Total Synthesis of (\pm) -Ishwarane, a Tetracyclic Sesquiterpenoid

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A total synthesis of (\pm) -ishwarane, a novel tetracyclic sesquiterpenoid possessing a tricyclo[3.2.1.0^{2.7}]octane system, is described. Completion of the synthesis of ishwarane firmly establishes the structure assigned to this sesquiterpenoid and provides corroboration of the structure assigned to the related sesquiterpenoid ishwarone. A total synthesis of (\pm) -isoishwarane, a transformation product of ishwarone, is also described.

Une synthèse totale de la (\pm) -ishwarane, nouveau sesquiterpène tétracyclique comportant le système tricyclo[3,2,1,0^{2,7}]octane, est décrite. L'aboutissement de cette synthèse établit de façon sûre la structure assignée à ce sesquiterpénoide et corrobore celle attribuée à l'ishwarone, sesquiterpène apparenté. Une synthèse totale de la (\pm) -isoishwarane, produit de transformation de l'ishwarone, est également donnée.

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The closely related pair of sesquiterpenoids ishwarane (1) and ishwarone (2) were discovered, together with other terpenoids, in the roots of Aristolochia indica Linn. (1-5). The isolation of the former (1) from the petals of Cymbopetalum penduliforum, Baill., a material used for flavoring beverages, has also been reported very recently (6).

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The isolation and characterization of ishwarone (2) was first reported in 1935 (1). It was not until 34 years later, however, that the novel and biogenetically interesting tetracyclic structure 2 was proposed for ishwarone (2, 5, see also 3). A year later, in 1970, the isolation of ishwarane was reported and, in the same communication, structure 1, having the same carbon skeleton as ishwarone, was assigned to this sesquiterpenoid (4). The assignment of structure 1 to ishwarane was based mainly on the fact that it could be obtained from ishwarone (2) simply by Wolff-Kishner reduction of the keto group (4). The validity of structure 1 for ishwarane is therefore dependent on the correctness of structure 2 for ishwarone. The latter structure (2) was



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adduced from chemical evidence, including the conversion of ishwarone into (+)-nootkatane, and spectral data (2, 3, 5).

Recently we completed a total synthesis of ishwarane (1) (7, 8), thereby providing proof of the validity of structure 1 for ishwarane and corroboration of structure 2 for ishwarone. We now wish to describe the details of the synthesis of (\pm) -ishwarane.¹

A novel structural feature of the carbon skeleton common to ishwarane (1) and ishwarone (2) is the tricyclo $[3.2.1.0^{2.7}]$ octane system. Another important stereochemical aspect of this skeleton is the pair of vicinal *cis* methyl groups at C-4 and -5 and their stereorelationship to the tricyclooctane system.² In designing a synthesis of ishwarane these stereochemical aspects must be taken into account.

In planning the synthesis of ishwarane, it was decided that the synthetic route should, at an early stage, proceed through a bicyclic intermediate in which the vicinal *cis* methyl groups had been established. Thus, one of the stereochemical problems associated with the synthesis would be solved early in the sequence of reactions. The octalone **3** was chosen as the intermediate since it not only satisfies the requirements with regard to the *cis* methyl groups but it also possesses functionality, in the form of an α,β -unsaturated ketone, suitable for the development of the tricyclooctane system.

¹Preliminary reports of some aspects of the work described in this article have appeared (refs. 7 and 8).

²The numbering system shown in 1 is adhered to throughout.



The octalone 3 was prepared either by annelation of *cis*-2,3-dimethylcyclohexanone (9) with methyl vinyl ketone and dehydration of the intermediate crystalline alcohol 4(cf. 10 and 11), or by a recently published, more lengthy synthesis (10). The two methods afforded the same octalone for which the stereostructure 3 has been firmly established (10).

Having obtained the required intermediate octalone 3, the next task was the elaboration of the tricyclooctane system. Briefly, this was accomplished by converting 3 into 5 by photo-addition of allene, skeletal rearrangement of 5, by a series of transformations, into intermediates possessing a bicyclo[2.2.2]octane system and, finally, the transformation of the bicyclo-octane system into the required tricyclooctane system (vide infra).

Photo-addition of allene to the octalone 3 afforded the adduct 5 in 75% yield as an oil. Consistent with the assigned structure (5), the i.r. spectrum of the adduct showed a keto band at 1695 cm⁻¹ and bands at 1660 and 880 cm⁻¹ due to the exocyclic methylene; in the n.m.r. spectrum a multiplet appeared at δ 4.96 (2H) attributable to the exocyclic methylene.³ The stereostructure assigned to the photo-adduct follows from the established stereospecificity of the photo-addition of allene to α,β -unsaturated ketones (12, 13).

Acetalization of 5 in the usual manner converted it into the oily ethylene acetal 6 in 75% yield. In agreement with this conversion, the

i.r. spectrum of the acetal was devoid of carbonyl bands and a multiplet (4H) due to the ethylene group of the acetal function appeared in the n.m.r. spectrum at δ 3.91.

Treatment of 6 with perbenzoic acid followed by chromatography on alumina furnished two epoxides 7a (m.p. 65°) and b (m.p. 30°), each in 39% yield. Both were converted individually, in two steps, to the same mixture of epimeric keto alcohols 9, thence, in a single step to the common intermediate 10 (Scheme 1). The i.r. spectra of the two epoxides were similar and both were devoid of olefinic bands; the n.m.r. spectra, however, were distinctly different. In the case of 7a, the signals for the methylene protons of the oxirane ring appeared as a pair of doublets (J = 5 Hz) at $\delta 2.27$ and 2.99 and the signal for the ethylene protons of the acetal function appeared as a 4-proton multiplet at δ 3.78; in contrast, the corresponding signals in the case of 7b were found at δ 1.95 and 2.11 (methylene protons of oxirane ring) and at δ 3.71 (ethylene of acetal function).

The stereostructures assigned to the epoxides are based on n.m.r. spectroscopy. An obvious difference in the n.m.r. spectra of the epoxides was the nature of the signal due to the ethylene group of the acetal function. In both spectra this signal appeared at ca. δ 3.75. However, in the case of the lower melting epimer, the signal was broader and considerably more complex than the corresponding signal in the spectrum of the other epimer. This difference was attributed to the closer proximity of the oxygen atom of the oxirane ring to the dioxolane ring in the lower melting epimer. Hence, structure 7b was assigned to the lower melting epimer and structure 7a to the other epimer (14). Consistently, a similar, but less pronounced effect was observed on comparison of the tertiary alcohols 8a and b which were derived from 7a and b, respectively (vide infra).

Corroborative evidence for the validity of the structures assigned to the epoxides (7a and b) was found on comparison of the n.m.r. chemical shifts for the methylene protons of the oxirane rings. Models show that the oxirane ring protons in structure 7a are significantly closer to the dioxolane ring than in 7b. As a consequence of the deshielding effect of the oxygen atoms of the dioxolane ring, it could therefore be expected

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³Only spectral data pertinent to the discussion will be given in this section; for further details see the Experimental.





that the n.m.r. signals for these protons in 7a would appear downfield relative to the corresponding signals in the spectrum of 7b. In agreement with expectation and the structures assigned to the epoxides, the pertinent signals in the spectrum of 7a appeared at δ 2.27 and 2.99 whereas the corresponding signals in the case of 7b appeared at δ 1.95 and 2.11.

The epoxides 7a and b were reduced with lithium aluminum hydride in excellent yield to the corresponding crystalline tertiary alcohols 8a and 8b, respectively. Stereochemically, the structures assigned to the epimeric tertiary alcohols follow from the stereostructures previously adduced for the precursor epoxides (*vide supra*). The i.r. spectrum of 8a showed a hydroxyl band at 3500 cm^{-1} and the corresponding band in the case of 8b was observed at 3525 cm^{-1} ; singlets due to the methyl group on the cyclobutane ring appeared in the n.m.r. spectra of both alcohols at *ca*. δ 1.30.

Treatment of either of the epimeric alcohols (8a or b) with aqueous hydrochloric acid in tetrahydrofuran resulted in deacetalization followed by skeletal rearrangement to a crystalline mixture of epimeric alcohols 9 in 97% yield. Obviously, the conversion of 8a and b into the same mixture of epimeric alcohols 9 involves deacetalization to give the corresponding keto cyclobutanols, retro-aldolization to give the common intermediate diketone 11, and, finally,



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aldol condensation to give 9. The mixture of epimeric alcohols 9 was barely separated into two components by t.l.c. but attempts to separate the mixture into two epimers by column chromatography were unsuccessful. The i.r. spectrum of the mixture (9) showed broad bands at 3350 (hydroxyl) and 1700 cm⁻¹ (ketone); in the n.m.r. spectrum there was a singlet (3H) at δ 1.25 due to the methyl group at C-12.

The failure to resolve the mixture of keto alcohols (9) into two epimers had no adverse effect on the synthesis since the mixture, on dehydration with *p*-toluenesulfonic acid in boiling benzene, afforded a single enone 10 as an oil in 89% yield. Consistent with structure 10, there were bands in the i.r. spectrum of the dehydration product at 1725 (ketone) and at 1650 cm⁻¹ (olefin) and, in the n.m.r. spectrum, there was a singlet (3H) at δ 1.81 (vinylic methyl), a multiplet (1H) at 2.80 (methine adjacent to ketone), and a multiplet (1H) at 5.88 (vinylic proton).

At this point it was decided to depart briefly from the main synthetic route in order to convert 10 into the olefinic hydrocarbon 12. The latter structure had been assigned to isoishwarane, a transformation product of ishwarone (2) (2, 3). In terms of structure 2 for ishwarone, the two-step transformation was envisaged as involving a rupture of the cyclopropane ring to give isoishwarone (13) which, on reduction of the keto group, afforded 12 (2, 3).



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The enone 10 was successfully converted, in 74% yield, into the hydrocarbon 12 by a Huang–Minlon reduction (15). The hydrocarbon was obtained as an oil with spectral properties in agreement with structure 12. The i.r. spectrum was devoid of carbonyl absorption but displayed a band at 1648 cm⁻¹ (olefinic); in the n.m.r. spectrum there was a doublet (3H) at δ 1.73 due to the vinylic methyl, a multiplet (1H) at 2.20 due to the allylic proton, and a multiplet (1H) at 5.61 due to the vinylic proton.

The synthetic hydrocarbon 12 was found to be

identical with an authentic sample of isoishwarane prepared from ishwarone by comparison of their i.r., n.m.r., and mass spectra fragmentation patterns. Completion of the total synthesis of isoishwarane provided proof of the correctness of structure 12 for this compound and corroboration of structures 1 and 2 for ishwarane and ishwarone respectively. Furthermore, it provided assurance that the synthesis of ishwarane was proceeding along the correct stereochemical lines.

Returning to the main synthetic route, there now remained the task of converting the enone 10 into an intermediate possessing the tricyclooctane system, thence to ishwarane (1). This was accomplished by reduction of 10 to the pair of epimeric alcohols 14a and b, conversion of the alcohols, individually, by a parallel sequence of transformations into the common intermediate cyclopropyl ketone 20, and reduction of the latter to ishwarane (see Scheme 2).

Reduction of the enone 10 with lithium aluminum hydride and chromatography of the product on silica gel resulted in the isolation of two epimeric alcohols 14*a* (m.p. 116°) and *b* (m.p. 110°), each in 38% yield. The i.r. spectra of the two alcohols were devoid of carbonyl absorption but each displayed an hydroxyl band and a band at 1648 cm⁻¹ due to olefinic absorption. In the n.m.r. spectra, the signal for the proton associated with the secondary alcohol appeared as a multiplet at δ 3.93 in the case of 14*a* and at 3.91 in the case of 14*b*.

Stereochemically, the two alcohols could be differentiated by n.m.r. spectroscopy. In the spectrum of the higher melting epimer, the signal for the angular methyl group appeared 12 Hz downfield relative to the corresponding signal in the spectrum of the other epimer. The deshielding effect on the angular methyl group in the case of the higher melting epimer is due to the hydroxyl group (16). Therefore, the epimer melting at 116° was assigned structure 14a in which the hydroxyl group is within effective deshielding range of the angular methyl group leaving the alternative structure 14b to be assigned to the epimer melting at 110°. A similar deshielding effect, due to the oxygen function at C-8 was observed consistently in the subsequent compounds 15a to 18a inclusive.

The pair of epimeric alcohols 14a and b were converted into their respective benzyl ethers 15a

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and b, both of which were obtained as oils. The i.r. spectra of both 15a and b were devoid of hydroxyl absorption but showed bands due to aromatic absorption; in the n.m.r. spectra of 15a and b, there was a singlet (2H) at $ca. \delta 4.40$ due to the benzylic methylene and a multiplet (5H) due to the aromatic protons.

Hydroboration of 15*a* and *b* gave, in each case, a single crystalline alcohol. The alcohol 16*a*, derived from 15*a*, was obtained in 82% yield. The i.r. spectrum was devoid of olefinic absorption but showed hydroxyl absorption at 3475 cm⁻¹; in the n.m.r. spectrum there appeared two doublets (3H each) at δ 0.78 and 1.20 due to the secondary methyls and a multiplet (1H) at 3.88 arising from the proton at C-11. The alcohol 16*b*, obtained from 15*b* in 71% yield, exhibited spectral properties similar to those of 16*a*.

A study, with the aid of models, of the steric

factors relevant to the hydroboration of 15a and b and an analysis of the spectral data for the resulting alcohols, 16a and b, revealed no reliable clues as to the precise stereochemical orientation about C-11 and -12 in the latter. This, however, was of no consequence in so far as the synthetic plan was concerned.

Jones oxidation (17) of the alcohols **16***a* and *b* gave the corresponding ketones **17***a* and *b* respectively in 80–90% yield, the former as an oil and the latter as a crystalline compound. The i.r. spectra of both **17***a* and *b* showed ketonic absorption at 1715 cm⁻¹; the n.m.r. spectrum of **17***a* showed a doublet (3H) at δ 1.13 due to the methyl group adjacent to the ketone and, in the case of **17***b*, the corresponding signal was found at δ 1.07.

Hydrogenolysis of the keto benzyl ethers 17a and b afforded the corresponding keto alcohols 18a and b, both as crystalline compounds in

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80–90% yield. The i.r. spectrum of 18a showed hydroxyl absorption at 3415 cm^{-1} and ketonic absorption at 1703 cm^{-1} ; the n.m.r. spectrum was devoid of signals due to aromatic protons and showed a multiplet (1H) at δ 4.05 due to the proton at C-8. The spectral properties of 18bwere similar to those of 18a: i.r. 3250 (hydroxyl) and 1710 cm⁻¹ (ketone); n.m.r. δ 4.20 (multiplet, proton at C-8).

The tosylate 19*a*, derived from the keto alcohol 18*a*, was smoothly transformed in 70% yield, into the cyclopropyl ketone 20 by heating at 60° for 2 h in dimethyl sulfoxide containing a 45% excess of methylsulfinyl carbanion (18). The epimeric tosylate 19*b* was also converted, under identical conditions to 20, although in somewhat lower yield (60%). The identity of the condensation product (20) obtained from the two sources was rigorously established (see Experimental).

The spectral properties of the condensation product were in accord with structure **20**. Thus, there was an absorption maximum in the u.v. spectrum at 208 nm (ε 4000) due to the cyclopropyl ketone moiety; the i.r. spectrum was devoid of bands attributable to a tosyl group or a hydroxyl group but showed a band at 1715 cm⁻¹ due to ketonic absorption; the n.m.r. spectrum showed a multiplet (partially obscured) at *ca.* δ 0.60 due to the protons on the cyclopropane ring and a singlet (3H) at 1.17 for the methyl group on the cyclopropane ring.

The fact that the epimeric tosylates 19a and b were both converted, under identical conditions, to the cyclopropyl ketone 20 invites speculation as to the mechanism of this conversion. The condensation $19a \rightarrow 20$ seems unexceptional since the tosylate function in 19a is favorably aligned for an S_N2i displacement by the carbanion at C-12. Such is not the case, however, with 19b. In the latter case a plausible mechanism involving a double displacement can be envisaged. Thus, the tosylate function in 19b could, conceivably, suffer S_N2 displacement either by methyl sulfinyl carbanion or a molecule of solvent to give the intermediates 21 or 22 which could readily undergo a classical $S_N 2i$ displacement resulting in the formation of **20**.

Another, less attractive mechanism, which could be envisaged for both 19a and b would involve an elimination to give the olefin 23. Attack by the carbanion at C-12 on the double



bond would result in the formation of an intermediate 24 in which the carbanion is homoconjugated with the ketone. Protonation of 24 would then give 20.

The final step in the synthesis of ishwarane was the reduction of the cyclopropyl ketone **20** to the hydrocarbon **1**. This was achieved, in 67% yield, by the Barton modification of the Wolff-Kishner (19) reduction followed by purification of the product by preparative t.l.c. The spectral properties of the hydrocarbon were consistent with structure **1**; the i.r. spectrum showed no carbonyl absorption, and the n.m.r. spectrum showed a multiplet (2H) at δ 0.50 due to the protons on the cyclopropane ring and a singlet (3H) at 1.12 due to the methyl group on the cyclopropane ring.

The synthetic hydrocarbon 1 was identical with a sample of authentic ishwarane by the following criteria: identity of i.r. and n.m.r. spectra; identity of the fragmentation patterns of the mass spectrum; identical retention times on v.p.c.

The completion of the synthesis of ishwarane firmly establishes structure 1 for this sesquiterpenoid and provides corroboration of structure 2 for the related sesquiterpenoid ishwarone.

Experimental

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The i.r. spectra were recorded on a Perkin-Elmer model 237 B spectrophotometer and u.v. spectra were determined with a Perkin-Elmer

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Coleman model 124 instrument. The n.m.r. spectra were recorded with a Varian T-60 instrument; chemical shifts are expressed in p.p.m. (δ -values) downfield from the signal for tetramethylsilane which is used as an internal standard.

V.p.c. was performed on a Hewlett-Packard model 5750 instrument fitted with a stainless steel column (6 ft \times 1/8 in.) packed with 10% of UC-W98 (silicone gum-rubber) on diatoports (80–100 mesh). The t.l.c. was carried out on Silica Gel GF-254 procured from Brinkman Instruments (Canada) Ltd.

Reaction products were isolated by the following procedure. The product was extracted into the specified solvent and the extract was washed two or three times with appropriate aqueous solutions as indicated. The original aqueous layer (if any) and the aqueous washings were extracted three times with the solvent and the combined extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated *in vacuo* on a rotary evaporator.

Petroleum ether refers to the fraction with boiling point range $30-60^{\circ}$.

Brine refers to a saturated solution of sodium chloride.

9-Hydroxy-5,10-dimethyl-2-decalone (4)

A mixture of 19.2 g of *cis*-2,3-dimethylcyclohexanone (9) and 0.6 ml of an ethanolic 3 *M* solution of sodium ethoxide was cooled to -15° . The mixture was treated, with efficient mechanical stirring and in a nitrogen atmosphere, with 12.1 g of methyl vinyl ketone over a period of 6 h. The reaction mixture was then left, under nitrogen, at -16° for 15 h after which it was dissolved in 200 ml of ether. The ether solution was worked-up in the usual manner by washing with brine. The residue, obtained by evaporation of the ether extract was distilled *in vacuo*. The first fraction (b.p. 71°/20 mm, 12.0 g) was 2,3-dimethylcyclohexanone and was used for recycling as above. The fraction with b.p. 120– $150^{\circ}/0.2$ mm, after crystallization from petroleum ether, yielded 3.07 g of 4, m.p. 134–135°; v_{max} (Nujol) 3350 (OH) and 1703 cm⁻¹ (ketone); n.m.r. (CDCl₃), δ 0.90 (d, J = 6.5Hz, 3H, secondary methyl), 0.92 (s, 3H, angular methyl).

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.39; H, 10.12.

Octalone (3)

A solution of 10.0 g of the keto alcohol 4 and 1.30 g of *p*-toluenesulfonic acid in 300 ml of benzene was refluxed for 1 h while water was collected in a Dean–Stark adapter. The cooled reaction solution was worked-up in the usual manner by washing with saturated sodium bicarbonate solution followed by brine. Evaporation of the solvent *in vacuo* and distillation of the residue afforded 8.71 g (97%) of 3, b.p. 95–97°/0.2 mm (lit. (10), 96–97°/0.2 mm); λ_{max} (EtOH) 240 nm (ε , 12 100); v_{max} (film) 1672 (ketone) and 1605 cm⁻¹ (olefin); n.m.r. (CDCl₃), δ 0.91 (d, J = 6 Hz, 3H, secondary methyl), 1.12 (s, 3H, angular methyl), 5.70 (s, 1H, vinylic H). The 2,4-dinitrophenyl hydrazone, crystallized from etha-

nol, melted at 139–140°.

Anal. Calcd. for $C_{18}H_{22}N_4O_4$: C, 60.32; H, 6.19; N, 15.63. Found: C, 60.56; H, 6.60; N, 15.83.

Photo-adduct 5

Photo-addition of allene to the octalone 3 was carried out at -70° using a 450 W mercury vapor immersion lamp with a Corex sleeve. A solution of 6.20 g of 3 and 14 g of allene in 1500 ml of freshly distilled hexane was irradiated for 6 h.

After irradiation, the reaction solution was left overnight in a fume hood to allow excess allene to evaporate. The solvent was evaporated *in vacuo* and the residue was chromatographed on a column of 255 g of silica gel with benzeneether (98:2) as solvent. Distillation of the eluted material afforded 5.70 g (75%) of 5, b.p. $105-109^\circ/0.18$ mm; v_{max} (film) 1695 (ketone) and 1660 and 880 cm⁻¹ (olefin); n.m.r. (CDCl₃), $\delta 0.75$ (s, 3H, angular methyl), 0.82 (d, J = 6.5 Hz, 3H, secondary methyl), 4.96 (m, 2H, vinylic protons).

Anal. Calcd. for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.33; H, 10.10.

Ethylene Acetal 6

A solution of 10.0 g of 5, 34.0 g of ethylene glycol, and 1.20 g of *p*-toluenesulfonic acid in 600 ml of benzene was refluxed under a nitrogen atmosphere for 18 h. During reflux, water was separated in a Dean–Stark adapter. The cooled reaction solution was worked-up in the usual manner with sodium bicarbonate solution and brine. The resulting oil was chromatographed on a column of 660 g of basic alumina (activity IV) starting with petroleum ether as solvent followed by gradually increasing proportions of benzene in petroleum ether. Thereby, 9.30 g (77%) of **6** was obtained as an oil, v_{max} (film) 1665 and 870 cm⁻¹ (olefin); n.m.r. (CDCl₃) δ 0.75 (poorly developed doublet, 3H, secondary methyl), 1.05 (s, 3H, angular methyl), 4.93 (m, 2H, vinylic protons).

Mol. Wt. Calcd. for $C_{17}H_{26}O_2$: 262. Found (mass spectrum): 262.

Epoxides 7a and b

A solution of 9.00 g of the acetal **6** in 300 ml of dry chloroform was treated with 3.66 g of solid sodium bicarbonate followed by 92.2 ml of a 0.43 M chloroform solution of perbenzoic acid. The resulting mixture was stirred at room temperature, in the dark, for 24 h. The reaction solution was shaken with 200 ml of 5% sodium bisulfite solution then worked-up in the usual manner with saturated sodium bicarbonate solution and brine. The crude product, an oil, was chromatographed on a column of 450 g of basic alumina (activity III) with gradually increasing proportions of benzene in petroleum ether as eluant. Two crystalline epoxides were separately eluted from the column.

Epoxide 7*a* was the first to be eluted from the column. Crystallization from pentane afforded 3.73 g (39%) of this compound, m.p. 65°; i.r. devoid of olefinic absorption; n.m.r. (CCl₄), δ 0.72 (poorly resolved doublet, 3H, secondary methyl), 1.03 (s, 3H, angular methyl), 2.27 and 2.99 (doublets, J = 5 Hz, 1H each, methylene of oxirane ring), 3.78 (m, 4H, ethylene of acetal group).

Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.31; H, 9.42.

Epoxide 7b was the more strongly absorbed epoxide. Crystallization from pentane afforded 3.68 g (39%) of this compound, m.p. 29-30°; i.r. no olefinic absorption; n.m.r. (CCl₄), δ 0.77 (poorly resolved doublet, 3H, secondary methyl), 0.91 (s, 3H, angular methyl), 1.95 and 2.11 (doublets, J = 5 Hz, 1H each, methylene of oxirane ring), 3.71 (broad complex multiplet, 4H, ethylene of acetal group).

Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.01; H, 9.43.

Tertiary Alcohol 8a

A mixture of 1.00 g of the epoxide 7*a*, 250 mg of lithium

aluminum hydride, and 50 ml of dry ether was refluxed for 15 min. The reaction mixture was cooled on an ice bath and treated with a few drops of brine. The ether solution was decanted from solid material and worked-up in the usual manner with brine. Crystallization of the product from ether-pentane afforded 839 mg (83%) of 8a, m.p. 114°; v_{max} (Nujol) 3500 cm⁻¹ (OH); n.m.r. (CCl₄), δ 0.70 (poorly resolved multiplet, 3H, secondary methyl), 0.98 (s, 3H, angular methyl), 1.28 (s, 3H, methyl on cyclobutane ring), 3.80 (s, 4H, ethylene of acetal group).

Anal. Calcd. for $C_{17}H_{28}O_3$: C, 72.82; H, 10.07. Found: C, 73.00; H, 10.20.

Tertiary Alcohol 8b

Reduction of the epoxide 7b as described in the preceding experiment and crystallization of the product from pentane afforded, in 93% yield, the tertiary alcohol 8b, $69-70^{\circ}$; v_{max} (Nujol) 3525 cm⁻¹ (OH); n.m.r. (CCl₄), $\delta 0.73$ (poorly resolved multiplet, 3H, secondary methyl), 0.93 (s, 3H, angular methyl), 1.27 (s, 3H, methyl on cyclobutane ring), 3.83 (m, 4H, ethylene of acetal group).

Anal. Calcd. for C₁₇H₂₈O₃: C, 72.82; H, 10.07. Found: C, 73.07; H, 9.96.

Keto Alcohols 9

(a) From Tertiary Alcohol 8a

A solution of 280 mg of 8*a* in 25 ml of tetrahydrofuran was treated with 20 ml of 1 *M* aqueous hydrochloric acid and left at room temperature under nitrogen for 20 h. Water (50 ml) was added to the reaction solution and it was extracted with chloroform. The chloroform extracts were worked-up in the usual manner by washing with water, saturated sodium bicarbonate solution, and water again. Evaporation of the chloroform extracts left an oil which, on crystallization from pentane, afforded 228 mg (97%) of 9 as a mixture of epimers, m.p. 90–114°; v_{max} (Nujol) 3350 (OH) and *ca.* 1700 cm⁻¹ (broad band, ketone); n.m.r. (CDCl₃), δ 0.80 (s, 3H, angular methyl), 0.85 (d, J = 6.5 Hz, 3H, secondary methyl), 1.25 (s, 3H, CH₃—C—OH).

The mixture was resolved by t.l.c. with benzene-ether (1:1) as solvent into two, barely separated, components (estimated ratio, 1:1).

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.41; H, 10.18.

(b) From Tertiary Alcohol 8b

The same mixture of epimeric alcohols (9) was obtained, in comparable yield, from 8b by the above procedure.

Enone 10

A solution of 250 mg of a mixture of the epimeric alcohols (9) and 25 mg of *p*-toluenesulfonic acid monohydrate in 100 ml of benzene was refluxed for 24 h. The cooled reaction solution was worked-up with saturated sodium bicarbonate solution and water. The product, an oil, was chromatographed on a column of 21 g of silica gel with benzene-ether (95:5) as solvent. The purified product was obtained as an oil (205 mg, 89%), v_{max} (film) 1725 (ketone) and 1650 cm⁻¹ (weak, olefin); n.m.r. (CDCl₃), δ 0.77 (d, J = 6.5 Hz, 3H, secondary methyl), 0.87 (s, 3H, angular methyl), 1.81 (m, 3H, vinylic methyl), 2.80 (m, 1H, methine adjacent to ketone), 5.88 (m, 1H, vinylic H).

Mol. Wt. Calcd. for $C_{15}H_{22}O$: 218. Found (mass spectrum): 218.

(\pm) -Isoishwarane (12)

The reduction of the enone 10 to isoishwarane (12) was carried out in a dry nitrogen atmosphere as follows (cf. 15). The enone 10 (150 mg) was dissolved in 6 ml of a stock solution prepared by dissolving 260 mg of dry potassium hydroxide in 26 ml of triethylene glycol. The solution was treated with 1 ml of anhydrous hydrazine (19) and allowed to reflux at 180° for 14 h. An additional 0.5 ml of hydrazine was added and reflux was continued for 1 h after which hydrazine was distilled from the reaction flask until the temperature (inside) of the reaction solution reached 210°. After keeping the reaction solution at 210° for 8 h, it was allowed to cool to room temperature then treated with 5 ml of water followed by 50 ml of ether. The ether solution was worked-up in the usual manner with dilute hydrochloric acid, saturated sodium bicarbonate solution, and brine. Chromatography of the product on a column of 10.7 g of silica gel with pentane as solvent followed by distillation in a small collar flask at 0.5 mm (bath temperature 98°) afforded 103 mg (74%) of (12) as an oil, v_{max} (film) 1648 cm⁻¹ (olefin); n.m.r. (CCl₄), $\delta 0.67$ (d, J = 6.5 Hz, 3H, secondary methyl), 0.87 (s, 3H, angular methyl), 1.73 (d, J = 2.0 Hz, 3H, vinylic methyl), 2.20 (m, 1H, allylic proton), 5.61 (m, 1H, vinylic proton).

The i.r. and n.m.r. spectra and fragmentation pattern of the mass spectrum of synthetic 12 were identical with the corresponding properties of an authentic sample of isoishwarane prepared from ishwarone.

Anal. Calcd. for C₁₅H₂₄: C, 88.16; H, 11.84. Found: C, 88.17; H, 11.72.

Enols 14a and b

A solution of 1.07 g of the enone 10 in 100 ml of dry ether was treated with 0.50 g of lithium aluminum hydride and the mixture was refluxed for 4 h. The cooled reaction mixture was treated dropwise with brine until the excess lithium aluminum hydride was deactivated and the ether solution was decanted from solid material. The ether solution was worked-up in the usual manner with brine. Column chromatography of the product on 107 g of silica gel, with gradually increasing portions of ether in benzene as solvent, gave two fractions.

Enol 14a. The first fraction eluted from the column afforded, after crystallization from pentane, 413 mg (38%) of 14a, m.p. 115-116°; v_{max} (Nujol) 3300 (OH) and 1648 cm⁻¹ (olefin); n.m.r. (CDCl₃), δ 0.72 (d, J = 6.5 Hz, 3H, secondary methyl), 0.98 (s, 3H, angular methyl), 1.73 (d, J = 2 Hz, 3H, vinylic methyl), 2.26 (m, 1H, allylic methine), 3.93 (m, 1H, H—C—OH), 5.65 (m, 1H, vinylic proton).

Anal. Caled. for C₁₅H₂₄O: C, 81.76; H, 10.98. Found: C, 82.13; H, 11.16.

Enol 14b. Crystallization of the second fraction from the column from pentane afforded 412 mg (38%) of 14b, m.p. 110° ; v_{max} (Nujol) 3250 (OH) and 1648 cm⁻¹ (olefin); n.m.r. (CDCl₃), δ 0.67 (d, J = 6.5 Hz, 3H, secondary methyl), 0.77 (s, 3H, angular methyl), 1.77 (d, J = 2.0 Hz, 3H, vinylic methyl), 2.29 (m, 1H, allylic methine), 3.91 (m, 1H, H–C–OH), 5.69 (m, 1H, vinylic proton).

Anal. Calcd. for C₁₅H₂₄O: C, 81.76; H, 10.98. Found: C, 81.62; H, 11.04.

Benzyl Ether 15a

The enol 14a was converted to the benzyl ether 15a in a

dry nitrogen atmosphere by the following procedure. A mixture of 250 mg of 14a, 100 mg of sodium hydride, and 8 ml of dry benzene was refluxed for 5 h. After cooling to room temperature the mixture was treated dropwise with 0.5 ml of benzyl chloride and refluxing was continued for 24 h. The cooled reaction mixture was treated dropwise with 2 ml of methanol then poured into a mixture of 150 g of ice and water. The aqueous mixture was extracted with ether and the extracts were washed with water. The product was chromatographed on a column of 86 g of silica gel with increasing proportions of benzene in petroleum ether as solvent. Elution of the column afforded 307 mg (87%) of 15a as an oil, v_{max} (film) 3030–3000, 2000–1600, and 800–680 (multiple bands, aromatic) and 1648 (olefin); n.m.r. $(CDCl_3)$, $\delta 0.70$ (d, J = 6.5 Hz, 3H, secondary methyl), 1.02 (s, 3H, angular methyl), 1.74 (d, J = 2.0 Hz, 3H, vinylic methyl), 2.43 (m, 1H, allylic proton), 3.57 (m, 1H, H—C—O), 4.43 (s, 2H, benzylic methylene), 5.67 (m, 1H, vinylic proton), 7.25 (m, 5H, aromatic protons).

Mol. Wt. Calcd. for $C_{22}H_{30}O$: 310. Found (mass spectrum): 310.

Benzyl Ether 15b

The enol 14b was converted into the benzyl ether 15b by the procedure described in the preceding experiment. The benzyl ether 15b was obtained in 82% yield as an oil, v_{max} (film) 3030-3000, 2000-1600, and 800-680 (multiple bands, aromatic) and 1648 cm⁻¹ (olefin); n.m.r. (CDCl₃), δ 0.69 (d, J = 6.5 Hz, 3H, secondary methyl), 0.73 (s, 3H, angular methyl), 1.77 (d, J = 2.0 Hz, 3H, vinylic methyl), 2.50 (m, 1H, allylic proton), 3.70 (m, 1H, H—C—O), 4.40 (s, 2H, benzylic methylene), 7.17 (m, 5H, aromatic protons).

Mol. Wt. Calcd. for $C_{22}H_{30}O$: 310. Found (mass spectrum): 310.

Benzyl Ether Alcohol 16a

The following reaction was carried out in a dry nitrogen atmosphere. A solution of 220 mg of the benzyl ether 15a in 3 ml of dry tetrahydrofuran was treated with 0.73 ml of a 1 M tetrahydrofuran solution of borane and stirred at room temperature for 12 h. The reaction mixture was treated with 0.5 ml of water followed by 1 ml of 1 M sodium hydroxide solution. The alkaline solution was treated, with cooling on an ice bath, with 1 ml of 30% hydrogen peroxide then stirred at 45° for 45 min. The reaction mixture was worked-up with ether and brine in the usual manner. Crystallization of the product from pentane afforded 190 mg (82%) of 16a, m.p. 104°, v_{max} (Nujol) 3475 (OH); n.m.r. (CDCl₃), δ 0.78 and 1.20 (doublets, J = 6.5 Hz, 3H each, secondary methyls), 1.10 (s, 3H, angular methyl), 3.60 (m, 1H, H-C-O), 3.88 (m, 1H, H—C—OH), 4.45 (s, 2H, benzylic methylene), 7.25 (m, 5H, aromatic protons).

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.43; H, 9.82. Found: C, 80.11; H, 10.01.

Benzyl Ether Alcohol 16b

The benzyl ether 15b (550 mg) was converted to the benzyl ether alcohol 16b by the procedure described in the preceding experiment. The product was purified by chromatography on a column of 33 g of silica gel in benzene–ether. Crystallization of the eluted product from pentane afforded 413 mg (71%) of 16b, m.p. 85–86°; v_{max} (film) 3410 cm⁻¹ (OH); n.m.r. (CDCl₃), $\delta 0.78$ and 1.05 (doublets, J = 6.5 Hz, 3H

each, secondary methyls), 0.85 (s, 3H, angular methyl), 3.73 (m, 2H, H—C—O and H—C—OH superimposed), 4.41 (s, 2H, benzylic methylene), 7.23 (m, 5H, aromatic protons). Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.43; H, 9.82. Found: C, 80.26; H, 9.73.

Keto Benzyl Ether 17a

A solution of 420 mg of the benzyl ether alcohol 16a in 20 ml of acetone was treated drop-wise with Jones reagent (17) until a persistent orange color was observed. The excess oxidizing reagent was then deactivated by dropwise addition of methanol until a permanent green color resulted. The reaction solution was treated with 5 ml of 1 M sodium bicarbonate solution and diluted with 150 ml of ether. The ethereal mixture was worked-up in the usual manner with sodium bicarbonate and brine. Purification of the oily product by preparative t.l.c. on silica gel with benzeneether (95:5) as solvent afforded 340 mg (82%) of 17a as an oil, v_{max} (film) 1715 cm⁻¹ (ketone); n.m.r. (CDCl₃), $\delta 0.83$ (d, poorly resolved, 3H, secondary methyl), 1.13 (d, J = 6.5Hz, 3H, secondary methyl adjacent to ketone), 1.15 (s, 3H, angular methyl), 3.68 (m, 1H, H-C-O), 4.47 (s, 2H, benzylic methylene), 7.27 (m, 5H, aromatic protons).

Anal. Calcd. for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 81.03; H, 9.07.

Keto Benzyl Ether 17b

The benzyl ether alcohol 16b was oxidized to the keto benzyl ether 17b by the procedure described in the preceding experiment. Crystallization of the product from pentane afforded 17b in 91% yield, m.p. $84-85^{\circ}$; v_{max} (film) 1715 cm⁻¹ (ketone); n.m.r. (CDCl₃), δ 0.78 (d, poorly resolved, 3H, secondary methyl), 0.92 (s, 3H, angular methyl), 1.07 (d, J = 6.5 Hz, 3H, secondary methyl adjacent to ketone), 3.83 (m, 1H, H-C-O), 4.45 (s, 2H, benzylic methylene), 7.17 (m, 5H, aromatic protons).

Anal. Calcd. for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 80.81; H, 8.85.

Keto Alcohol 18a

The keto benzyl ether (17a, 340 mg) in 50 ml of ethanol was hydrogenated over 180 mg of a palladium-charcoal catalyst (10% Pd) at atmospheric pressure for 1 h. Removal of the catalyst by filtration, evaporation of the solvent *in vacuo*, and crystallization of the product from ether-pentane afforded 218 mg (89%) of 18a, m.p. $90-91^{\circ}$; ν_{max} (Nujol) 3415 (OH) and 1703 cm⁻¹ (ketone); n.m.r. (CDCl₃), δ 0.83 (d, poorly resolved, 3H, secondary methyl), 1.15 (s, 3H, angular methyl), 1.16 (d, J = 6.5 Hz, 3H, secondary methyl adjacent to ketone), 4.05 (m, 1H, H—C—OH).

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 75.83; H, 10.20.

Keto Alcohol 18b

The keto benzyl ether 17*b* was converted to the keto alcohol 18*b* by the procedure described in the preceding experiment. Crystallization of the product from ether-pentane afforded 18*b* in 80% yield, m.p. 111-112°; v_{max} (Nujol) 3250 (OH) and 1710 cm⁻¹ (ketone); n.m.r. (CDCl₃), δ 0.80 (d, poorly resolved, 3H, secondary methyl), 0.92 (s, 3H, angular methyl) 1.10 (d, J = 6.5 Hz, 3H, methyl adjacent to ketone), 4.20 (m, 3H, H—C—OH).

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 75.98; H, 10.54.

Cyclopropyl Ketone 20

From Keto Alcohol 18a

A solution of 225 mg of 18a in 2 ml of dry pyridine was treated with 580 mg of *p*-toluenesulfonyl chloride and the resulting solution was kept under a nitrogen atmosphere at 3° for 3 days. The solution was then cooled on an ice bath, treated with 2 ml of ice-water, and stirred at 0° for 20 min. Ice-cold ether (60 ml) was added to the cold reaction mixture and the ethereal solution was worked-up in the usual manner with ice-cold 2 *M* hydrochloric acid and brine. The semi-crystalline product (370 mg) was used immediately for the next step.

The following reaction was carried out in a dry nitrogen atmosphere. The tosylate (370 mg) was dissolved in 5 ml of dry dimethyl sulfoxide and the solution was treated with 2.8 ml of a 0.5 M dimethyl sulfoxide solution of methylsulfinyl carbanion (18). The reaction solution was kept at 60° for 2 h, cooled to room temperature, and treated with 0.5 ml of water then diluted with 60 ml of ether. The ether solution was worked-up with brine in the usual manner. The product was purified by t.l.c. on silica gel with benzeneether (95:5) as solvent. Elution of the silica gel afforded 147 mg (71%) of 20 as an oil which gave rise to a single peak on v.p.c. having a retention time of 15 min, 40 s (column temperature programmed from 50 to 250° at 10°/mm), λ_{max} (EtOH) 208 nm (ε 4000); ν_{max} (film) 1715 cm⁻¹ (ketone); n.m.r. (CDCl₃), $\delta ca. 0.60$ (m, partially obscured, protons on cyclopropane ring), 0.73 (d, J = 6.5 Hz, 3H, secondary methyl), 0.97 (s, 3H, angular methyl), 1.17 (s, 3H, methyl on cyclopropane ring).

Anal. Calcd. for C₁₅H₂₂O: C, 82.52; H, 10.16. Found: C, 82.39; H, 9.88.

From Keto Alcohol 18b

The keto alcohol 18b was converted into the cyclopropyl ketone 20 in 60% yield by the procedure described in the preceding experiment. The product was identical with the cyclopropyl ketone obtained in the preceding experiment (i.r. and n.m.r. spectra, identical retention time on v.p.c. and inseparability on t.l.c. in various solvent systems).

(\pm) -Ishwarane (1)

The reduction of the cyclopropyl ketone 20 to ishwarane was carried out in a dry nitrogen atmosphere as follows (cf. 19). The cyclopropyl ketone 20 was dissolved in 6 ml of a stock solution prepared by dissolving 690 mg of sodium in 60 ml of ethylene glycol. The resulting solution was treated with 0.2 ml of anhydrous hydrazine (19) and heated with an oil bath until the temperature of the reaction solution reached 180°. More anhydrous hydrazine was added until the reaction solution refluxed freely at 180° and reflux at this temperature was continued for 14 h. Hydrazine was then distilled from the reaction flask until the temperature of the reaction solution reached 210°. After heating the reaction solution at 210° for 24 h, it was allowed to cool to room temperature and diluted with 60 ml of ether. The ether solution was worked-up in the usual manner with ice-cold 1 M hydrochloric acid, saturated sodium bicarbonate, and brine. Purification of the product by t.l.c. on silica gel with hexane as solvent afforded 64 mg (67%) of 1 as an oil which gave rise to a single peak on v.p.c. having a retention time of 17

min, 20 s (column temperature programmed from 50 to 250° at 8°/min), i.r., devoid of carbonyl absorption; n.m.r. (CCl₄), δ 0.50 (m, 2H, protons on cyclopropane ring), 0.72 (d, J = 6.5 Hz, 3H, secondary methyl), 0.78 (s, 3H, angular methyl), 1.12 (s, 3H, methyl on cyclopropane ring).

Anal. Calcd. for $C_{15}H_{24}$ (mol. wt. 204): C, 88.16; H, 11.84. Found (204 (mass spectrum)): C, 88.31; H, 11.65.

The synthetic hydrocarbon 1 was identical with an authentic sample of ishwarane obtained from natural sources (i.r. and n.m.r. spectra, retention times on v.p.c., fragmentation pattern of the mass spectra).

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