Total Synthesis of the *trans*-Clerodane Diterpenoid (±)-Stephalic Acid

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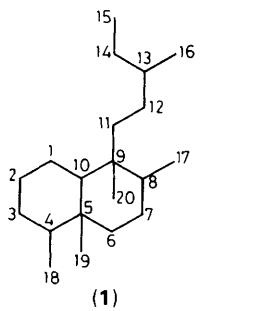
The *trans*-clerodane diterpenoid (±)-stephalic acid (**3**) was obtained from the α,β-unsaturated nitrile (**4**) *via* a stereocontrolled 13-step sequence of reactions.

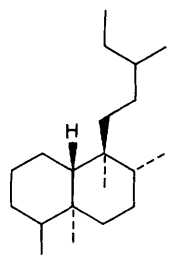
The clerodane family of diterpenoids share the common carbon skeleton shown in (**1**). With respect to stereochemistry, clerodanes with both *cis*- and *trans*-fused bicyclo[4.4.0]octane carbon frameworks have been isolated and structurally characterised.[1] The relative stereochemistry of most of the known *trans*-clerodanes is that in which the three one-carbon substituents at C-5, C-8, and C-9 are *cis* to one another, as indicated in (**2**). However, there are a (relatively small) number of *trans*-clerodanes that exhibit stereochemistry at C-8 or C-9 different from that shown in (**2**).

The diterpenoid (+)-stephalic acid has been isolated from the methanolic extract of *Stevia polycephala*, which was collected in the state of Tlaxcala, Mexico.[2] Primarily on the basis of a single crystal *X*-ray analysis, this natural product was shown[2] to possess the constitution and relative stereochemistry shown in (**3**). Thus, in stephalic acid, the methyl group at C-8 is *trans* to the one-carbon units at C-5 and C-9 and has an axial orientation on the substituted cyclohexane ring [see (**3A**)]. We report here a stereocontrolled total synthesis of (±)-stephalic acid (**3**) *via* the route summarised in Scheme 1.

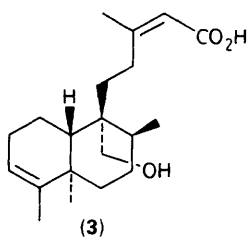
Reduction of the previously reported α,β-unsaturated



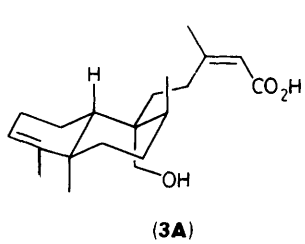
(**1**)



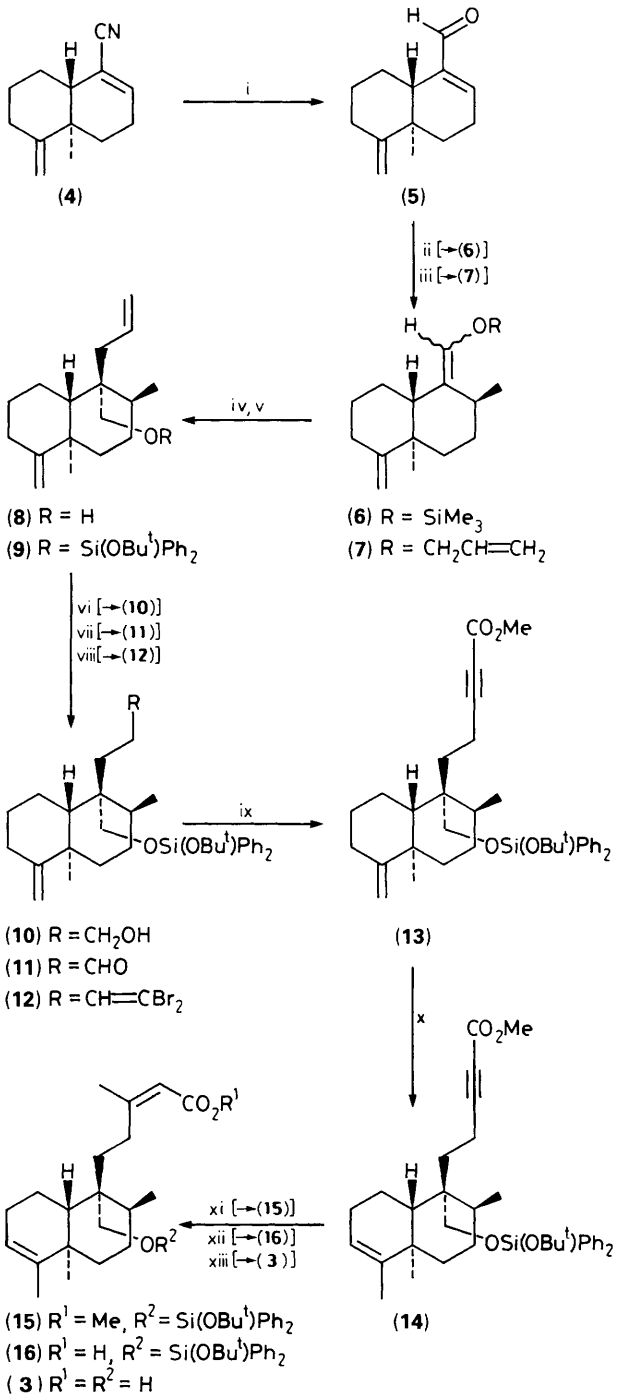
(**2**)



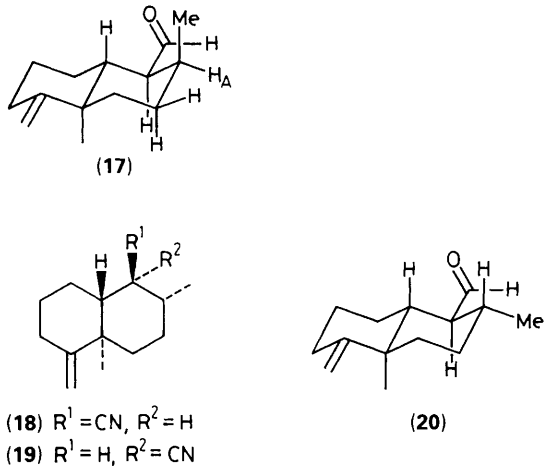
(**3**)



(**3A**)



Scheme 1. *Reagents and conditions*: i, Bu$^i_2$AlH, CH_2Cl_2, room temp.; 10% H_2SO_4, H_2O, 89%; ii, MeCu(CN)Li (5 equiv.), Me_3SiCl (5.3 equiv.), tetrahydrofuran (THF), −78 °C, 2 h, 86%; iii, MeLi (1.2 equiv.), hexamethylphosphoramide (HMPA), room temp.; CH_2=$CHCH_2Cl$ (2 equiv.); iv, Bu$^i_3$Al, CH_2Cl_2, room temp., 1 h, 52% from (**6**); v, Ph_2(Bu^{t}O)SiCl (1.1 equiv.), Et_3N (1.5 equiv.), 4-(*N*,*N*-dimethylamino)pyridine (0.1 equiv.), CH_2Cl_2, room temp., 91%; vi, (Me$_2$CHCMe)$_2$BH (1.3 equiv.), THF; H_2O_2, NaOH, 80%; vii, C_5H_5N·CrO_3·HCl, NaOAc, CH_2Cl_2, 85%; viii, Ph_3P (4 equiv.), CBr_4 (2 equiv.), CH_2Cl_2, 96%; ix, Bu^{n}Li (2 equiv.), THF, −78 °C, 3 h; $ClCO_2Me$ (2 equiv.), 76%; x, *p*-Me$C_6H_4SO_3H$ (0.1 equiv.), CH_2Cl_2, room temp., 15 h, 56%; xi, Me_2CuLi (1 equiv.), THF, −78°, 2 h, 65%; xii, PhSeNa, THF, HMPA, reflux, 6.5 h; HCl, H_2O, 64%; xiii, Bu$^n_4$NF, THF, room temp., 4 h, 15%.



nitrile (**4**)[3] provided the aldehyde (**5**).† Treatment of the latter substance with lithium methyl(cyano)cuprate in the presence of Me_3SiCl[4] gave, cleanly and efficiently, the enol silyl ether (**6**) (mixture of geometric isomers). The fact that the newly introduced secondary methyl group had a β (axial) orientation was shown as follows. Hydrolysis (H_2SO_4, H_2O, THF) of (**6**) produced a single aldehyde (**17**). In the ^{1}H n.m.r. spectrum of (**17**), the signals due to the secondary methyl group and the adjacent proton H_A appeared at δ 1.04 (d, *J* 7 Hz) and 2.57 (m, $w_{1/2} \approx 18$ Hz), respectively. In a decoupling experiment, irradiation at δ 1.04 changed the H_A resonance to a narrow signal with $w_{1/2} \approx 9$ Hz. It is thus evident that H_A is equatorially oriented and, therefore, (**17**) must possess the desired stereochemistry. Also, the ^{1}H n.m.r. spectrum of (**17**) is significantly different from that of the aldehyde (**20**), which was readily prepared by reduction–hydrolysis of the known[5] 85 : 15 mixture of the nitriles (**18**) and (**19**).

Reaction of the enol silyl ether (**6**) with MeLi in HMPA, followed by alkylation of the resultant enolate anion with 3-chloropropene, provided the enol ether (**7**).‡ Subjection of (**7**) to a tri-isobutylaluminium-promoted Claisen rearrangement–reduction process[6]§ gave, stereoselectively, the diene alcohol (**8**). In this overall transformation, very little, if any, of the epimer at C-9 (clerodane numbering) was produced. Apparently and, perhaps, not unexpectedly, the [3,3]sigmatropic rearrangement of (**7**) proceeded with migration of the allyl moiety to the less hindered equatorial face of the substituted cyclohexane ring, thus affording the desired stereochemistry at C-9. In the ^{1}H n.m.r. spectrum of the product (**8**), the angular methyl group gives rise to a singlet at δ 1.06, while the C*H*$_2$OH protons appear as a pair of doublets (*J* 12 Hz) at δ 3.68 and 3.81. In a nuclear Overhauser enhancement difference experiment, irradiation at δ 3.81 caused an increase in the intensity of the resonance at δ 1.06. Thus, it is clear that the C-5 Me group and the C-9 CH_2OH moiety have a *cis* relationship.

† All new compounds reported herein exhibited spectra in full accord with assigned structures and gave satisfactory results in molecular mass determinations (high resolution mass spectrometry).

‡ Treatment of the enolate anion derived from (**6**) with 3-iodopropene under a variety of experimental conditions failed to give satisfactory yields of *C*-alkylation product(s).

§ Attempts to effect thermal Claisen rearrangement of (**7**) led to mixtures containing many compounds.

Transformation of (**8**) into the corresponding t-butoxydiphenylsilyl ether (**9**),[7]¶ followed by chemoselective hydroboration of (**9**), gave the alcohol (**10**), which was readily converted, *via* the aldehyde (**11**), into the dibromo-alkene (**12**).[8] Reaction of (**12**) with 2 equiv. of Bu^nLi[8] gave the corresponding lithium acetylide, which, upon treatment with $ClCO_2Me$, produced the α,β-acetylenic ester (**13**).

Treatment of (**13**) with toluene-*p*-sulphonic acid in CH_2Cl_2 effected the required isomerisation of the exocyclic double bond at C-4. Reaction of the resultant product (**14**) with lithium dimethylcuprate in THF at −78 °C[9] gave, stereoselectively, the α,β-unsaturated ester (**15**), which, upon treatment with PhSeNa,[10] was converted into the corresponding carboxylic acid (**16**). Cleavage of the silyl ether function in (**16**) with Bu^n_4NF afforded crude (±)-stephalic acid (**3**) in good yield. Unfortunately, this material, which contained a small amount of an unknown impurity, proved to be exceptionally difficult to purify. Eventually, using a combination of column chromatography (Sephadex® LH-20), preparative t.l.c. (silica gel and Whatman KC_{18} reversed phase), and careful fractional crystallisation, a pure sample of (±)-(**3**) (m.p. 119—121 °C) was obtained in low yield. Racemic stephalic acid (**3**) exhibited δ_H (400 MHz, $CDCl_3$) 1.01 (d, 3H, *J* 7 Hz), 1.09 (td, 1H, *J* 12, 4 Hz), 1.15 (s, 3H), 1.21—1.34 (m, 2H), 1.39—2.08 (diffuse m, 12H), 1.60 (br. s, 3H), 1.96 (br. s, 3H), 3.14—3.23 (m, 1H), 3.68 (d, 1H, *J* 12 Hz), 4.24 (d, 1H, *J* 12 Hz), 5.18 (br. s, 1H), 5.72 (br. s, 1H). The ^{1}H n.m.r. spectrum of (±)-(**3**) was identical with that of a sample of natural (+)-(**3**).

¶ Use of the t-butyldimethylsilyl ether proved to be unsatisfactory in the latter stages of the synthetic sequence.

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