# Carbon atom insertion bicycloannulation: total syntheses of ishwarane and ishwarone

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*This paper is dedicated to Professor Paul de Mayo on the occasion of his 60th birthday*

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Insertion of a carbon atom into a methyl cyclohexene, leading in a single synthetic step to a bicyclo[3.2.1.$0^{2,7}$]octane by carbene addition to the double bond and carbene insertion into a methyl C—H bond, has been accomplished by treating the cyclohexene with carbon tetrabromide and methyllithium at low temperatures. This new bicycloannulation method has been employed in a total synthesis of ishwarane (**1**), the naturally occurring parent hydrocarbon of the ishwarane class of tetracyclic sesquiterpenes. Although this reaction was not successful with various possible precursors of ishwarone (**2**), this natural product was prepared in low yield by a two-step version of the carbon atom insertion bicycloannulation (CAIB) procedure involving addition of bromoform-derived dibromocarbene to the octalone (**5**) followed by treatment of the resulting dibromocyclopropane (**56**) with methyllithium. The same two-step sequence was also successful in the first synthesis of norishwarane (**20**), the hydrocarbon comprising the bare ring system of the ishwarane sesquiterpenoids. The Diels–Alder synthesis used in the preparation of the octalin precursor (**18**) of norishwarane could not be used for the terpenes themselves because of the lack of dienophilic reactivity of the required cyclohexenone (**7**). A regioselective Diels–Alder equivalent sequence was therefore developed, consisting of conjugate addition of lithium di(3-methyl-3-butenyl)cuprate (**42**) to 2,3,4-trimethylcyclohex-2-en-1-one (**7**), epoxidation, base-catalyzed cyclization of the resulting epoxide (**47**) to a mixture of primary and tertiary alcohols (**50** and **49**, respectively), and dehydration of **49** to give **5**. In the case of ishwarane, the octalin precursor (**62**) was synthesized by conjugate addition of lithium dimethylcuprate to octalone **59**, addition of methyl magnesium bromide to the resulting decalone (**60**) to give octalol **61**, and dehydration.

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En faisant réagir le cyclohexène avec le tétrabromure de carbone et le méthyllithium à basse température, on a réalisé l'insertion d'un atome de carbone dans le méthylcyclohexène; on a ainsi obtenu en une seule étape le bicyclo[3.2.1.$0^{2,7}$]octane par l'addition de carbène sur la double liaison et par une insertion de carbène dans une liaison C—H du méthyle. On a utilisée cette nouvelle méthode de bicycloannellation dans une synthèse totale de l'ishwarane (**1**), l'hydrocarbure naturel parent des sesquiterpènes tétracycliques de la classe de l'ishwarane. Bien que cette réaction n'aie pas pu être appliquée avec succès à divers précurseurs possibles de l'ishwarone (**2**), on a préparé ce produit naturel avec un faible rendement en faisant appel à une version en deux étapes de la méthode de bicycloannellation par insertion d'un atome de carbone (BIAC) impliquant une addition d'un dibromocarbène, provenant du bromoforme, sur l'octalone (**5**), puis une réaction du dibromocyclopropane (**56**) qui en résulte avec du méthyllithium. On a aussi utilisé cette méthode avec succès pour réaliser la première synthèse du norishwarane (**20**), l'hydrocarbure comportant le système cyclique de base du sesquiterpène ishwarane. Dû au faible caractère diènophile de la cyclohexènone (**7**) requise, on ne peut pas se servir de la synthèse de Diels–Alder pour la synthèse des terpènes eux-mêmes, même si cette synthèse peut être utilisée pour la préparation de l'octaline (**18**) précurseur du norishwarane. On a donc mis au point une série de réactions régiosélectives équivalentes à la réaction de Diels–Alder qui comprend une addition conjuguée du di(méthyl-3 butényl-3) cuprate de lithium (**42**) sur la triméthyl-2,3,4 cyclohexène-2 one-1 (**7**), une époxydation, une cyclisation, catalysée par les bases, de l'époxyde (**47**) formé qui conduit à un mélange d'alcools primaire et tertiaire (respectivement **50** et **49**) et finalement une déshydratation de l'alcool **49** permet d'aboutir au composé **5**. Dans le cas de l'ishwarane, on a préparé son précurseur, l'octaline (**62**), par une addition conjuguée de diméthylcuprate de lithium sur l'octalone **59**, suivie d'une addition de bromure de méthylmagnésium sur la décalone obtenue (**60**) qui permet d'obtenir l'octalol (**61**) dont la déshydration permet d'accéder au produit désiré.

[Traduit par le journal]

## Introduction

Ishwarane (**1**) (1), a tetracyclic sesquiterpene, is found in an interesting variety of tropical plants which seem to have little else in common: *Aristolochia indica* L. (Aristolochiaceae)[2] (2), *Cymbopetalum penduliflorum* (Dunal) Baill. (Annonaceae)[3] (3), and *Bixa orellana* L. (Bixaceae)[4] (7). A small family of

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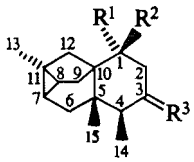
[2]This is the so-called Indian birthwort, the roots of which have been used for centuries in India as a folk remedy for snake and insect bites and a variety of other complaints. The name ishwarane for the sesquiterpene is derived from the Kanada name for this plant, *ishwari beru* (4). The extract of the roots has recently been found to have potent contraceptive properties, and the active principles have been isolated and characterized (5).

[3]The "ear flower" of the ancient peoples of Mexico, still used as a spice for flavouring food and beverages in Guatemala, is obtained from this tree, which occurs in the mountains of Guatemala and southern Mexico (6).

[4]The lipstick tree, cultivated widely throughout the tropical and subtropical areas of the world, is the source of annatto, an important natural food dye used in the colouration of butter, cheese, and margarine. In ancient times the Aztecs added it (along with the flavouring agent from *C. penduliflorum*) to the world's first chocolate beverage (*xocoatl*) to colour it red (15).

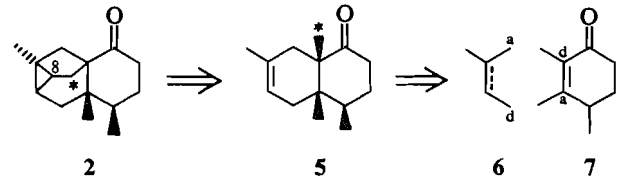


| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **1** | H | H | $H_2$ |
| **2** | —O— | | $H_2$ |
| **3** | H | OH | $H_2$ |
| **4** | H | H | O |

sesquiterpenoids,[5] of which ishwarane is the parent hydrocarbon, comprises ishwarone (**2**) (8) and ishwarol (**3**) (9) (both congeners of ishwarane in *A. indica*), and 3-oxoishwarane (**4**) (10) (from *A. debillis*). Because of the unusual polycyclic structure of these molecules, they have attracted the attention of a number of synthetic organic chemists, and total syntheses of ishwarane (11–13), ishwarone (13, 14), and ishwarol (13) have been reported. We now wish to describe in detail our own total syntheses of ishwarane and ishwarone.[6]

From a synthetic standpoint, the strategically central structural moiety of the ishwarane terpenes is the tricyclo-[3.2.1.$0^{2,7}$]octane system containing rings B, C, and D.[7] Our plan (Scheme 1) was based on the retrosynthetic removal of a single carbon atom (C-8) from that portion of the ishwarone framework,[8] resulting in a significant simplification of structure and leaving behind an octalone system (**5**), the construction of which would, on the most naive level, be a simple matter using the Diels–Alder strategy. Unfortunately, however, on the basis of the lack of dienophilic reactivity observed (19) for 2,3-dimethylcyclohexenone, cyclohexenone **7** would not be expected to react at all with isoprene.[9] Nonetheless, the ready availability of cyclohexenone **7** led us to propose an *equivalent* of the Diels–Alder synthesis employing a *polarized* isoprene synthon of type **6**, having either an intact or a latent double bond (*vide infra*).[10]

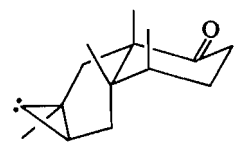
Provided an efficient procedure could be devised for the insertion of the carbon atom into the octalone **5** in the desired fashion, one would have in hand an extremely concise route to a fairly complex terpene structure. In the absence of functional groups other than the olefin and carbonyl in **5** with which to activate this intermediate toward attack by an appropriate reagent, the only viable approach along these lines (Scheme 2) is via a carbon atom equivalent capable of acting as a dicarbene synthon, sequentially adding to the olefin to form the cyclopropane (ring D) and inserting into a C—H bond of a specific methyl group (pro-C-9). In order for this to be of synthetic



**2** **5** **6** **7**

SCHEME 1. Retrosynthetic analysis of ishwarone.

utility, the normal preference for attack on the less hindered convex face of the *cis* octalone (25) must obtain so that the reagent adds stereoselectively to the β side of the olefin, and, equally important, intramolecular insertion of the intermediate cyclopropylidene (**8**) must occur regioselectively, so that little or no insertion into the other angular methyl group or any of the ring C—H bonds takes place. The latter condition was expected to be fulfilled by the fact that conformation **8** should be the preferred one, due to an unfavourable 1,3-diaxial interaction between methyl groups in the other chair conformer (**9**),[11] and by the fact that in conformer **8** the carbene and the



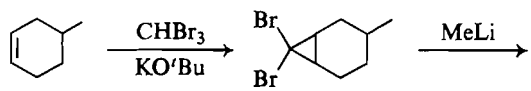
**9**

methyl into which insertion is desired are within bonding distance of each other.[12] In spite of these encouraging considerations, however, it was apparent from the outset that a source of naked carbon atoms woud not be synthetically useful for this purpose in light of the high reactivity and low selectivity of this simplest of all organic reactive intermediates (29). We therefore sought a less direct means of accomplishing the desired carbon atom insertion.

## Results and discussion

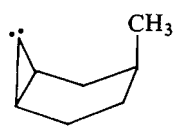
### *Model studies*

As we began our work in this area, we were spurred on by the important observation by Paquette *et al.* (30) that applica-




**10** **11**

**12** **13** **14**




**15**

[5]For a review of the chemistry of the eremophilane sesquiterpenes, including the ishwarane family, see ref. 16.

[6]For preliminary accounts of portions of this work see refs. 11, 14, and 17. An attempted, but unsuccessful, synthesis of ishwarone has also been reported (18).

[7]This ring system is also present in another sesquiterpene, cycloseychellene (20), and in the trachylobane (21) and helifulvane (22) series of diterpenoids. For an alternative approach to the rapid construction of this system, see our synthesis of trachyloban-19-oic acid (23) and ref. 12*a*.

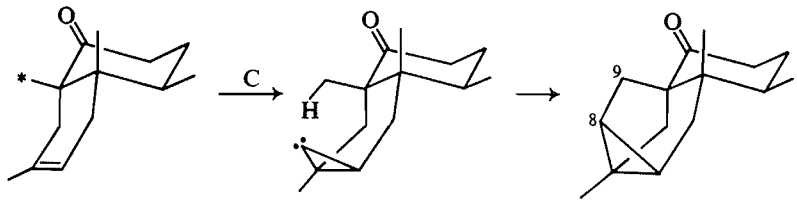
[8]Since ishwarone has been converted to ishwarane by Wolff–Kishner reduction (8*a*), any synthesis of the former constitutes a formal synthesis of the latter.

[9]We have confirmed this under a variety of conditions.

[10]For annulations via a related conjunctive reagent see ref. 24.

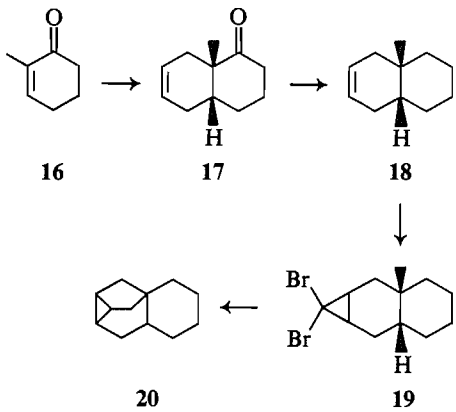
[11]This interaction costs approximately 3.7 kcal $mol^{-1}$ (15.5 kJ $mol^{-1}$) (26).

[12]Interestingly, this plan would have been rejected by the computer-assisted design program LHASA on the grounds that a bond to a cyclopropane ring is not a strategic one (27). For a related violation of this rule see ref. 28.



5 8 2

SCHEME 2. Carbon atom insertion.

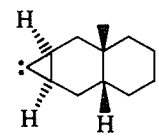


16 17 18 19 20

SCHEME 3. Synthesis of norishwarane.

tion of Moore's bicyclobutane synthesis (31)[13] to 4-methylcyclohexene (**10**) via the dibromocyclopropanes **11** led not only to the expected ring C—H insertion products **12** and **13**, but also to the parent tricyclo[3.2.1.$0^{2,7}$]octane (**14**), resulting from *methyl* C—H insertion, surprisingly, as the major product.[14] Furthermore, it was deduced on the basis of mass balance considerations that this tricyclooctane must have been the *exclusive* product from debromination of *cis*-**11**, while the other two products were derived only from the *trans* dibromide. Methyl insertion was explained by involving kinetic control, in which the *proximity* of the carbenoid[15] and methyl groups in the *cis* axial conformer **15** outweighed all other factors, including the greater nucleophilicity of secondary C—H bonds[16]. Thus, our prediction that ring C—H insertion should not be a problem seemed to be confirmed by this experiment, and carbon atom insertion via a dibromocyclopropane intermediate appeared to be a viable approach to the ishwarane structure.

Accordingly, a model study (Scheme 3) was carried out to test the accommodation of the Moore sequence to the requirement that initial attack on the octalone **5** must be on its β face. In this we followed the plan of Scheme 1, where all structures were simplified by lacking one or more methyl groups. Thus, when the *cis* octalin **18**, prepared by Lewis acid-catalyzed Diels–Alder reaction (19) of 2-methylcyclohex-2-enone (**16**) with 1,3-butadiene followed by Wolff–Kishner reduction of the resulting octalone **17**, was treated with bromoform and aqueous sodium hydroxide under phase-transfer conditions (35), the dibromocarbene adduct **19** was produced in 48% yield. Contrary to expectations, however, this appeared to be a mixture of α and β diastereomers by gas chromatographic analysis, which showed two overlapping peaks in a ratio of about 2:1,[17] in spite of the fact that only one methyl singlet was visible in the $^1$H nmr spectrum. On reaction of this mixture with methyllithium at −10°C there were obtained three debromination products in a total yield of 77%, of which two could not be separated from each other. Although the latter material could not be completely characterized due to the fact that it was a mixture, the presence of two methyl singlets at δ 0.77 and 0.91 (ca. 2:1 ratio) in its $^1$H nmr spectrum indicated that *both* of the components had resulted from *ring* C—H insertion rather than methyl C—H insertion. The third product, however, which was produced in 28% yield, lacked a singlet in its $^1$H nmr spectrum, as expected for methyl insertion, and this compound was therefore assigned the structure of the desired product, norishwarane (**20**), possessing the complete ring system of ishwarane itself (**1**) but divested of the three methyl groups of the natural product.[18] As in the case of the Paquette study (30), mass balance considerations led us to tentatively propose that while the two ring C—H insertion products were derived only from the undesired α dibromocarbene adduct (concave attack on octalin **18**), norishwarane (**20**) was the exclusive product from intramolecular insertion of cyclopropylidene (**21**) (corresponding to **8**). These conclusions, on



**21**

the other hand, would appear to imply that the preferred attack of dibromocarbene on octalin **18** is from the (presumably more hindered) concave face of the olefin, a seemingly untenable inference. For this reason, it is believed that at least a portion of one or both of the ring C—H insertion products was derived from the β dibromocyclopropane. Possible factors responsible for this observation, which contradicts Paquette's findings for the simpler 4-methylcyclohexene adduct, are discussed below.

Whatever the causes of the mixed results of this model study, the production of even some of the desired norishwarane was at least encouraging, and a means of inserting the carbon atom in a *single* step, as opposed to the two-step sequence required

[13]For recent applications of this procedure see ref. 32.

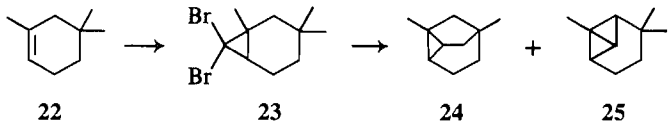
[14]Other instances of preferential insertion into primary C—H bonds have been reported (33). This amounts, in this case, to insertion of the cyclopropylidene into a δ C—H bond. For other examples see ref. 34.

[15]For recent work on the elucidation of the nature of this intermediate see ref. 36. For a review of the chemistry of lithium halocarbenoids see ref. 37.

[16]For a recent discussion of the selectivity of the insertion of cyclopropylidenes into C—H bonds see ref. 38.

[17]A 0.2 in × 10 ft copper column packed with 10% SE-30 on Diatoport S was employed at 200°C.

[18]For further proof of this structure by $^{13}$C nmr see ref. 39.

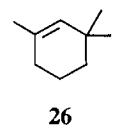



22 23 24 25

SCHEME 4. Carbon atominsertion model study.

by the Moore procedure, was devised to avoid the isolation and purification of the heat sensitive dibromocyclopropane intermediate. Our one-step method is based on the Skattelbøl allene synthesis (40)[19], in which an olefin is converted to the corresponding allene by insertion of a carbon atom between the two carbons of the olefinic double bond. This procedure involves treatment of the olefin with carbon tetrabromide and excess methyllithium at low temperatures, thus generating dibromocarbene by lithium–bromine exchange[20] and converting the resulting dibromocyclopropane *in situ* to the cyclopropylidine, which collapses to the allene. Encouraged by the fact that an excess of cyclohexene had previously been found to give a low yield of the corresponding dibromocyclopropane on reaction with carbon tetrabromide and *n*-butyllithium at −50°C (42), we chose to investigate the use of carbon tetrabromide as a carbon atom equivalent for insertion into cyclohexenes in a single step. In order to allow for the maximum chance of success, a cyclohexene having a methyl substituent on at least one of the olefinic carbons was desirable in view of the higher reactivity toward dichlorocarbene offered by methylcyclohexene over cyclohexene itself (43)[21]. Such a substrate would have the added advantage of having an olefinic group identical in structure to that of the proposed ishwarone precursor, **5**. Furthermore, a cyclohexene having *two* methyl groups at the 4-position, so that *cis* and *trans* dibromocyclopropanes are not possible, would not suffer from any lack of stereoselectivity of the dibromocarbene addition, as do addition to 4-methylcyclohexene and, apparently, octalin **18**.

Accordingly, the substrate chosen for the model study of the one-step carbon atom insertion was 1,5,5-trimethylcyclohexene (**22**), which was obtainable (47) from isophorone as an 85:15 mixture with 1,3,3-trimethylcyclohexene (**26**).[22] Initially, the Moore two-step procedure was tested on this material to serve as a benchmark for comparison with the proposed one-step method (Scheme 4). Thus, treatment of the olefinic mixture of **22** and **26** with bromoform and aqueous base under the same conditions as for octalin **18** (35) gave a 45% yield of dibromocyclopropane **23**, while the more hindered olefin **26** was recovered unchanged. Debromination of **23** with methyllithium at −10°C produced not one product, as expected on the basis of Paquette's earlier report on 4-methylcyclohexene, but *two* tricyclic hydrocarbons: only a 21% yield of the expected tricyclo[3.2.1.$0^{2,7}$]octane **24** and a surprising 33% yield of the



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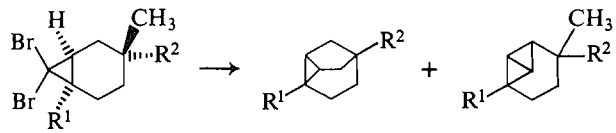



27 28 29

(**a**, R' = Me, $R^2$ = H; **b**, R' = H, $R^2$ = Me; **c**, R' = Me, $R^2$ = Me)

tricyclo[4.1.0.$0^{2,7}$]heptane **25** (yields determined by gas chromatographic analysis).[23] Paquette and Taylor (49) have since found similar behavior for the dibromocyclopropanes **27**, which provide mixtures of tricyclooctane **28** and tricycloheptane **29** on reaction with methyllithium. Both we (50) and these authors have ascribed this increased tendency toward *ring* C—H insertion (vis-à-vis *cis*-**11**) at least partly to a ponderal effect in which additional substituents slow down the rate of conformational interconversion of the intermediate cyclopropylidenes to such an extent that ring C—H insertion becomes competitive with the faster methyl C—H insertion. The latter, however, can only occur when the methyl into which insertion is possible is oriented axially (as in **15**). The behaviour of the dibromocyclopropane (**19**) derived from octalin **18** can be attributed to the same sort of competition between C—H insertion and conformational mobility. In fact, it is the parent 4-methylcyclohexene-derived dibromocyclopropane **11** which is the anomaly, such that ring flipping is apparently *faster* than ring C—H insertion in the intermediate cyclopropylidene (**15**), thus allowing methyl insertion to take over completely. At any rate, these results did not deter us from the pursuit of our goal since, as mentioned above, the conformation shown for the proposed intermediate cyclopropylidene **8** was expected to greatly predominate.

Suitable conditions for the *one*-step conversion of cyclohexene **22** to the carbon atom insertion products **24** and **25** were found after a number of unsuccessful experiments, and it appears on the basis of these results that the reaction is quite sensitive to temperature and concentration. For example, when a solution of cyclohexene **22** and an equimolar amount of carbon tetrabromide in diethyl ether at −78°C was treated with an equimolar amount of methyllithium, and the mixture was stirred at that temperature for 1.5 h and then allowed to warm to 0°C, followed by addition of a *second* equimolar quantity of methyllithium, the tricyclic products **24** and **25** were obtained in 17% and 39% yields (by gas chromatographic analysis), respectively. These yields were, even at this level of development, a significant improvement over the overall yields from the Moore two-step procedure (9% and 15%, respectively), but further increases were observed when a more dilute solution in diethyl ether was used, amounts of carbon tetrabromide and methyllithium were *doubled*, and the second addition of methyllithium was carried out at −30°C instead of 0°C. Under these optimum conditions (17) not only the total yield of carbon atom insertion products, but also the relative proportion of the desired tricyclooctane (**24**) was increased, such that **24** and **25**

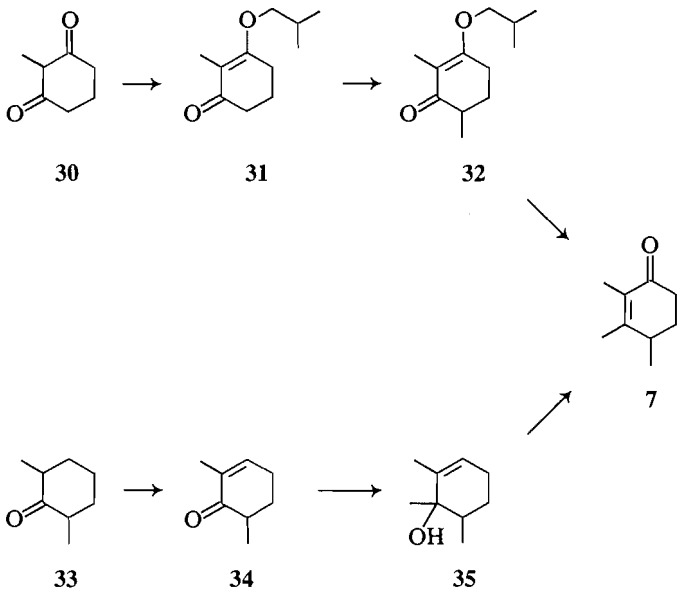
[19]For more recent applications of this reaction see ref. 41.

[20]For the determination of the structure of the intermediates in this reaction by $^{13}C$ nmr see refs. 36 and 44.

[21]Methylcyclohexene is 8.43 times more reactive than cyclohexene toward dichlorocarbene generated from chloroform and potassium *tert*-butoxide, as quoted in ref. 45. Although the sensitivity of dibromocarbene to electronic effects (greater reactivity toward more electron-rich olefins) is somewhat attenuated by steric hindrance, relative to the chlorine analogue, this factor is not so important as to override the electronic one in the cases studied thus far (46).

[22]These olefins, commonly known as α- and β-cyclogeraniolene, occur in the defense secretions of the major soldiers of the African termite *Ancistrotermes cavithorax* (48).

[23]For spectral data establishing the structure of these compounds see refs. 17 and 39.




SCHEME 5. Synthesis of 2,3,4-trimethylcyclohexenone.

were obtained in a combined yield of 80%, containing *equal* amounts of the two isomers. Thus our one-step method is, at least in this case, far superior to the Moore two-step sequence, being much more convenient and providing a greater than 300% enhancement in the yield of the ishwarane model compound, **24**. This new synthetic method, which accomplishes the insertion of a single carbon atom into a molecule by addition to a C—C double bond and insertion into a C—H bond in one smooth operation, thereby forming a tricyclic system from a monocyclic one, will hereafter be referred to as *carbon atom insertion bicycloannulation* (CAIB).[24]

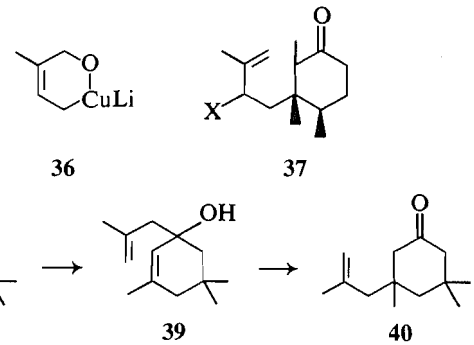
*Total synthesis of ishwarone*

Although cyclohexenone **7** (53) (Scheme 1) had been prepared from Hagemann's ester (54), the low yield of this process (16%) dictated a search for a more efficient route. We therefore explored two relatively new methods which held out the promise of higher yields (Scheme 5). The first of these, based on a sequence suggested by Stork and Danheiser (55), involved kinetically controlled methylation of enol ether **31** to give **32**, which was then converted to cyclohexenone **7** by addition of methyllithium and hydrolysis.[25] The overall yield from the relatively expensive dione, **30**, was a respectable 74%. However, a more economical approach proved to be by way of the allylic oxidation method of Dauben and Michno (56). Thus, chlorination–dehydrochlorination (57) of 2,6-dimethylcyclohexenone (**33**), followed by addition of methyllithium to the resulting cyclohexenone, **34**, provided allylic alcohol **35**, which without purification was directly converted to cyclohexenone **7** by PCC oxidation. In this case the overall yield of **7** from cyclohexenone **33** was 48%, but the greater convenience and less expensive materials used for this sequence made it the method of choice for large scale preparations of **7**.

[24]To the best of our knowledge, only one other type of CAIB has been reported, the Katz-Cheung bicycloannulation of aromatic and other conjugated carbanions (51). For recent applications of this highly useful reaction see ref. 52.

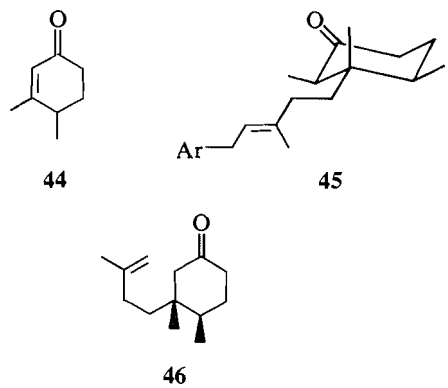
[25]Following our preliminary publication in which this synthesis was described (14), the same route to enol ether **32** was reported by Piers *et al.*, and experimental details have been provided by them (58).

A suitable chemical realization of synthon **6** (Scheme 1) having an intact double bond might be the complex organocuprate **36**, in which the alkoxide moiety is present in the



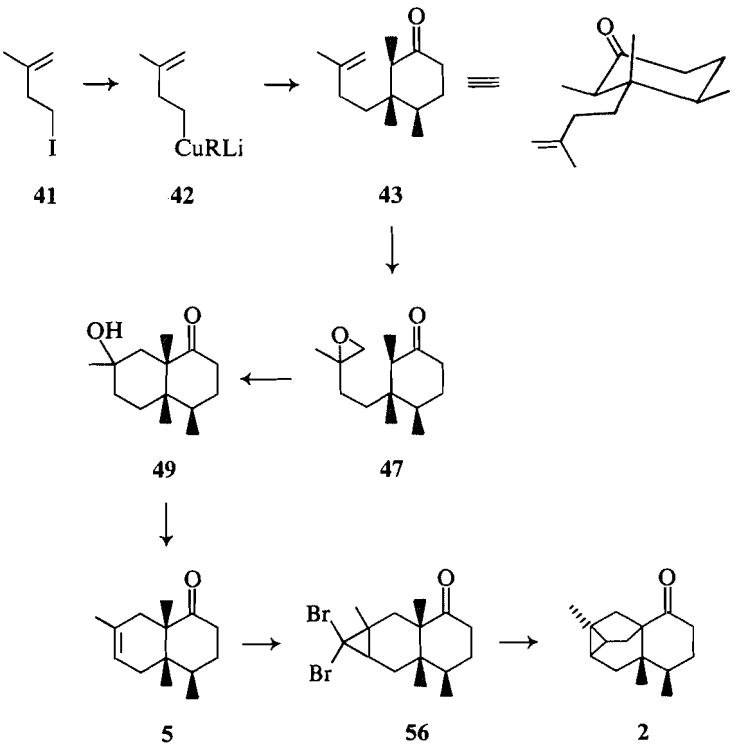

capacity of a latent leaving group (59). Athough it is even conceivable that such a conversion of cyclohexenone **7** to octalone **5** could be carried out in a single pot, where the initial conjugate addition of the organocopper moiety would be followed by addition of a sulfonyl chloride and *in situ* formation of a sulfonate leaving group, our experiments with model compounds did not prove sufficiently promising to justify a full investigation of any version of this plan.

However, a less direct implementation of the protocol embodied in synthon **6** was ultimately successful (Scheme 6).[26] The organocuprate **42** (R = $CH_2CH_2C(CH_3)CH_2$) was prepared without incident from homoallyl iodide **41** (64) by addition of *tert*-butyllithium at −78°C followed by copper(I) iodide at −50°C.[27] Addition of cyclohexenone **7** to the resulting solution in diethyl ether at −45°C and aqueous work-up gave a 45% yield (60% based on consumed **7**) of the keto-olefin, **43**, after chromatography on alumina. Athough this product appeared to be a mixture of epimers by nmr, the major component is believed to have the stereochemistry shown. This assumption is based partly on the previously known preference for attack of organocuprates on 3,4-dimethylcyclohexenone (**44**) to give the




[26]An alternative approach would have involved an allylic precursor, **37**, which was intended to undergo an internal $S_N2'$ ($S_{cN'}$) reaction (60) on treatment with base. Unfortunately, this plan was thwarted at an early stage when it was found in a model study that the anionic oxy-Cope rearrangement (61) of the tertiary allylic alcohol, **39**, prepared from isophorone (**38**) and allyl magnesium chloride, gave mainly isophorone and only a 14% yield of the desired ketone, **40**. The primary pathway of this reaction is thus a β hydroxy olefin cleavage (62) and this has also been observed by Evans *et al.* as a side reaction in some of their anionic oxy-Cope rearrangements with compounds closely related to allylic alcohol **39** (63).

[27]For recent applications employing this same cuprate see ref. 65.

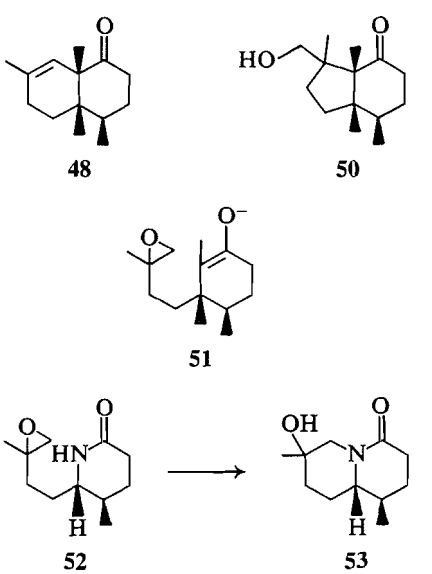



SCHEME 6. Total synthesis of ishwarone.

adduct having *cis* methyl groups with high stereoselectivity (66, 67), and partly on the occurrence of a high field singlet absorption in the nmr at δ 0.57 attributable to an axial methyl at C-3 shielded by the carbonyl group (cf. the microbial metabolite **45**, in which the corresponding absorption appears at δ 0.55 (68)). An attempt to develop a more efficient synthesis of keto-olefin **43** via trapping of the intermediate enolate from addition of **42** to cyclohexenone **44** with methyl iodide (69) produced only the adduct, **46**, none of the desired methylation being observed. Similar lack of success has been obtained in closely related studies by Mori and Fujioka with the same substrate (70).

Epoxidation of keto-olefin **43** with *m*-chloroperbenzoic acid was not accompanied by any detectable amounts of lactones resulting from Baeyer–Villiger oxidation, giving the desired keto-epoxide (**47**) as a mixture of diastereomers.[28] Direct treatment of this mixture, without purification, with potassium *tert*-butoxide in *tert*-butyl alcohol at reflux provided a crude mixture of keto-alcohols which, as a solution in cyclohexane, was subjected to dehydration with 50% aqueous sulfuric acid (25*a*). The major product of these reactions (38% from keto-epoxide **47**) was shown to be a 4.3:1 mixture of the desired octalone, **5**, and its position isomer, **48**, by spectrosopic analysis and ultimate conversion of **5** to ishwarone (**2**). It therefore follows that the major product of the base-catalyzed cyclization was keto-alcohol **49** (presumably as a mixture of diastereomers). However, this compound was accompanied by minor quantities of keto-alcohol **50**, which survived the dehydration conditions used here as a result of its being a primary alcohol. It was therefore convenient to wait until this stage for purification of the intermediates, since octalone **5** was easily separated from keto-alcohol **50** by chromatography on alumina. Although, in the absence of definite information as to the stereochemistry of keto-alcohols **49** and **50** and their precursors, it is not possible to speculate on the factors responsible for the observed low regioselectivity for attack of the enolate moiety of intermediate **51** on the primary carbon of the epoxide moiety, the formation of the five-membered ring of **50** by attack on the tertiary carbon of the epoxide was not surprising in light of previous studies of epoxide – keto-enolate cyclizations (25*a*, 66, 71). However, it is worthy of note that the analogous cyclization of the epoxy-lactam **52** with sodium hydride in benzene has been reported to form exclusively a six-membered ring, giving hydroxy-lactam **53** (72).

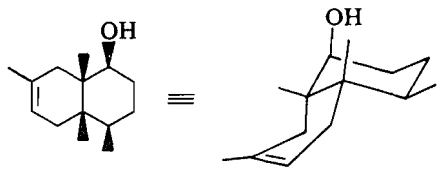
With the obtention of octalone **5** the Diels–Alder equivalent



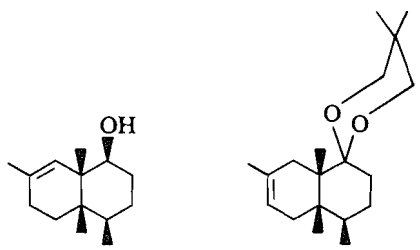

[28]For a more recent, closely related sequence from cyclohexenone **44** see ref. 67.

sequence, which represents overall addition of isoprene to cyclohexenone **7** in a specific regiochemical and stereochemical sense, was complete. It remains to be seen how general this process will be in view of the mixture of products obtained in the epoxide cyclization, but the loss of almost half of the material through formation of the side product, **50**, was not so discouraging as to deter us from our goal. Accordingly, the stage was now set for the proposed CAIB of octalone **5**, which was designed to give ishwarone (**2**) in a single step. In spite of the presence of the carbonyl group and the potential for addition of methyllithium or other carbanionic intermediates to it during the application of our new CAIB method, we were led to believe that protection of the ketone function would not be necessary by a report from Sydnes and Skattebøl (73) describing the reaction of methyllithium with dibromocyclopropyl ketones to give exclusively C—H insertion products resulting from bromine–lithium exchange, none of which involved attack at the carbonyl group.[29] Nevertheless, treatment of octalone **5**[30] with carbon tetrabromide and methyllithium under the conditions established in the model studies gave only intractable material.

Accordingly, although the reasons for the failure of the CAIB were not understood, it was decided that the carbonyl group of octalone **5** should be reduced to the alcohol in the hope that the resulting octalol, **54**, would undergo the desired CAIB to give ishwarol (**3**). Reduction of the mixture of octalones **5** and **48** with lithium aluminium hydride gave a mixture of octalols **54** and **55**, the $^1$H nmr spectrum of which showed a




**54**




**55** **57**

triplet ($J$ = 3Hz) at δ 3.37 for the carbinol C—H, indicating an axial hydroxyl group for the major component, **54**. Since the spectrum of ishwarol (**3**) exhibits a very similar absorption, and it has been obtained by hydride reduction of ishwarone (**2**) (8*a*, 9), it was apparent that attack of the hydride had occurred on the α side of the octalone, away from the hindering methyl groups, as expected. Thus, it can be concluded that **54** has the conformation shown, and, assuming the corresponding intermediate carbenoid in the CAIB adopts an analogous one, intramolecular C—H insertion should occur at the desired methyl group as in Scheme 2. Again, however, attempted CAIB with **54** under our standard conditions failed to produce any identifiable materials.[31]

It would thus appear that our CAIB method is considerably more limited than we had hoped, and that the success or failure of carbon atom insertion with methyllithium – carbon tetrabromide is dependent to a large extent on the structure of the olefinic reactant and other functional groups present. Be that as it may, there was still a chance that the two-step procedure involving bromoform/base followed by lithium–bromine exchange with the resulting dibromocyclopropane could convert our intermediate octalone, **5**, to ishwarone and (or) the corresponding octalol, **54**, to ishwarol. In the latter case, reaction of the octalol with bromoform and aqueous base under the same phase-transfer conditions used for octalin **18** gave a crude tarry product, the nmr of which indicated that the alcohol group was no longer present.[32] Ketones, on the other hand, are generally somewhat less reactive under these conditions than alcohols are (78, 79), and treatment of the mixture of octalones **5** and **48** with bromoform and aqueous sodium hydroxide in the presence of tributylamine (80) gave dibromocyclopropane **56** mixed with unreacted **48**, as expected. When this crude mixture was treated with methyllithium in ether at −10°C, and the crude products were subjected to gas chromatographic analysis, a small amount of material having the same retention time as that of authentic ishwarone (**2**)[33] was collected. This proved to be a mixture, but preparative thick-layer chromatography enabled the separation of a minute amount of material having spectroscopic properties ($^1$H and $^{13}$C nmr) identical with those of the authentic ishwarone. Athough the yield of this reaction, and therefore of the overall total synthesis, was very low, the synthesis from the cyclohexanedione, **30**, or the cyclohexenone, **33**, consisted of only nine steps, comparing favourably, in length, at least, with the previously reported synthesis of racemic ishwarone, which required some 19 steps from cyclohexenone **44** (13).

*Total synthesis of ishwarane*

In spite of the failure of our CAIB method in the synthesis of ishwarone, we were confident that the procedure would be

[29]More recently, mixed results have been obtained with other dibromocyclopropyl ketones (74). For a review of the generation and reactions of carbenes and carbenoids having neighbouring heteroatoms see ref. 75. Adding further complexity to this subject, it has been found that bromolithiocyclopropanes can be induced to add intermolecularly to ketones and aldehydes (76). It thus would appear that the course of reaction which a given substrate takes is dependent to a large extent on its structure and the conditions. In any case the carbonyl group of octalone **5** is a very hindered one, and no interference with the CAIB was expected from it.

[30]The mixture of octalones **5** and **48** was used due to the difficulty in separating these isomers and in the expectation that **48** would be unreactive, as was the analogous olefin, **26**.

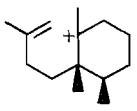
[31]Mixed results have been obtained regarding the reactivity of hydroxyl groups under the conditions of alkyllithium-induced bromine–lithium exchange in dibromocyclopropanes (75, 77). Protection of the carbonyl group of octalone **5** as the ketal (**57**) also failed to enable the CAIB.

[32]Although phase transfer catalyzed addition of dibromocarbene to the double bond of olefinic alcohols can usually be accomplished without interference, reaction of dibromocarbene and dichlorocarbene with alcohols is known to give a variety of products, most based on "deoxidation" to carbocations (78). We have also demonstrated that cyclohexanol gives 7,7-dibromonorcarane under the same conditions, presumably by way of cyclohexyl cation and dibromocarbene addition to cyclohexene resulting from loss of a proton from the carbocation.

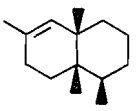
[33]We are greatly indebted to Dr. P. C. Parthasarathy, C.I.B.A.–Geigy Research Centre, Bombay, for generous samples of ishwarone and ishwarane.

viable for the corresponding hydrocarbon since it seemed reasonable to assume that the difficulties which prevented us from using it for ishwarone and ishwarol were somehow associated with the presence of the functional groups, and since our model studies, which were carried out on hydrocarbons (e.g. **22**), had already proven the utility of the CAIB methodology. Although the octalin, **62** (Scheme 7), required for a CAIB synthesis of ishwarane (**1**) could conceivably have been prepared from octalone **5** by Wolff–Kishner reduction, the length of the sequence leading to **5** as well as the loss of considerable material at the epoxide cyclization stage dictated a search for more efficient possibilities for the synthesis of the octalin.[34]

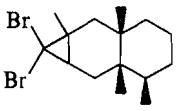
The ultimately successful plan (Scheme 7),[35] involved conjugate addition of a methyl group to the octalone, **59**, which has also been employed in two other syntheses of ishwarane (12), followed by addition of a methyl group to the carbonyl of the resulting decalone, and dehydration. When the octalone, **59**, obtainable stereoselectively by the elegant method of Boeckman *et al.* (83)[36] was treated with lithium dimethylcuprate – dimethyl sulfide complex (84), the desired decalone, **60**, was obtained in 77% yield. The assignment of the *cis* stereochemistry to this decalone was based on the eventual success of the total synthesis as well as literature precedent (25*c*, 81*h*). Addition of methyl magnesium iodide gave a mixture of tertiary alcohols, **61**, which, without purification, was dehydrated



**58**



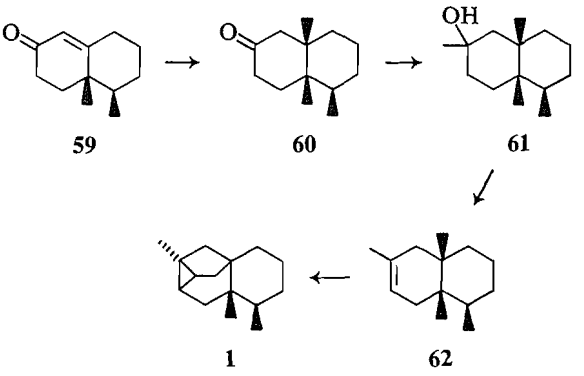
**63**




**64**

as for the analogous ishwarone intermediate, **49**, providing an 87% yield of a 1:1 mixture of octalins **62** and **63**. Although these isomers could not be separated, as was the case with octalone **48**, octalin **63** has the more hindered olefinic group and thus would not be expected to react with dibromocarbene in the next step.

With octalin **62** in hand, the stage was set for the application




**59** **60** **61**

**1** **62**

SCHEME 7. Total synthesis of ishwarane.

of our CAIB reaction, and, indeed, treatment of the mixture of octalins **62** and **63** with carbon tetrabromide and methyllithium under the standard conditions gave a mixture of isomeric hydrocarbons from which ishwarane (**1**), identical with an authentic sample,[33] was separated in 20% yield using gas chromatography[37]. Thus, the total synthesis of ishwarane was accomplished in remarkably few steps, namely four from octalone **59**, compared with 12 steps for the Hagiwara synthesis (12*a*) and 10 steps for the Kelly synthesis (12*b*). Unfortunately, the nature of the side products of the CAIB step are not known, since they could not be separated from each other, but it is clear that ishwarane was formed in fairly good yield from octalin **62**, in view of the fact that a 40% yield of octalin **63** was recovered from the reaction.

In summary, the CAIB method that we have developed for the synthesis of the tricyclo[3.2.1.$0^{2,7}$]octane ring system seems to be useful only in cases in which (a) the cyclohexene substrate bears an alkyl substituent on the double bond and (b) there are no interfering functional groups in the substrate, ketone and alcohol groups being the two which we have shown to be detrimental. In the proper cases, limited though they may be, it is clear that CAIB can save a tremendous amount of time and materials over more traditional, multistep procedures.

## Experimental

*General*

All reactions were conducted under a positive pressure of argon. Ethyl ether (when used as a reaction solvent), tetrahydrofuran, and 1,2-dimethoxyethane were distilled from sodium–benzophenone, diisopropylamine and *tert*-butyl alcohol were distilled from calcium hydride, and hexamethylphosphoramide was distilled from 13× molecular sieves. Methyllithium (in ethyl ether), *n*-butyllithium (in hexane), and *tert*-butyllithium (in pentane) were obtained from Ventron. These solutions were titrated (85) with 2-butanol in xylene (bipyridyl indicator) before use.

Preparative thick-layer chromatography was performed on precoated E. Merck silica gel GF (2 mm thick) on glass plates. Ethyl acetate was used to extract the separated components from the silica gel. Gas chromatography was carried out by using 1.5% OV-101 on Chromosorb G (100/120 mesh) in a 0.2 in. × 6 ft stainless-steel column with a helium flow rate of 60 mL/min unless otherwise noted.

[34]Although one could argue that a total synthesis of ishwarane is a redundant exercise at this point,[8] the unsatisfactory yield of the last step in our synthesis of ishwarone and a desire to put our new CAIB method to good use were sufficient reasons to approach ishwarane via octalin **62**.

[35]An alternative approach would have involved a carbocation–olefin cyclization (81) of tertiary carbocation **58** followed by loss of a proton to give **62**. Unfortunately, however, this plan was thwarted at an early stage by the fact that when cyclohexenone **16** was treated with lithium dimethyl cuprate in diethyl ether at 0°C, the solvent was replaced by 1,2-dimethoxyethane, and the resulting solution of enolate was treated with iodo alkene **41**, the major product isolated was that of simple conjugate addition, 2,3-dimethylcyclohexenone, very little alkylation of the enolate having taken place. This undesired result can be attributed at least in part to β elimination from the homoallylic iodide, **41**, (thus providing a source of protons for ketonization of the enolate) under the highly basic conditions of the reaction, although other workers have reported no problems with the same alkylating reagent and related carbanionic substrates (64, 82).

[36]This octalone was prepared, in the early stages of our work, by the method of Kelly and Zamecnik (12*c*), but we later found the more selective Boeckman sequence to be somewhat more satisfactory. We are most grateful to Yousry M. A. Naguib for the preparation of sufficient quantities of octalone **59**.

[37]In one small-scale experiment, probably due to loss of methyllithium during addition, the intermediate dibromocyclopropane, **64**, was isolated and could be completely characterized. It appeared to be a mixture of diastereomers, indicating that the addition of dibromocarbene to the octalin was non-stereoselective (cf. addition to octalin **18**) and presumably accounting for at least some of the side products accompanying the formation of ishwarane in the C—H insertion step.

Nuclear magnetic resonance (nmr) spectra were recorded on a Varian Model HA-100 or Model XL-100 spectrometer, and proton and carbon-13 chemical shifts are reported in parts per million (δ) downfield from internal tramethylsilane. Infrared (ir) spectra were obtained on a Perkin–Elmer Model 621 spectrophotometer, and mass spectra (ms) were determined on a Varian MAT Model 311A spectrometer employing an ionizing voltage of 70 eV. Melting and boiling points are uncorrected.

*Cis-9-Methyl-2-octalin (18)*

A solution of 22.3 g (0.136 mmol) of octalone **17** (19) and 150 mL of hydrazine hydrate (99%) in 750 mL of diethylene glycol was heated at 120°C for 11 h. After the resulting solution had been allowed to cool, 94 g of potassium hydroxide was dissolved in it, and the temperature of the oil bath was slowly raised to 210°C over 1 h during which water was removed in a flow of argon and condensed. The mixture was then heated at 210°C for 3 h, cooled, and poured into water. The aqueous phase was extracted with petroleum ether (boiling range 30–60°C) and the combined extracts were washed with water and saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. The aqueous distillate carried over in the initial heating with hydroxide was worked up in the same manner, and the resulting extracts were combined with the others. The solvent was removed by distillation through a Vigreux column, and the residue was distilled to give 12.0 g (59%) of the octalin (**18**); bp 55–58°C/6 Torr (1 Torr = 133.32 Pa) nmr as previously reported (86).

*2,3-(Dibromomethano)-9-methyl-*cis*-decalin (19)*

To a solution of 2.00 g (13.3 mmol) of octalin **18**, 2.33 mL (6.74 g, 26.7 mmol) of bromoform, 27 mg of benzyltriethylammonium chloride, and 0.054 mL of ethanol was added dropwise, with stirring and cooling, 6.7 mL of 50% aqueous sodium hydroxide over 10 min, while the temperature of the mixture was maintained at 40–45°C. The mixture was stirred vigorously for 3 h at 40–45°C, during which 1.5 mL of methylene chloride was added to prevent the emulsion from becoming too thick, and it was then partitioned between 50 mL of water and 25 mL of methylene chloride. The aqueous phase was extracted with methylene chloride (2 × 25 mL), and the combined extracts were washed with 25 mL of water; 25 mL of 5% aqueous hydrochloric acid, another 25 mL of water, and 25 mL of saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was subjected to bulb-to-bulb distillation to give 2.06 g (48%) of dibromocyclopropane **19** as a colorless oil; bp 75°C/0.05 Torr; $^1$H nmr ($CCl_4$) δ: 0.93 (s, 3H); ms *m/e* (relative intensity): 41(51), 55(48), 67(62), 81(100), 95(48), 109(70), 123(40), 135(29), 149(65), 161(37), 210(10), 212(19), 214(9), 305(15), 307(31), 309(15), 320(5, $M^+$), 322(11, $M^+$), 324(5, $M^+$); high resolution ms, *m/e* calcd. for $C_{12}H_{18}Br_{12}$: 321.9755; found: 321.9799.

*Norishwarane (20)*

To a solution of 1.54 g (4.8 mmol) of dibromocyclopropane **19** in 8.5 mL of ethyl ether at −10°C was added dropwise, with stirring 3.7 mL of 1.5 *M* methyllithium (5.5 mmol) over 2.5 h. After the resulting yellow solution had been stirred at −10°C for an additional 30 min, followed by 1 h of stirring at room temperature, it was recooled to 5°C and 10 mL of water was added dropwise, with stirring. The aqueous phase was extracted with 10 mL of ethyl ether and the combined extracts were washed with 10 mL of saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. The solvent was removed by distillation through a Vigreux column, and bulb-to-bulb distillation of the residue gave 0.60 g (77%) of colorless oil; bp 70°C/5 Torr. This material was then subjected to preparative gas chromatography,[38] which gave two peaks at 32 min and 39 min with relative areas of 64% and 36%, respectively. The first of these appeared to be a 2:1 mixture of two isomers of norishwarane resulting from ring C—H insertion as judged from its nmr and ms data; $^1$H nmr ($CDCl_3$) δ: 0.77 (s, larger of the two singlets), 0.91 (s), 1.82 (d, $J$ = 12 Hz); $^{13}$C nmr ($CDCl_3$) δ: 5.1, 7.0, 11.5, 13.8, 18.6, 19.1, 22.2, 22.4, 22.9, 23.0, 26.3, 27.3, 27.5, 27.6, 27.7, 29.9, 30.4, 30.5, 32.1, 34.9, 37.8, 38.0, 38.8, 41.0, 42.1, 53.6; high resolution, ms, *m/e* calcd. for $C_{12}H_{18}$: 162.1409; found 162.1411. The component with a retention time of 39 min was norishwarane (**20**); ir ($CCl_4$): 3040 $cm^{-1}$; $^1$H nmr ($CDCl_3$) δ: 0.62 (m, 1H), 1.97 (d, $J$ = 11.5 Hz, 1H); $^{13}$C nmr ($CDCl_3$) δ: 13.1, 16.7, 17.7, 23.9, 26.4, 26.6, 29.9, 32.1, 37.2, 39.2, 40.2, 41.6; ms *m/e* (relative intensity): 67(25), 79(61), 95(70), 108(25) 120(76), 133(40), 147(18), 162(100, $M^+$); high resolution ms, *m/e* calcd. for $C_{12}H_{18}$: 162.1409; found: 162.1408.

*1,3,3-Trimethyl-7,7-dibromobicyclo[4.1.0]heptane (23)*

To a mixture of 4.0 g (32 mmol) of bromoform, 2.0 g (16 mmol) of 1,5,5-trimethylcyclohexene (**22**) (47) (containing 15% of the isomer, 1,3,3-trimethylcyclohexene, **26**), and 0.032 g of benzyltriethylammonium chloride was added dropwise, with stirring, 8 mL of 50% aqueous sodium hydroxide over 10 min, keeping the temperature in the range 40–45°C by means of a cold water bath. Stirring was continued at this temperature for 3 h, and the mixture was then poured into 250 mL of water. The aqueous phase was extracted with methylene chloride and the combined extracts were washed with water, dilute aqueous hydrochloric acid, and more water and dried over anhydrous sodium sulfate. The solvent was removed by distillation, and distillation of the residue gave 1.8 g (45%) of dibromocyclopropane **23**: bp 60°C/0.25 Torr; ir ($CCl_4$): 1370, 1390 $cm^{-1}$; $^1$H nmr ($CDCl_3$) δ: 0.85 (s, 6H), 1.45 (s, 3H); ms *m/e* (relative intensity): 55(65), 69(100), 84(89), 91(50), 107(27), 123(71), 135(65), 147(15), 159(24), 173(24), 199(18), 215(33), 226(18), 281(11), 296(5, $M^+$).

*1,5-Dimethyltricyclo[3.2.1.0$^{2,7}$]octane (24) and 1,3,3-trimethyltricyclo[4.1.0.0$^{2,7}$]heptane (25)*

To a solution of 1.0 g (3.5 mmol) of dibromocyclopropane **23** in 6 mL of ethyl ether at −10°C was added dropwise, with stirring, 2.6 mL (3.9 mmol) of a 1.5 *M* solution of methyllithium in ethyl ether over 2 h. Stirring was continued for 1 h after the addition was complete, and 6 mL of water was then added. The organic layer was washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated by distillation. The residue was subjected to preparative gas chromatography, and yields of 21% for **24** and 33% for **25** were determined using *trans*-decalin as internal standard; spectral data as previously reported (17).

*2,3,4-Trimethylcyclohex-2-en-1-one (7)*

(a) To a solution of 32.5 g (0.166 mol) of 3-isobutoxy-2,6-dimethylcyclohex-2-en-1-one (**32**) (14, 58) in 300 mL of ethyl ether at 0–4°C was added dropwise, with stirring, 130 mL of 1.5 *M* methyllithium (0.195 mol) over 2 h. After the solution had been allowed to stir at room temperature for 13 h, 1.15 L of 5% aqueous hydrochloric acid was added slowly, and the resulting mixture was stirred vigorously for 3.5 h. The aqueous phase was extracted with petroleum ether (boiling range 30–60°C) and the combined extracts were washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the remaining yellow oil was distilled to give 20.0 g (87%) of enone **7**; bp 103–108°C/15 Torr (lit. (54) bp 93–98°C/8 Torr); ir and nmr as previously reported (53); ms *m/e* (relative intensity): 67(77), 81(55), 96(95), 110(59), 123(23), 138(100, $M^+$); high resolutions ms, *m/e* calcd. for $C_9H_{14}O$: 138.1045; found: 138.1047.

(b) To a solution of 50.5 g (0.40 mol) of 2,6-dimethylcyclohexanone in 200 mL of carbon tetrachloride was added dropwise, with stirring and cooling with a room temperature water bath, 35.5 mL (59.4 g, 0.44 mol) of sulfuryl chloride in 60 mL of carbon tetrachloride over 75 min, while the evolved hydrogen chloride and sulfur dioxide were removed with an aspirator trap. After the mixture had been stirred for an additional 2 h, it was washed with water (3 × 60

[38]A 0.2 in. × 10 ft copper column packed with 10% SE-30 on Diatoport S was employed at 135°C.

mL), saturated aqueous sodium bicarbonate (2 × 60 mL), and 60 mL of saturated aqueous sodium chloride and dried over anhydrous sodium sulfate and anhydrous magnesium sulfate. The solvent was distilled off using a Vigreux column, first at atmospheric pressure and then at aspirator pressure, to give the crude chloro ketone which was used directly for the next step. This material was combined with 10.4 g (0.245 mol) of lithium chloride in 100 mL of *N,N*-dimethylformamide, and the mixture was heated at 100°C for 50 min, after which it was cooled to room temperature and added to a mixture of 400 mL of ethyl ether and 400 mL of 2.5% aqueous sulfuric acid. The resulting mixture was stirred vigorously for 4 h, and the aqueous phase was saturated with sodium chloride and extracted with ethyl ether (1 × 100 mL and 3 × 70 mL). The combined extracts were washed with saturated aqueous sodium bicarbonate (2 × 100 mL) and saturated aqueous sodium chloride (2 × 100 mL) and dried over anhydrous sodium sulfate and anhydrous magnesium sulfate. The solvent was removed by distillation through a Vigreux column, and the residue was distilled to give 39.9 g (80%) of 2,6-dimethylcyclohex-2-en-1-one (**34**); bp 71–82°C/15–16 Torr (lit. (87) bp 72–74°C/13 Torr); nmr and ms as reported previously (88).

To this lot of enone **34** in 400 mL of ethyl ether at −78°C was added dropwise, with stirring, 176 mL of 1.95 *M* methyllithium (0.34 mol) over 1.25 h. The mixture was allowed to warm to room temperature and stirred for 4.5 h, after which 200 mL of water was added dropwise, with stirring, and the mixture was allowed to stand overnight. The aqueous phase was extracted with ethyl ether (2 × 200 mL), and the combined extracts were washed with water (2 × 400 mL) and dried over anhydrous sodium sulfate and anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residual crude alcohol was used without purification for the next step. To a suspension of 77.66 g (0.36 mol) of pyridinium chlorochromate (PCC) in 540 mL of methylene chloride was added, all at once, 25.3 g of the crude alcohol in 180 mL of methylene chloride, and the mixture was stirred for 2 h. The mixture was then diluted with 750 mL of ethyl ether, the solution was decanted, and the black insoluble residue was washed with ethyl ether (1 × 300, 2 × 250, and 1 × 200). The combined extracts were divided into two equal portions, each of which was washed with 5% aqueous sodium hydroxide (2 × 750 mL), 750 mL of 5% aqueous hydrochloric acid, and saturated aqueous sodium bicarbonate (2 × 400 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the remaining orange oil was distilled to give 15.7 g (60%) of enone **7**.

*2,3,4-Trimethyl-3-(3-methyl-3-butenyl)cyclohexanone (**43**)*

To a solution of 5.32 g (27.1 mmol) of 4-iodo-2-methyl-1-butene (**41**) in 20 mL of ethyl ether at −78°C was added dropwise, with stirring, 25 mL of 1.7 *M tert*-butyllithium (42.5 mmol) over 20 min. After the mixture had been allowed to stir at −78°C for an additional 30 min, the Dry Ice – acetone bath was replaced by a Dry Ice – aqueous calcium chloride bath at −50°C, and 2.71 g (14.7 mmol) of copper(I) iodide was added all at once. The resulting grey suspension was stirred at −40 to −50°C for 3.5 h, after which 1.60 g (11.6 mmol) of 2,3,4-trimethylcyclohex-2-en-1-one (**7**) in 20 mL of ethyl ether was added dropwise, with stirring, over 20 min. After 3 h of stirring at −45°C the mixture was quenched by the addition of 10 mL of saturated aqueous sodium bicarbonate and poured into a mixture of 40 mL of ethyl ether and 60 mL of 10% aqueous ammonium hydroxide. The aqueous phase was extracted with ethyl ether and the combined extracts were washed with 10% aqueous ammonium hydroxide, water, and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure leaving an oil which was subjected to open column liquid chromatography on activity III neutral alumina. The fractions eluted with 1% ethyl acetate in hexane gave 1.1 g (45% yield) of oily ketone **43**, while 2% ethyl acetate in hexane gave 0.47 g of the starting ketone (**7**). The yield of **43** based on consumed **7** was thus 60%; ir ($CCl_4$): 1715, 1645, 896 $cm^{-1}$; $^1H$ nmr ($CCl_4$) δ: 0.57 (s, 3H), 0.84 (d, $J$ = 7 Hz, 3H), 0.90 (d, $J$ = 7 Hz, 3H), 1.71 (bs, 3H), 4.63 (bs, 2H); ms *m/e* (relative intensity): 55(68), 69(82), 97(96), 139(100), 163(9), 208(10, $M^+$); high resolution ms, *m/e* calcd. for $C_{14}H_{24}O$: 208.1827; found: 208.1825.

*3-(3,4-Epoxy-3-methylbutyl)-2,3,4-trimethylcyclohexanone (**47**)*

To a solution 1.04 g (5.0 mmol) of enone **43** in 30 mL of methylene chloride at 0°C was added dropwise, with stirring, 1.12 g (5.5 mmol) of 85% *m*-chloroperbenzoic acid in 25 mL of methylene chloride over 45 min. After the mixture had been allowed to stir for 9 h at room temperature, 75 mL of methylene chloride was added, and the solution was washed with 10% aqueous sodium bisulfite, 5% aqueous sodium hydroxide, water, and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give 1.11 g of a light yellow oil which was a sufficiently pure mixture of diastereomers for use in subsequent reactions; ir ($CCl_4$): 1715 $cm^{-1}$; $^1H$ nmr ($CCl_4$) δ: 0.58 (s, 3H), four doublets ($J$ = 7 Hz) at 0.85, 0.87, 0.92, and 0.93 (combined 6H), 1.43 (s, 3H), 2.67 (bs, 2H); ms *m/e* (relative intensity): 43(43), 49(81), 55(41), 67(42), 84(100), 96(65), 110(42), 111(42), 123(19), 138(77), 139(88), 154(10), 163(3), 196(2), 208(2), 224(1, $M^+$); high resolution ms, *m/e* calcd. for $C_{14}H_{24}O_2$: 224.1776; found: 224.1772.

*4,7,9,10-Tetramethyl-6-octal-1-one (**5**), 4,7,9,10-tetramethyl-7-octal-1-one (**48**), and 7-hydroxymethyl-1,2,6,7-tetramethylbicyclo[4.3.0]nonan-5-one (**50**)*

To a solution of 1.11 g (5.0 mmol) of the crude mixture of epoxyketones (**47**) in 6 mL of *tert*-butyl alcohol was added 23 mL of a solution of potassium *tert*-butoxide (26 mmol) freshly prepared by reaction of 1.11 g of potassium with 25 mL of *tert*-butyl alcohol at 50°C. The resulting orange solution was refluxed for 14 h, after which 15 mL of water was added, and the bulk of the solvent was evaporated under reduced pressure. The remaining orange gum was partitioned between 100 mL of water and 80 mL of ethyl ether, and the aqueous phase was extracted with two 50-mL portions of ethyl ether. The combined extracts were washed with water and saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give 1.3 g of a mixture of keto-alcohols as a crude yellow oil which was used for the next step without purification. To a solution of the above crude product in 20 mL of cyclohexane was added 17 mL of 50% aqueous sulfuric acid, and the mixture was stirred vigorously for 0.5 h. The mixture was then partitioned between ethyl ether and water, and the aqueous phase was neutralized with solid sodium carbonate and extracted with ethyl ether. The combined extracts were washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate, anhydrous sodium sulfate, and potassium carbonate. The solvent was evaporated under reduced pressure, giving a yellow oil which was subjected to open column liquid chromatography on 32 g of activity III alumina, eluting first with hexane, then with 1% ethyl acetate in hexane, and finally with pure ethyl acetate. Fractions eluted with ethyl acetate – hexane gave 0.39 g (38%) of a 4.3:1 mixture (analysis of integration of the olefinic proton signals in the nmr) of octalones **5** and **48** as a light yellow oil; ir ($CCl_4$): 1708 $cm^{-1}$; $^1H$ nmr ($CCl_4$) δ (relative LIS (for **5** only) with added $Eu(fod)_3$ in brackets): 0.66[2.2] (s, 3H), 0.82[1.0] (d, $J$ = 7 Hz, 3H), 0.92[4.1] (s, 3H), 1.63[0.6] (bs, 3H), 4.99 and 5.28[0.9] (m, width at half-height 4 Hz and 11 Hz, respectively, combined 1H, vinyl protons for **48** and **5**, respectively); ms *m/e* (relative intensity): 55(71), 67(74), 79(68), 91(82), 107(100), 121(87), 163(74), 173(34), 188(11), 191(11), 206(45, $M^+$); high resolution ms, *m/e* calcd. for $C_{14}H_{22}O$: 206.1670; found 206.1668. A small amount of nearly pure **48** was isolated from an early fraction; ir ($CCl_4$): 1708 $cm^{-1}$; $^1H$ nmr ($CCl_4$) δ: 0.66 (s, 3H), 0.88 (d, $J$ = 7 Hz, 3H), 0.94 (s, 3H), 1.64 (bs, 3H), 4.99 (m, 1H). Fractions eluted with pure ethyl acetate gave 0.34 g of a yellow oil (ca. 80% pure by $^1H$ nmr) from which pure keto-alcohol **50** could be isolated as a very light yellow oil by preparative gas chromatography (140°C); ir ($CCl_4$): 3425, 1687, 1055 $cm^{-1}$; $^1H$ nmr ($CCl_4$) δ: 0.97 (s, 3H), 0.99 (d, $J$ = 7 Hz, 3H) 1.11 (s, 3H), 1.17 (s, 3H), 3.25 (d, $J$ = 12 Hz, 1H), 3.67 (d, $J$ = 12 Hz, 1H); ms *m/e*

(relative intensity): 55(10), 67(18), 81(14), 95(20), 109(35), 121(20), 139(100), 163(19), 175(7) 191(5), 206(3), 224(1, $M^+$); high resolution ms, *m/e* calcd. for $C_{14}H_{24}O_2$: 224.1776; found: 224.1776.

*4,7,9,10-Tetramethyl-6-octal-1-ol (**54**) and 4,7,9,10-tetramethyl-7-octal-1-ol (**55**)*

To a suspension of 30 mg (0.79 mmol) of lithium aluminum hydride in 1.0 mL of ethyl ether at 0°C was added dropwise, with stirring, 0.117 g (0.57 mmol) of a 4.3:1 mixture of octalones **5** and **48** in 1.0 mL of ethyl ether, followed by 1.5 mL of ethyl ether. The mixture was allowed to warm to room temperature and stirred for 24 h, after which 0.030 mL of water was added followed by 0.045 mL of 10% aqueous sodium hydroxide and 0.90 mL of water. The resulting suspension was filtered, the solid was washed with ethyl ether, and the filtrate was extracted with ethyl ether. The combined extracts were washed with saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give 0.100 g (85%) of a light yellow oil; ir ($CCl_4$): 3640, 3510(b) $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 1.54 (bs, 3H), 3.37 (t, $J$ = 3 Hz, 1H), 4.80 (small m, 1H, vinyl of **55**), 5.14 (m, 1H, vinyl of **54**); high resolution ms, *m/e* calcd. for $C_{14}H_{24}O$: 208.1827; found: 208.1828.

*Racemic ishwarone (**2**)*

To a solution of 0.104 g (0.50 mmol) of a 4.3:1 mixture of octalones **5** and **48**, 0.060 mL (0.173 g, 0.69 mmol) of bromoform and ca. 3 mg of tributylamine in 0.065 mL of methylene chloride was added dropwise, with stirring, 0.17 mL of 50% aqueous sodium hydroxide. The mixture was stirred vigorously and heated at 40−50°C for 115 h, during which time small amounts of methylene chloride were added occasionally to replace that lost due to evaporation. The cooled mixture was partitioned between ethyl ether and water, and the aqueous phase was neutralized with 50% aqueous sulfuric acid and extracted with ethyl ether. The combined extracts were washed with 5% aqueous hydrochloric acid and saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, leaving a brown oil which was subjected to preparative thick-layer chromatography using carbon tetrachloride. The dibromocyclopropane **56** was isolated as a yellow oil containing unreacted octalin **48**; $^1H$ nmr ($CDCl_3$) δ: 0.80 (s), 0.87 (d, $J$ = 7 Hz), 1.10 (s), 1.52 (s); high resolution ms, *m/e* calcd. for $C_{15}H_{22}Br_2O$: 378.0017; found: 378.0027. To a solution of this mixture of **56** and **48** in 1.5 mL of ethyl ether at −10°C was added dropwise, with stirring, over 2 h, 0.25 mL (0.40 mmol) of 1.6 *M* methyllithium diluted with 1.5 mL of ethyl ether. The mixture was allowed to warm slowly to room temperature and was partitioned between ethyl ether and water. The aqueous phase was extracted with ethyl ether, and the combined extracts were washed with saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residual oil was subjected to preparative gas chromatography,[39] and the peak having a retention time corresponding to that of authentic ishwarone was collected and subjected to preparative thick-layer chromatography on alumina using 5% ethyl ether in cyclohexane. The band having the same $R_f$ value as that of authentic ishwarone was extracted with ethyl acetate, and the solvent was evaporated under reduced pressure to give 1.5 mg (2%) of an oil, the $^1H$ and $^{13}C$ nmr spectra of which were identical to those of authentic ishwarone (**2**); $^1H$ nmr ($CDCl_3$) δ: 0.56 (m, 1H), 0.73 (s, 3H), 0.87 (d, $J$ = 6.5 Hz, 3H), 1.15 (s, 3H); $^{13}C$ nmr ($CD_2Cl_2$) δ: 15.8, 17.9, 19.4, 19.7, 21.7, 22.7, 28.1, 30.7, 34.9, 38.0, 38.9, 39.7 39.8 (the quaternary carbon resonance observed at 58.6 in the spectrum of authentic ishwarone could not be discerned above the noise in the spectrum of the synthetic material due to the small amount available, and the signal due to the carbonyl carbon was not looked for). A 270 MHz $^1H$ nmr spectrum[40] of natural ishwarone was also obtained, and all resonances could be assigned, partly by decoupling ($CDCl_3$) δ: 0.56 (m, 1H, C-7 cyclopropyl), 0.73 (s, 3H, C-15 tertiary methyl), 0.87 (d, $J_{4,14}$ = 6.5 Hz, 3H, C-14 secondary methyl), 0.94 (dd, $J_{7,8}$ = 7.5 Hz, $J_{8,9\alpha}$ = 3 Hz, 1H, C-8 cyclopropyl), 1.15 (s, 3H, C-13 tertiary methyl), 1.35 (d, $J_{9\alpha,9\beta}$ = 12.5 Hz, 1H, C-9 βH), 1.42 (qd, $J_{2\alpha,3\beta} = J_{3\alpha,3\beta} = J_{3\beta,4}$ = 13.5 Hz, $J_{2\beta,3\beta}$ = 4 Hz, 1H, C-3 βH), 1.59 (dd, $J_{6\alpha,6\beta}$ = 14 Hz, $J_{6\beta,7}$ = 4 Hz, 1H, C-6 βH), 1.73 (dddd, $J_{3\alpha,3\beta}$ = 13.5 Hz, $J_{2\alpha,3\alpha}$ = 6.5 Hz, $J_{2\beta,3\alpha}$ = 4 Hz, $J_{3\alpha,4}$ = 2 Hz, 1H, C-3 αH), 1.86 (d, $J_{12\alpha,12\beta}$ = 12 Hz, 1H, C-12 βH), 1.90 (dd, $J_{6\alpha,6\beta}$ = 14 Hz, $J_{6\alpha,7}$ = 2 Hz, 1H, C-6 αH), 1.99 (dd, $J_{9\alpha,9\beta}$ = 12.5 Hz, $J_{8,9\alpha}$ = 3 Hz, 1H, C-9 αH), 2.13 (dqd, $J_{3\beta,4}$ = 13.5 Hz, $J_{4,14}$ = 6.5 Hz, $J_{3\alpha,4}$ = 2 Hz, 1H, C-4), 2.22 (dt, $J_{2\alpha,2\beta}$ = 13.5 Hz, $J_{2\beta,3\alpha} = J_{2\beta,3\beta}$ = 4Hz, 1H, C-2 βH), 2.25 (d, $J_{12\alpha,12\beta}$ = 12 Hz, 1H, C-12 αH), 2.46 (td, $J_{2\alpha,2\beta} = J_{2\alpha,3\beta}$ = 13.5 Hz, $J_{2\alpha,3\alpha}$ = 6.5 Hz, 1H, C-2 αH).

*5β,9β,10β-Trimethyl-2-decalone (**60**)*

To a solution of 10.7 g (52 mmol)) of the copper(I) bromide − dimethyl sulfide complex (84) and 70 mL of dimethyl sulfide in 70 mL of ethyl ether was added dropwise, with stirring, 64 mL of 1.6 *M* methyllithium (96 mmol), followed by 6.83 g (38 mmol) of octalone **59** (83) in 10 mL of ethyl ether. After the yellow suspension had been stirred for 4 h, the mixture was partitioned between petroleum ether (boiling range 30−60°C) and aqueous ammonium hydroxide (buffered to pH 8 with ammonium chloride). The aqueous phase was extracted with petroleum ether, and the combined extracts were washed with water and saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residual oil was distilled to give 5.8 g (77%) of decalone (**60**); bp 80°C/0.02 Torr; ir ($CCl_4$): 1713 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 0.88 (m, 9H, methyl, not resolved), 3.05 (bd, $J$ = 14 Hz, 1H); ms *m/e* (relative intensity): 55(100), 67(90), 81(60), 95(38), 110(44), 123(44), 179(15), 194(29); high resolution ms, *m/e* calcd. for $C_{13}H_{22}O$: 194.1671; found: 194.1669.

*2,5β,9β,10β-Tetramethyl-2-octalin (**62**) and 2,5β,9β,10β-tetramethyl-1-octalin (**63**)*

To a solution of methylmagnesium bromide (prepared from 0.35 g (14 mmol) of magnesium turnings and 0.95 mL (2.16 g, 15 mmol) of methyl iodide in 4.3 mL of ethyl ether) was added dropwise, with stirring, 1.1 g (5.7 mmol) of decalone **60** in 14.2 mL ethyl ether over 2.5 h. After the mixture had been stirred for 3h, the mixture was quenched with aqueous ammonium chloride, and the aqueous phase was extracted with ethyl ether. The combined extracts were evaporated under reduced pressure to give 1.02 g (85%) of crude gummy decalol **61**, which was used directly for the next step, but which could be purified by preparative thick-layer chromatography on silica gel using 10% ethyl acetate in cyclohexane; ir ($CCl_4$): 3615, 3490 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 0.76 (s, 3H), 0.76 (d, $J$ = 6.5 Hz, 3H), 1.08 (s, 3H), 1.21 (s, 3H), 2.12 (bd, $J$ = 15 Hz, 1H). To a solution of 0.90 g (4.3 mmol) of the crude decalol in 18 mL of cyclohexane was added 14 mol of 50% aqueous sulfuric acid, and the two-phase mixture was stirred vigorously for 2 h and then partitioned between 25 mL of ethyl ether and 25 mL of water. The aqueous phase was extracted with ethyl ether (3 × 25 mL) and the combined extracts were washed with 50 mL of saturated aqueous sodium bicarbonate, 50 mL of water, and 50 mL of saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give 0.69 g (87%) of a 1:1 mixture of octalins **62** and **63**, which could not be separated; ir ($CCl_4$): 1670 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ: 0.77 (s, 3H), 0.80 (d, $J$ = 6.5 Hz, 3H) 0.84 (s, 3H), 1.64 (bs, 3H), 4.98 and 5.21 (broad singlets for **63** and **62**, respectively, 1H); ms *m/e* (relative intensity): 55(29), 67(34), 79(28), 91(30), 109(100), 124(33), 177(9), 192(9, $M^+$); high resolution, ms, *m/e* calcd. for $C_{14}H_{24}$: 192.1878; found: 192.1880.

*Racemic ishwarane (**1**)*

To a solution of 0.40 g (2.1 mmol) of octalins **62** and **63** and 1.38 g (4.2 mmol) of carbon tetrabromide in 14 mL of ethyl ether at −78°C was added dropwise, with stirring, 2.3 mL of 1.8 *M* methyllithium (4.2 mmol) over 1 h, and the resulting yellow solution was

[39]A 0.2 in. × 6 ft stainless-steel column packed with 5% OV-101 on 80/100 mesh Chromosorb W was employed at 150°C.

[40]Recorded on a Bruker Model WH-270 spectrometer at the University of Wisconsin, Madison.

stirred at −78°C for 45 min. The mixture was then allowed to warm to −30°C over 1.75 h, during which time the color changed from yellow to black. While the temperature of the mixture was maintained at −30°C, an additional 2.3 mL of 1.8 *M* methyllithium (4.2 mmol) was added dropwise, with stirring, over 45 min, and the black mixture was stirred at −30°C for an additional hour, after which it was allowed to warm to 0°C over 1 h. At this point 10 mL of water was added dropwise, with stirring, and the aqueous phase was extracted with petroleum ether (2 × 25 mL). The combined extracts were washed with 50 mL of water and 50 mL of saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residual oil was subjected to preparative thick-layer chromatography on silica gel using hexane, followed by preparative gas chromatography,[41] which gave four peaks: retention time (relative area, amount collected, identity) 20 min (40%, 11 mg, unreacted octalin **63**), 22 min (21%, 4 mg, unreacted octalin **62**), 26 min (19%, 6 mg, unidentified isomer or isomers of ishwarane; high resolution ms, *m/e* calcd. for $C_{15}H_{24}$: 204.1878; found: 204.1879), and 31 min (20%, 10 mg, racemic ishwarane). The latter material was found to have $^1H$ and $^{13}C$ nmr spectra which were identical to those of authentic ishwarane (**1**); $^1H$ nmr ($CDCl_3$) δ: 0.48 (m, 1H), 0.75 (d, $J$ = 6.5 Hz, 3H), 0.80 (s, 3H), 1.14 (s, 3H), 1.88 (bd, $J$ = 12 Hz, 1H), 2.09 (bd, $J$ = 12 Hz, 1 H); $^{13}C$ nmr ($CDCl_3$) δ: 16.6, 16.7, 19.9, 20.3, 22.4, 23.0, 23.9, 30.9, 33.6, 34.7, 35.7, 35.8, 38.7, 39.3, 44.0; high resolution ms, *m/e* calcd. for $C_{15}H_{24}$: 204.1878; found: 204.1877. A 270 MHz $^1H$ nmr spectrum[40] of natural ishwarane was also obtained ($CDCl_3$) δ: 0.47 (m, 1H, C-7 cyclopropyl), 0.74 (d, $J_{4,14}$ = 6.4 Hz, 3H, C-14 secondary methyl), 0.79 (s, 3H, C-15 tertiary methyl), 1.00 (d, $J_{9\alpha,9\beta}$ = 11.2 Hz, 1 H, C-9 βH), 1.14 (s, 3H, C-13 tertiary methyl), 1.51 (dd, $J_{6\alpha,6\beta}$ = 14 Hz, $J_{6\beta,7}$ = 4 Hz, 1H, C-6 βH), 1.68 (dd, $J_{6\alpha,6\beta}$ = 14 Hz, $J_{6\alpha,7}$ = 2 Hz, 1H, C-6 αH), 1.87 (d, $J_{12\alpha,12\beta}$ = 12 Hz, 1H, C-12 βH), 2.09 (d, $J_{12\alpha,12\beta}$ = 12 Hz, 1H, C-12 αH).

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