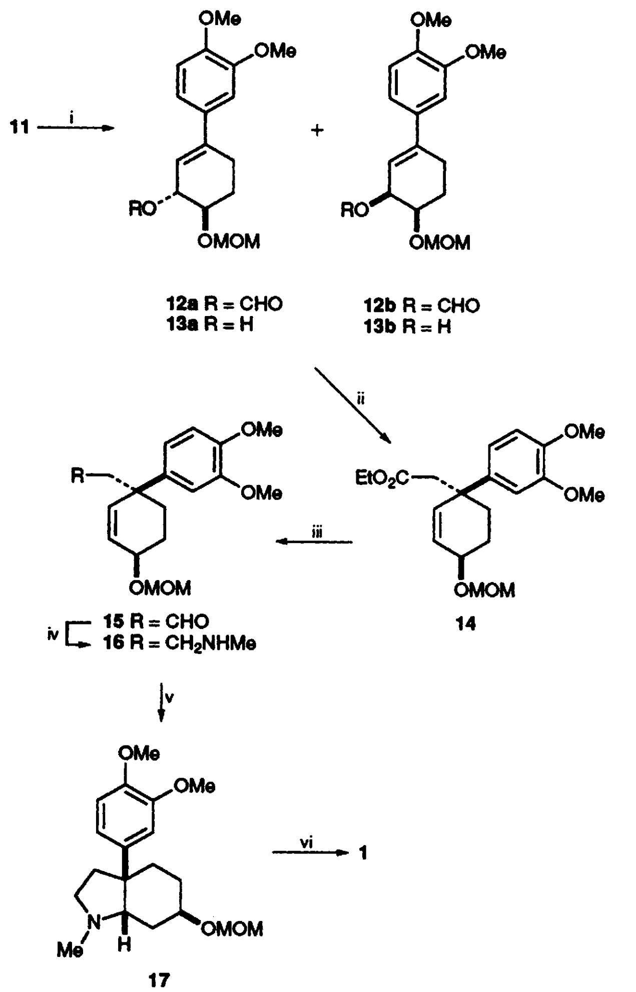
With optically active, protected allyl ether **11** in hand, its conversion into perhydroindole skeleton was explored. Treatment of **11** with aqueous formic acid gave a mixture consisting of allyl alcohols **13a**, **13b**, allyl formates **12a**, **12b**, and the starting material.‡ Alkaline hydrolysis of this mixture and subsequent chromatographic separation provided **13a** (39%), **13b** (18%) and recovered **11** (23%) (Scheme 2). Claisen rearrangement[11] of **13a** with triethyl orthoacetate in the presence of powdered molecular sieves 3 Å and a catalytic amount of propionic acid effectively generated the quaternary carbon to afford rearranged product **14** in 56% yield. Reduction of the ester function in **14** with diisobutylaluminium hydride (DIBAL) at −78 °C gave the corresponding aldehyde **15** (82%), which was converted into the secondary amine **16** by reductive amination (methylamine and $NaBH_3CN$, 65% yield). The crucial step, construction of the perhydroindole skeleton, was successfully achieved by intramolecular aminomercuration–demercuration[12] to provide



(−)-Mesembranol **1**



Scheme 1 MOM = $MeOCH_2$−. *Reagents and conditions*: i, see ref. 6; ii, chloromethyl methyl ether, Pr^i_2NEt, CH_2Cl_2, reflux, 18 h; iii, NBS, $BaCO_3$, CCl_4, 1,1,2,2-tetrachloroethane, reflux, 20 h; iv, DBU, toluene, 75 °C, 20 h; v, $Hg(OCOCF_3)_2$ (0.5 mol%), acetone–H_2O (2:1), room temp., 72 h; vi, MsCl, Et_3N, CH_2Cl_2, room temp., 30 min; vii, 3,4-dimethoxyphenyllithium, diethyl ether, −78 °C then MeONa, MeOH; viii, H_2, $Pd(OH)_2$, EtOAc; ix, 1,1′-thiocarbonyldiimidazole, acetone, reflux, 48 h; x, $P(OMe)_3$, reflux, 72 h.



Scheme 2 *Reagents and conditions*: i, 30% aq. HCO_2H, 30 °C, 72 h then K_2CO_3, MeOH, room temp.; ii, triethyl orthoacetate containing 2% (v/v) propionic acid, molecular sieves 3 Å, 135 °C, 48 h; iii, DIBAL, toluene, −78 °C; iv, methylamine (30% methanol solution), $NaBH_3CN$, MeOH, room temp., 24 h; v, $Hg(OAc)_2$, THF, room temp. then $NaBH_4$, THF–aq. NaOH, room temp., vi, 6 mol dm^{-3} HCl–THF (1:2; v/v), room temp.

protected mesembranol **17** in quantitative yield. Treatment of **17** with aqueous HCl followed by basic extraction afforded (−)-mesembranol **1** as crystals in 68% yield. The ^{1}H (270 MHz) and ^{13}C (67 MHz) NMR spectral data of **1** were fully identical with those reported by Ishibashi and Ikeda,[5d] and the physical properties of **1** [mp 146–147 °C, $[\alpha]_D^{24}$ −28 (*c* 0.2, $CHCl_3$), lit.[5a] mp 144–146 °C, $[\alpha]_D^{30}$ −32 ($CHCl_3$)] showed a good accord with those reported in the literature.[5a]

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Footnotes

† The newly formed stereocentre in compound **8** was assigned by NOE measurement of the *O*-benzoyl derivative of compound **9**; the observed NOE between C(2)-H and aromatic protons suggested the stereochemistry at C(1) should be *S*.

‡ The reaction condition in this step has not been optimised. Apparently, this reaction involved the allyl cation intermediate generated by elimination of allylic (methoxymethyl)oxy group. The more forcing conditions (higher temp. or using stronger acid such as HCl) caused the complete aromatisation of the cyclohexene ring.

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