Stereoselective Total Synthesis of (±)-Ishwarone

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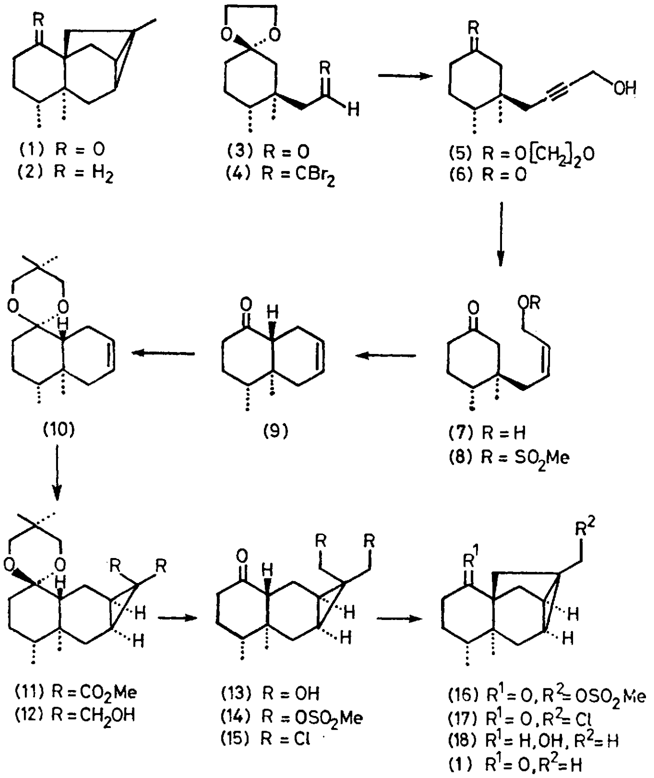
Summary An efficient, stereoselective total synthesis of the racemic modification of the tetracyclic sesquiterpenoid ishwarone (**1**) is described.

The structurally novel ketone ishwarone (**1**),[1] along with the corresponding hydrocarbon ishwarane (**2**), represent two of a relatively small number of tetracyclic sesquiterpenoids.

Although racemic ishwarane (**2**) has been obtained by total synthesis,[3] the preparation of ishwarone (**1**) has not yet been reported. We describe herein an efficient and completely stereoselective total synthesis of (±)-ishwarone (**1**),



Conversion[4] of the known aldehyde (**3**)[5] into the dibromoalkene (**4**),† followed by treatment of the latter with 2 equiv. of n-butyl-lithium in tetrahydrofuran (THF) at −78 °C[4] and trapping[6] of the resultant lithium acetylide with formaldehyde, afforded (55% overall yield) the prop-2-ynylic alcohol (**5**). Hydrolysis (hydrochloric acid, acetone) of the latter gave the ketone (**6**) (90%) (m.p. 43—45 °C) which was hydrogenated (Pd/BaSO$_4$, ethanol containing *purified* quinoline) to afford (**7**) (95%). Mesylation[7] of (**7**), followed by intramolecular alkylation ($\mathrm{Bu^tOK}$, $\mathrm{Bu^tOH}$) of the resultant keto-mesylate (**8**), resulted in efficient formation (> 70%) of the octalone (**9**). Since both (**9**) and the corresponding decalone [obtained by hydrogenation of (**9**)] were recovered unchanged from methanolic sodium methoxide, it was clear that these compounds contained a *trans*-fused ring system.

The olefinic acetal (**10**) (m.p. 100·5—102·5 °C), obtained from (**9**) by a standard procedure, reacted smoothly with dimethyl diazomalonate[8] in the presence of copper bronze to afford a single adduct (**11**) (80%) (m.p. 132—133·5 °C). The stereochemistry of the latter was assigned as shown, since, for steric reasons, cyclopropane ring formation should have occurred *trans* to the angular methyl group. Conversion of the diester (**11**) into the keto-dimesylate (**14**), *via* compounds (**12**) (m.p. 168—170 °C) and (**13**) (m.p. 138—139·5 °C), was effected smoothly (67% overall yield) by standard methods (LiAlH$_4$ reduction, hydrolysis with hydrochloric acid in acetone, mesylation[7]).

Attempted intramolecular alkylation of (**14**) under a variety of conditions failed to produce the desired product (**16**). Although it is highly probable that the desired transformation occurred, the initially formed product (**16**) (cyclopropylcarbinyl mesylate) was apparently not sufficiently stable under the reaction conditions to allow for isolation. This difficulty was avoided as follows. The dimesylate (**14**) was smoothly converted (LiCl, hexamethylphosphoric triamide–ether, room temp., > 90% yield) into the corresponding dichloride (**15**), m.p. 74—76 °C. When the latter was treated with freshly prepared potassium t-butoxide in dry THF, the isolable keto chloride (**17**) was obtained in 90% yield. Reduction of (**17**) with lithium triethylborohydride[9] in THF, followed by oxidation (pyridinium chlorochromate[10] in CH$_2$Cl$_2$) of the resultant product (**18**), afforded (75% overall yield) (±)-ishwarone (**1**), m.p. 80—81 °C. The latter exhibited i.r. and ^{1}H n.m.r. spectra identical with those reported.[1] Furthermore, Wolff–Kishner reduction[2] of synthetic (±)-ishwarone (**1**) gave (±)-ishwarane (**2**), identical with a sample of the same material previously prepared by Kelly and his co-workers.[3]

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† All new compounds exhibited the expected spectral properties and gave satisfactory elemental analyses and/or molecular weight determinations (high-resolution mass spectrometry).

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