A Versatile Method for the Synthesis of Clerodane Diterpenoids: Syntheses of *cis* and *trans* Representatives

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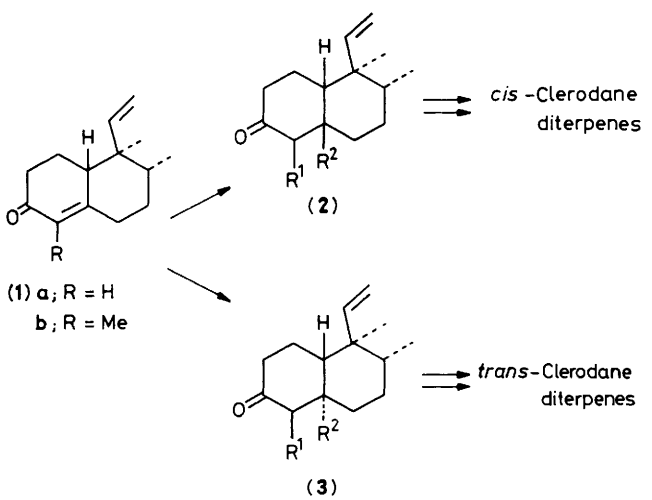
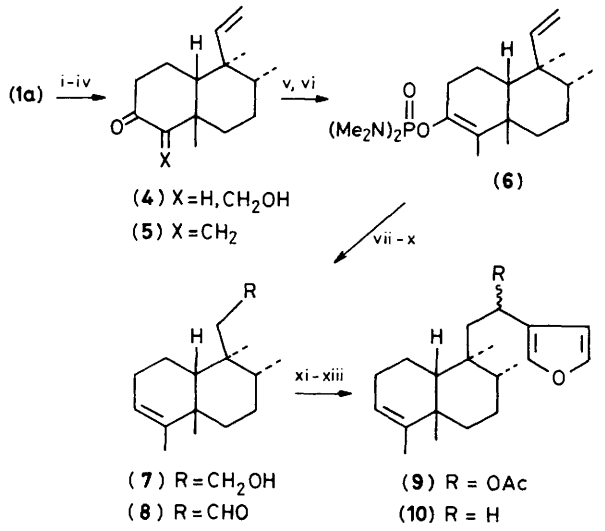
Application of stereospecific conjugate addition reactions to Δ^4-3-octalone intermediates has led to the total synthesis of both *cis*- and *trans*-clerodane diterpenes.

Bicyclic clerodane-type diterpenes, which have been found in increasing number in nature,[1] are divided into two major classes: *cis* and *trans* with respect to the ring junction. We report here a general method for the construction of the clerodane skeleton,[2] the usefulness of which has been demonstrated by the total syntheses[3] of both *cis*- and *trans*-clerodane diterpenes.

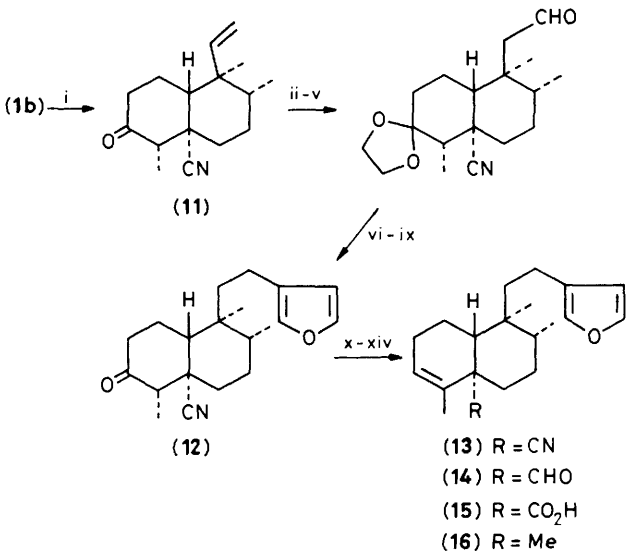


Scheme 1

Our strategy is based on the preparation of the octalone intermediate (**1**) which would afford the *cis* and *trans* compounds (**2**) and (**3**) stereoselectively by the proper choice of conjugate addition reactions (Scheme 1). The octalone derivatives (**1a**) [ν_{max} 3080, 1680, 1620, and 910 cm^{-1}; ^1H n.m.r. δ 0.81 (3H, d, J 6.8 Hz, C-8 Me), 0.82 (3H, s, C-9 Me), 5.03, 5.12, and 5.63 (each 1H, ABX signals, J_{AB} 2, J_{AX} 11, and J_{BX} 17 Hz, vinyl group), and 5.63 (1H, s, C-4 H)] and (**1b**) [ν_{max} 3090, 1670, and 910 cm^{-1}; ^1H n.m.r. δ 1.78 (3H, br. s, C-4 Me)] were synthesized from 3,4-dimethylcyclohex-2-en-1-one in 60 and 55% overall yields respectively by the following sequence of reactions. (i), Stereospecific conjugate addition[4] of the CH_2=$CHMgBr\cdot(Bu^n_3PCuI)_4$ complex (−70 to 0 °C, 5 h) followed by trapping of the resulting enolate with HCHO; (ii), mesylation ($MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C); (iii), reaction with $MeCOCH_2CO_2Me$ or $MeCH_2COCH_2CO_2Me$ (NaOMe, MeOH–benzene, room temp., 15 h, then 40—50 °C, 3 h); (iv), refluxing with 2 M HCl–MeOH for 7 h. In these preparations (**1a**) and (**1b**) were obtained as single isomers with respect to the stereochemistry at C-10 as verified by completion of the syntheses. The result was not unexpected in view of the possible thermodynamic equilibrium in the last reaction step. Having obtained the key intermediates (**1a**) and (**1b**) we decided to synthesise the natural products 15,16-epoxy-*cis*-cleroda-3,13(16),14-triene (**10**) (isolated from *Solidago arguta*)[5] and maingayic acid (**15**) (a piscicidal constituent isolated from *Callicarpa maingayi*)[6] as representatives of *cis*- and *trans*-clerodane diterpenoids, respectively.



Scheme 2. *Reagents:* i, Me_2CuLi (2.5 equiv., prepared from 1.6 M MeLi, low halide content, and Me_2S·CuBr), Et_2O–pentane, −20 °C, 2 h; ii, HCHO; iii, $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C; iv, 1,8-diazabicyclo[5.4.0]undec-7-ene, tetrahydrofuran (THF), reflux; v, $LiB(CHMeEt)_3H$, THF, −78 °C; vi, $(Me_2N)_2POCl$, Et_3N, THF–hexamethylphosphoramide; vii, B_2H_6 (1.4 equiv.), THF, room temp., 7 h; viii, H_2O_2, NaOH; ix, Li, $EtNH_2$, Bu^tOH; x, Me_2SO, $(COCl)_2$, CH_2Cl_2, −78 °C, 10 min, then Et_3N; xi, 3-furyl-lithium, Et_2O, −17 to −5 °C; xii, Ac_2O, pyridine; xiii, Li, liq. NH_3, −78 °C.



Scheme 3. *Reagents:* i, Et_2AlCN, benzene–toluene, 30—35 °C, 1.5 h; ii, ethylene glycol, camphorsulphonic acid, benzene; iii, B_2H_6, THF; iv, H_2O_2, NaOH; v, Me_2SO, $(COCl)_2$, CH_2Cl_2, then Et_3N; vi, 3-furyl-lithium, Et_2O; vii, Ac_2O, pyridine; viii, Li, liq. NH_3, −78 °C; ix, 2 M HCl, Me_2CO, room temp., 1.5 h; x, $LiB(CHMeEt)_3H$, THF, −78 °C; xi, $POCl_3$, pyridine, room temp., overnight; xii, Bu^i_2AlH, toluene, 0 °C, 1.5 h; xiii, AcOH, THF–H_2O, 100 °C, 2 h; xiv, $NaClO_2$, NaH_2PO_4, Bu^tOH–H_2O, $Me_2C{=}CHMe$, room temp., overnight.

In the synthesis of (**10**) from (**1a**)† the conjugate addition of Me_2CuLi was used since the reaction of organo copper reagents with Δ^4-3-octalone is known to result in the introduction of the *cis*-substituent.[8] When (**1a**) was treated with Me_2CuLi and then HCHO gas,‡ the hydroxy ketone (**4**) was produced in 46% yield. The ^1H n.m.r. spectrum of (**4**) exhibits a singlet due to the newly introduced methyl group at δ 1.18 and ABX signals due to the hydroxymethylene moiety at δ 3.07, 3.66, and 3.94 (J_{AB} 11.2, J_{AX} 3.4, and J_{BX} 9.0 Hz). The α,β-unsaturated enone (**5**) derived from (**4**) was reduced with L-Selectride and the resulting enolate quenched with $(Me_2N)_2POCl$ to give (**6**) [^1H n.m.r. δ 1.66 (3H, br. s, C-4 Me)] in 49% yield. After selective hydroboration§ of the vinyl group, the phosphate group was removed[9] and the alcohol (**7**) obtained was oxidized to the aldehyde (**8**), which shows ABX resonances due to CH_2CHO grouping at δ 2.39, 2.57, and 9.90 (J_{AB} 15.1, J_{AX} 3.5, and J_{BX} 3.5 Hz). The 3-furyl group was formed by an established procedure[10] to complete the synthesis of the target compound (**10**) in 45% yield from (**7**) (Scheme 2). The i.r. and ^1H n.m.r. spectra of the synthetic product are indistinguishable from those of the natural product.[5]

The synthesis of (**15**) from (**1b**) utilized hydrocyanation which was known to give the *trans* product preferentially under thermodynamically controlled conditions.[11] The reaction of (**1b**) with Et_2AlCN in benzene at 30—35 °C afforded the cyanoketone (**11**) [m.p. 78.5 °C; ν_{max} 3110, 2235, 1725, and 915 cm^{-1}; ^1H n.m.r. δ 0.82 (3H, d, *J* 6 Hz, C-8 Me), 1.04 (3H, s, C-9 Me), 1.12 (3H, d, *J* 6.5 Hz, C-4 Me)] in 83% yield as the sole product. The *trans* nature of the cyano group in (**11**) was assigned on the basis of the diamagnetic shift in the 20-methyl proton signal in the ^1H n.m.r. spectra compared with that of (**1b**) (Δδ = 0.23). After protection of the keto group the vinyl side chain in (**11**) was transformed into the 2-(3-furyl)ethyl group as described above. Deprotection of the product furnished (**12**), which, on reduction and dehydration, was converted into (**13**). Reduction of (**13**) with Bu^i_2AlH proceeded smoothly¶ and, after hydrolysis, the corresponding aldehyde (**14**) was obtained in 94% yield. Although oxidation of the aldehyde group in (**14**) was rather difficult, the target compound (**15**) was finally obtained by the application of the $NaClO_2$ method (Scheme 3).[12] The identity of (**15**) as maingayic acid[6] was confirmed by spectral comparison of both the acid itself and the corresponding methyl ester. Moreover, since the aldehyde (**14**)** derived from maingayic acid had been converted into annonene (**16**),[13] the present work also provides the formal total synthesis of (**16**).

A large number of *trans*- and *cis*-clerodane diterpenes, which have various combinations of substituents at C-4 and C-5 and different degrees of oxidation, occur in nature. The above method will be useful for the syntheses of these natural products.

† Compound (**1b**) was found to react more slowly with Me_2CuLi than (**1a**) as expected from consideration of the reduction potential (ref. 7).

‡ The reactivity of MeI was not sufficient to trap the kinetic enolate.

§ Although the selectivity of the hydroboration of the vinylic double bond was complete with respect to the enol double bond a considerable amount (29%) of the corresponding secondary alcohol was also obtained.

¶ The smooth reduction with Bu^i_2AlH is noteworthy in view of the fact that the cyano group in (**13**) is strongly hindered as shown by hydrolysis experiments. Even after treatment with KOH in ethylene glycol at 180 °C for 42 h the starting material was recovered largely unchanged and other attempts at this reduction were also fruitless.

** The spectra[13] of the aldehyde (**14**) obtained from natural (**15**) were in agreement with those of the synthetic product.

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