Total Synthesis of the Sesterterpenoid (±)-Palauolide

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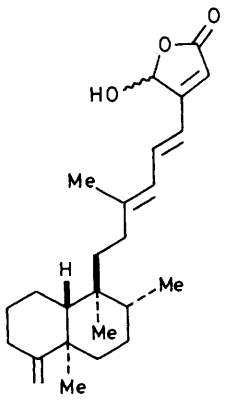
Transformation of 3,6-dimethylcyclohex-2-enone (**2**) into the sesterterpenoid (±)-palauolide (**1**) was accomplished *via* a 17-step sequence of reactions.

Palauolide, a structurally unique antimicrobial sesterterpenoid isolated from a mixture of sponges collected from Palau, Western Caroline Islands, has been shown previously[1] to possess the constitution and relative stereochemistry depicted in structure (**1**). We report here a total synthesis of racemic palauolide.

Methylenecyclohexane annelation[2] of 3,6-dimethylcyclohex-2-enone (**2**)[3] afforded the *trans*-fused decalone (**3**)† (see Scheme 1), accompanied by a small amount of an isomer. Conversion[4] of (**3**) into the nitriles (**4**) (85 : 15 mixture of β- and α-isomers, respectively), followed by alkylation with $I[CH_2]_3OCH_2OMe$,[5] gave *exclusively* (steric approach control) the nitrile (**5**). Thus, the sequence (**2**) → (**5**) allowed a high degree of control of the relative stereochemistry of the four chiral centres present in the decalin portion of (±)-palauolide.



(**1**)

The alcohol (**7**), readily derived from the nitrile (**5**), was converted into the phosphorodiamidate (**8**) by the method of Liu *et al.*[6] Reduction of (**8**) with Li–$EtNH_2$–Bu^tOH[7] gave, in addition to the desired material (**9**), a significant amount of product in which the carbon–carbon double bond had also been reduced. Eventually, it was found that treatment of (**8**) with Li–$MeNH_2$ at −20 °C, in the *absence* of Bu^tOH, provided (**9**) in excellent yield.

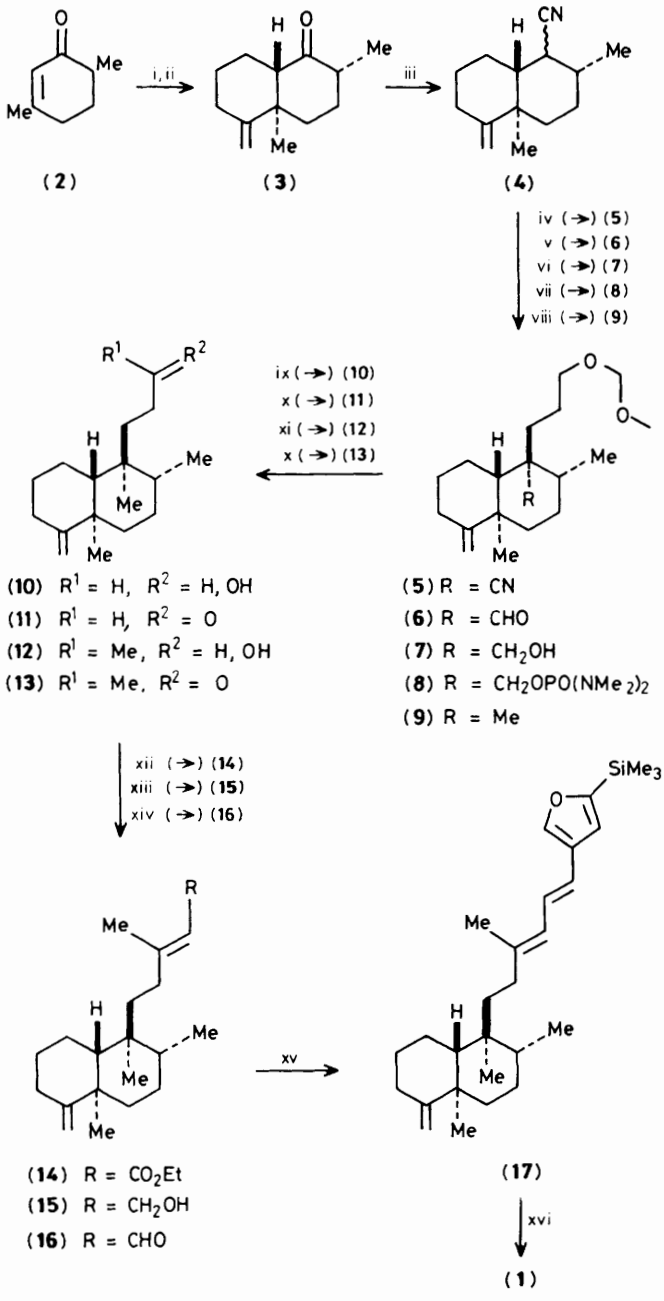
A straightforward sequence of reactions efficiently converted (**9**) into the methyl ketone (**13**). Reaction of the latter with $[EtO_2CCHPO(OEt)_2]K$ in THF provided, in nearly quantitative yield, a 10 : 1 mixture of (**14**) and its geometric isomer, which could be separated easily by column chromatography on silica gel. Reduction of (**14**) gave the alcohol (**15**).

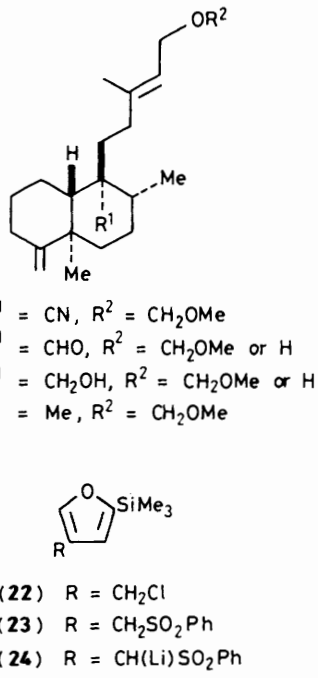
In an earlier attempt to effect a convergent conversion of (**4**) into (**15**), the nitrile (**4**) was alkylated with (*E*)-5-iodo-1-methoxymethoxy-3-methylpent-2-ene‡ to give (**18**) in high yield. Substance (**18**) could be converted readily into the aldehydes (**19**) or the alcohols (**20**). However, extensive investigations into the transformation of (**19**) and (**20**) into (**21**) or (**15**), *via* a variety of derivatives, methods, and reaction conditions, failed to provide the desired material(s) in synthetically useful yields.

Treatment of the substituted furan (**22**)[9] with $PhSO_2Na$ in

† All compounds reported herein exhibit spectra consistent with assigned structures. New compounds gave satisfactory results in molecular mass determinations (high-resolution mass spectrometry).

‡ This material was prepared from $Bu^tMe_2SiO(CH_2)_2C{\equiv}CCO_2Et$ as follows: i, $[Me_3SnCuSPh]Li$, THF, −48 °C; NH_4Cl, H_2O, 91% (ref. 8); ii, Bu^i_2AlH, THF, 95%; iii, $MeOCH_2Cl$, Pr^i_2NEt, CH_2Cl_2, 90%; iv, MeLi, THF −78 °C; MeI, 90%; v, Bu^n_4NF, THF, 98%; vi, *p*-$MeC_6H_4SO_2Cl$, 4-dimethylaminopyridine, CH_2Cl_2; NaI, *N*,*N*-dimethylformamide, 68%.





Scheme 1. *Reagents and conditions*: i, 2-(5-chloropent-1-enyl)magnesium bromide, $CuBr{\cdot}Me_2S$, $BF_3{\cdot}Et_2O$, tetrahydrofuran (THF), −78 °C, 3 h; NH_4Cl, H_2O, 77%; ii, Bu^tOK, Bu^tOH, 30 °C, 10 h, 82%; iii, (*p*-tolylsulphonyl)methyl isocyanide, Bu^tOK, Bu^tOH–hexamethylphosphoramide (HMPA), 40—55 °C, 3 days, 64%; iv, lithium di-isopropylamide, THF–HMPA, 0 °C; $I[CH_2]_3OCH_2OMe$, 0 °C → room temp., 99%; v, Bu^i_2AlH, 1,2-dimethoxyethane (DME), 60 °C, 6 h; HOAc–H_2O, THF, room temp., 10 h, 85%; vi, $LiAlH_4$, Et_2O, room temp., 91%; vii, Bu^nLi, DME-*N*,*N*,*N*′,*N*′-tetramethylethylenediamine; Cl_2PONMe_2, room temp., 10 h; Me_2NH, O °C, 2 h, 88%; viii, Li, $MeNH_2$, −20 °C, 10 min, 81%; ix, pyridinium toluene-*p*-sulphonate, Bu^tOH, reflux, 91%; x, pyridinium chlorochromate, NaOAc, CH_2Cl_2, 99%; xi, MeLi, Et_2O, 98%; xii, $[EtO_2CCH\text{-}PO(OEt)_2]K$, THF, room temp., 18 h, 88%; xiii, Bu^i_2AlH, Et_2O, −78 → 0 °C, 98%; xiv, MnO_2, hexane, room temp., 88%; xv, (**24**), THF, −78 °C, 3 h; PhCOCl, −78 °C → room temp.; Na(Hg), MeOH–THF, −20 °C, 3 h, 51%; xvi, *hν* (tungsten halogen lamp, aqueous $NaNO_2$ filter), O_2, Rose Bengal (catalyst), MeOH–CH_2Cl_2, −78 °C, 8 min; purge reaction mixture with argon and then keep at room temp. in the dark for 3 h, 68%.

N,*N*-dimethylformamide (80 °C, 2.5 h) gave (72%) the sulphone (**23**), which, upon treatment with Bu^nLi (THF, −78 °C), provided (**24**). Reaction of this reagent with the aldehyde (**16**) (Scheme 1), trapping of the alkoxide with PhCOCl, and reduction of the resultant benzoyloxy phenyl sulphone[10] afforded the furyl triene (**17**). Photosensitized oxygenation[11] of the latter provided (±)-palauolide (**1**), an oil which exhibited δ_H (400 MHz, $CDCl_3$) 0.75 (s, 3H), 0.82 (d, 3H, *J* 6 Hz), 1.05 (s, 3H), 1.87 (s, 3H), 4.51 (s, 2H), 5.86 (s, 1H), 5.96 (d, 1H, *J* 11 Hz), 6.22 (d, 1H, *J* 8.5 Hz, collapsed to s on addition of D_2O), 6.28 (d, 1H, *J* 15.5 Hz), and 7.14 (dd, 1H, *J* 15.5, 11 Hz), spectroscopically identical with natural palauolide.§

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