Total Synthesis of the *ent*-Clerodane Diterpenoids (±)-Isolinaridiol and (±)-Isolinaridiol Diacetate

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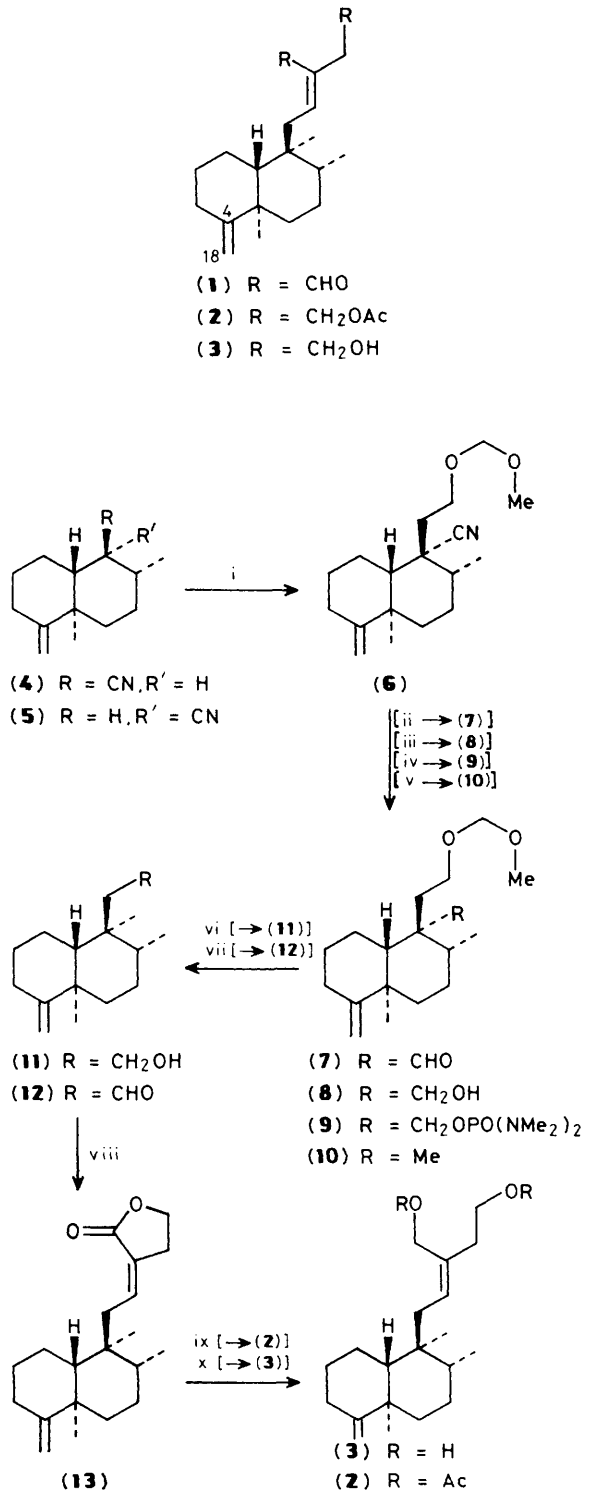
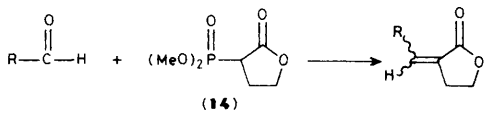
A previously described mixture of bicyclo[4.4.0]decanecarbonitriles [(**4**) and (**5**)] was converted, *via* a nine-step sequence of reactions, into (±)-isolinaridiol (**3**), which was readily transformed into the corresponding diacetate (**2**).

The structurally interesting *ent*-clerodane diterpenoids isolinaridial and isolinaridiol diacetate, isolated from *Linaria saxatilis*, have been shown[1,2] to possess the structures, including absolute stereochemistry, represented by formulae (**1**) and (**2**), respectively. These substances are two of a relatively small number of *ent*-clerodanes that contain an exocyclic olefinic bond connecting C-4 and C-18 (clerodane numbering). Reduction ($LiAlH_4$) of (**1**) and saponification of (**2**) provide the same product, isolinaridiol (**3**).[2] Apparently (**3**) has not yet been isolated from natural sources. We report here the first total syntheses of (±)-(**3**) and (±)-(**2**) *via* the route summarised in Scheme 1.



Scheme 1. *Reagents and conditions:* i, lithium di-isopropylamide, tetrahydrofuran (THF)–hexamethylphosphoramide (HMPA), 0 °C; $ICH_2CH_2OCH_2OMe$, 0 °C to room temp., 99%; ii, Bu^i_2AlH, 1,2-dimethoxyethane (DME), 60 °C, 6 h; HOAc–H_2O, THF, room temp., 10 h, 92%; iii, $LiAlH_4$, Et_2O, room temp., 95%; iv, Bu^nLi, DME–*N,N,N',N'*-tetramethylethylenediamine; Cl_2PONMe_2, room temp., 12 h; Me_2NH, 0 °C, 2 h, 63%; v, Li, $MeNH_2$, −20 °C, 10 min, 80%; vi, pyridinium toluene-*p*-sulphonate, Bu^tOH, 70 °C, 12 h, 91%; vii, $(COCl)_2$–Me_2SO, CH_2Cl_2, −78 °C, 30 min; Et_3N, −78 °C to room temp., 85%; viii, (**14**), $KN(SiMe_3)_2$, (18-crown-6)–*n*MeCN complex, THF, −78 °C, 4 h, 58%; ix, Bu^i_2AlH, THF, −78 °C to 0 °C, 96%; x, Ac_2O, 4-(dimethylamino)pyridine, pyridine, room temp., 90%.

Table 1. Wittig–Horner reactions with the phosphonate (**14**).



(**14**)

Entry	R	Reaction conditions[a]	Product ratio, *Z* : *E*[b,c]	Yield(%)[d]
1	Me_2CHCH_2	A	64 : 36	69
2	Me_2CHCH_2	B	73 : 27	81
3	Me_2CHCH_2	C	77 : 23	80
4	Me_2CHCH_2	D	>99 : <1	86
5	n-C_6H_{13}	D	>99 : <1	94
6	Cyclohexyl	D	83 : 17	68
7	Ph	D	50 : 50	91

[a] A: NaH, PhH, room temp., 15 h; B: $KOBu^t$, THF, −78 °C, 4 h; C: $KOBu^t$, THF–HMPA, −78 °C, 4 h; D: $KN(SiMe_3)_2$, (18-crown-6)–*n*MeCN complex, THF, −78 °C, 4 h. [b] In each case, the product ratio was determined by gas–liquid chromatographic and ^1H n.m.r. analyses of the crude product. [c] The stereochemistry of the products was readily determined by ^1H n.m.r. spectroscopy. For example, as expected, the olefinic protons of the *Z*-isomers consistently resonated at higher field than the olefinic protons of the *E*-isomers. [d] Combined yield of chromatographically separated, purified *Z*- and *E*-isomers.

The known[3] mixture of nitriles (**4**) and (**5**) (85 : 15, respectively) was alkylated with $ICH_2CH_2OCH_2OMe$†‡ to provide, as expected (steric approach control), a single product (**6**). A sequence of reactions similar to that employed in earlier work[3] effected efficient conversion of (**6**), *via* intermediates (**7**)—(**9**), into the alkene (**10**). Hydrolysis[4] of the acetal linkage in (**10**), followed by oxidation[5] of the resulting alcohol (**11**), provided, in high yield, the aldehyde (**12**).

Completion of the syntheses of (±)-(**3**) and (±)-(**2**) required a suitable olefination of the aldehyde (**12**). After considerable experimentation with various reagents, we chose to employ α-dimethoxyphosphonyl-γ-butyrolactone (**14**).§ Initially, in order to acquire information regarding the stereochemistry of olefination of aldehydes with the reagent (**14**), the experiments summarised in Table 1 were carried out. Reaction of 3-methylbutanal with the anion of (**14**) under a variety of conditions (entries 1—3) produced variable, but unimpressive, stereoselectivity. However, when 3-methylbutanal was treated [in tetrahydrofuran (THF) at −78 °C] with the potassium salt of (**14**) in the presence of (18-crown-6)–acetonitrile complex,[6,7] the *Z*-product was formed exclusively (entry 4). A similar result was obtained with heptanal (entry 5), while the stereoselectivity was somewhat lower in the reaction involving cyclohexanecarbaldehyde as substrate (entry 6). Interestingly, when these conditions were applied to benzaldehyde, the reaction was devoid of stereoselectivity (entry 7).

† This material was prepared by the following two-step sequence: i, $ClCH_2CH_2OH$, $ClCH_2OMe$, Pr^i_2NEt, CH_2Cl_2, room temp., 12 h (80% yield); ii, NaI, Me_2CO, 60 °C, 30 h (50% yield).

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

§ This material was prepared by treatment (150 °C, 8 h) of commercially available α-bromo-γ-butyrolactone with trimethyl phosphite. Flash chromatography (silica gel; 7 : 3 Et_2O–Me_2CO) of the crude product provided (**14**) as a colourless oil.

Treatment of the aldehyde (**12**) (Scheme 1) with the reagent (**14**) under conditions D (Table 1) provided a mixture of the unsaturated lactone (**13**) and the corresponding geometric isomer, in the ratio *ca.* 3:1, respectively. Although the stereoselectivity of this process was not as high as might have been expected on the basis of the reactions carried out on structurally simpler aliphatic aldehydes (Table 1, entries 4—6), the two products could, fortunately, be separated readily by column chromatography on silica gel (4:1 light petroleum–Et_2O). The desired *Z*-isomer (**13**) and the corresponding *E*-isomer were isolated in yields of 58 and 19%, respectively. Reduction of (**13**) afforded (±)-isolinaridiol (**3**), m.p. 70—71 °C (from pentane), which exhibited spectra identical with those of authentic (+)-(**3**).[2] Acetylation of (±)-(**3**) provided (±)-isolinaridiol diacetate (**2**), an oil that exhibited δ_H (400 MHz; $CDCl_3$) 0.76 (s, 3H), 0.92 (d, 3H, *J* 6 Hz), 1.04 (s, 3H), 1.05—1.64 (m, 9H), 1.81—1.89 (m, 1H), 1.98—2.17 (m, 3H), 2.03 (s, 3H), 2.06 (s, 3H), 2.30 (dt, 1H, *J* 5 and 14 Hz), 2.40 (t, 2H, *J* 7 Hz), 4.07—4.21 (m, 2H), 4.50 (br. s, 2H), 4.62 (br. s, 2H), 5.45 (t, 1H, *J* 7.5 Hz). The spectra of the (±)-(**2**) obtained were identical with those of natural (**2**), derived by acetylation of (+)-(**3**).

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