A Synthetic Approach to Cadinane- and Amorphane-type Sesquiterpenoids via Annelation of Cyclohexanone Derivatives with (E)-2-Methyl-3-hepten-5-one. A Simple Synthesis of (+)-Cadinene Dihydrochloride

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The annelation of the pyrrolidine enamine of cyclohexanone with (E)-2-methyl-3-hepten-5one (7) afforded a 7:3 mixture of the octalones 12 and 13. Lithium-ammonia reduction of the former afforded the *trans*-fused decalone 14, whereas, in contrast, a similar reduction of 13 gave exclusively the *cis*-fused decalone 16. Annelation of the pyrrolidine enamine of 4-hydroxycyclohexanone with the unsaturated ketone 7 yielded a 7:3 mixture of the octalones 22 and 23. The former was converted via a short, efficient synthetic sequence into (\pm) -cadinene dihydrochloride (30).

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L'énamine dérivant de la pyrrolidine et de la cyclohexanone soumise à une réaction d'annelation avec la méthyl-2 heptène-3 one-5 (E) (7) conduit à un mélange 7:3 des octalones 12 et 13. La réduction par le lithium dans l'ammoniac de 12 conduit à la décalone *trans* 14 alors qu'une réduction similaire de 13 conduit uniquement à la décalone *cis* (16). L'énamine dérivée de la pyrrolidine et de l'hydroxy-4 cyclohexanone soumise à une réaction d'annelation avec la cétone non-saturée 7 conduit à un mélange 7:3 des octalones 22 et 23. Une séquence synthétique courte et efficace permet de transformer 22 en dichlorhydrate de (\pm)-cadinène (30).

The fairly large number of sesquiterpenoids which possess the basic carbon skeleton as shown in 1^1 have by convention been divided into four classes or subgroups, differing only in the relative stereochemistry at C₁, C₆, and C₇ (1, 2). Thus, the cadinane-type (2) and bulgaranetype (3) sesquiterpenoids possess *trans*-fused six-membered rings and differ only in the relative stereochemical orientation of the isopropyl or related side chain. On the other hand, in the muurolanes (4) and the amorphanes (5), the decalin systems are *cis*-fused. Again, these two types differ only in the relative stereochemistry at C₇.

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The four sesquiterpenoid classes mentioned above are constituted mainly of olefinic hydrocarbons and alcohols. Structurally speaking, many of the individual members of these classes are very closely related and often differ from one another only in the position of an olefinic double bond and/or in a diastereomeric sense. Because of this, it has often been difficult to separate mixtures of these types of compounds into individual components, and the structural



and stereochemical elucidation of the cadinane and related sesquiterpenoids was, in the past, often carried out with impure materials. Consequently, the chemical literature dealing with this area contains many conflicting and erroneous reports. A classic and, perhaps, extreme example of this involves the naturally occurring olefinic alcohol δ -cadinol. Since its isolation in 1922, no fewer than seven different proposals have been put forward regarding the structure and sterochemistry of this compound, the latest (3) being that δ -cadinol is actually a muurolane derivative.

¹The numbering system shown in structure 1 is that normally used for the cadinane and related sesquiterpenoids.

Up to the present time, relatively little work has been reported concerning the synthesis of the cadinane and related sesquiterpenoids.² We report in this paper a simple synthetic approach which, with appropriate development and modification, should allow for the efficient synthetic entry into both the cadinane- and amorphane-type sesquiterpenoids.

Of the number of synthetic approaches which we considered and investigated in varying detail (5), the one involving annelation of a substituted cyclohexanone derivative (6) with (E)-2-methyl-3-hepten-5-one (7) appeared, in principle, to be the simplest and most direct (see Scheme 1).



Success of this general reaction would introduce, in one step, 14 of the 15 carbon atoms necessary for the synthesis of the cadinane and/or related sesquiterpenoids. An appropriate functional group (X) at C_6 in the annelation product **8** would then presumably allow for the introduction of the final required carbon atom.

The required α,β -unsaturated ketone 7 was prepared as follows (see Scheme 2). Treatment of isobutyraldehyde with the anion of trimethylphosphonoacetate (6) in dimethyl sulfoxide afforded, in 65% yield, the trans-olefinic ester 9. Hydrolysis of the latter with potassium carbonate in aqueous methanol gave the corresponding carboxylic acid 10. When compound 10 was allowed to react with freshly prepared ethyllithium under carefully controlled conditions $(-78^\circ, 2 h)$, the desired α,β -unsaturated ketone 7 was formed in excellent yield. It should be noted that the success of the latter reaction depended, to a large extent, upon a judicious choice of reaction temperature, reaction time, and reactant concentration. That is, use of reaction temperatures greater than -40° , or use of longer reaction times, resulted in the formation of considerable amounts of alcoholcontaining products. On the other hand, milder reaction conditions (more dilute solutions, shorter reaction times, low temperatures) resulted in the recovery of fairly copious amounts of starting material. However, to eliminate the formation of alcohol-containing product, it was necessary to tolerate the recovery of some starting material. The latter could then be recycled and, eventually, the desired unsaturated ketone 7 was obtained in 92% yield.

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Attempted annelation of cyclohexanone, 2carbomethoxycyclohexanone, and 2-hydroxymethylenecyclohexanone with the heptenone 7, using a variety of bases and reaction conditions, proved unsuccessful. However, when the pyrrolidine enamine of cyclohexanone (11) was allowed to react with 7 under carefully chosen conditions, the corresponding annelated material was formed in 83% yield (see Scheme 2). Analysis of this material by gas-liquid chromatography (g.l.c.) indicated that it consisted of a mixture of the two epimeric compounds 12 and 13, in a ratio of approximately 7:3, respectively. Treatment of this mixture with sodium methoxide in refluxing methanol afforded a mixture of the same two components, now in a ratio of 3:1. The two compounds could be separated readily by preparative g.l.c. and spectral and analytical data clearly showed that the two materials were indeed epimers.

On the basis of conformational analysis, one would expect the octalone 12, containing an equatorially oriented isopropyl group (cf. 12a), to be more stable than octalone 13, possessing an axially oriented isopropyl group (cf. 13a). Hence, the major and minor products obtained from the annelation reaction were assigned structures 12 and 13, respectively.

In order to obtain additional information regarding the stereochemistry of octalones 12 and 13, each was subjected to reduction with lithium in liquid ammonia. Reduction of the major annelation product 12 afforded, in 78% yield, the corresponding *trans*-fused decalone 14. Application of internuclear double resonance (INDOR) techniques $(7-9)^3$ to a detailed study of the proton magnetic resonance (p.m.r.) spectrum of 14 fully supported the assigned structure and stereochemistry. Specifically, the INDOR studies revealed the following firstorder coupling constants: $H_{3a}-H_{3e}$ 12.6 \pm 0.4 Hz, $H_{3a} - H_4$ 12.6 ± 0.4 Hz, $H_{3e}-H_4$

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²For an excellent and comprehensive review of sesquiterpenoid synthesis, see ref. 4.

 $^{^{3}}$ We are very grateful to Professor L. D. Hall and Dr. C. W. M. Grant for carrying out the INDOR studies. Details of these experiments will be published elsewhere.

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3.9 + 0.4 Hz. It can readily be seen that these first-order coupling constants for compound 14 are fully consistent with the assigned stereochemistry (cf. 14a). Furthermore, the p.m.r. studies also revealed that the H₁ transitions for compound 14 were spread over at least 32 Hz, indicating that the H_1-H_9 coupling (cf. 14a) was an axial-axial coupling. If the H_1-H_9 coupling had been axial-equatorial, the H₁ transitions would have been spread over only 22-25 Hz, at most. These facts clearly showed that the lithium-ammonia reduction of the major annelation product (12) had not produced a cis-fused decalone, which would have had the conformation shown in 15. The latter structure, although consistent with the observed coupling pattern for the C_3 and C_4 protons, was clearly inconsistent with the observed line width for the H_1 resonance.

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> Lithium-ammonia reduction of the minor annelation product 13 afforded steroselectively, in 75% yield, the corresponding *cis*-fused decalone 16. The stereochemistry of the latter was confirmed in two ways. First of all, hydrogenation of the olefinic double bond of 13 would be expected to take place from the side opposite the axially oriented isopropyl group

(cf. 13a) (steric approach control) and also produce the cis-fused decalone 16. Indeed, hydrogenation of 13 over palladium-on-charcoal, followed by equilibration (sodium methoxide in methanol) of the initially formed product, afforded only decalone 16, identical in all respects with the product obtained from the lithium-ammonia reduction. Secondly, INDOR $(7-9)^3$ studies on compound 16 again fully supported the assigned stereochemistry. Thus the observed first-order coupling constants (H_{3a}–H_{3e} 13.0 \pm 0.4 Hz, H_{3a}–H₄ 13.0 \pm 0.4 Hz, $H_{3e}-H_4$ 3.9 \pm 0.4 Hz) were clearly consistent with structure 16 (cf. 16a) but were inconsistent with a corresponding decalone possessing a trans ring fusion (cf. 17). Furthermore, the p.m.r. studies again showed that the H_1 transitions for compound 16 were spread over at least 33 Hz. As in the case of compound 14, this fact clearly indicated that the H_1-H_9 coupling (cf. 16a) was an axial-axial coupling.

It is well known that the alkali metal – ammonia reduction of simply substituted $\Delta^{1(9)}$ -2octalones generally affords, in each case, a high proportion of the corresponding *trans*-fused 2-decalone (10–12). Therefore, the steroselective formation of the *cis*-fused decalone **16** from the

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lithium-ammonia reduction of octalone 13 was initially surprising and clearly seemed to suggest that the presence of an axially-oriented substituent at the C₄ position of $\Delta^{1(9)}$ -2-octalones can exert a profound effect on the stereochemical outcome of the reduction. A more detailed study and discussion of this observation can be found in the accompanying paper (13).

Having successfully realized the annelation of cyclohexanone with the α , β -unsaturated ketone 7, we next turned our attention to the annelation of a cyclohexanone derivative containing a substituent suitable for the (later) introduction of the last one-carbon unit necessary for the synthesis of cadinane-type (or related) sesquiterpenoids. To this end, the pyrrolidine enamine of 4,4-ethylenedioxycyclohexanone (18) (14) was allowed to react with 7 under conditions similar to those used in the above mentioned condensation (see Scheme 3). However, the annelated product, a 4:1 mixture of octalones 19 and 20, respectively, was obtained in only very poor yield (<10%). Attempts to improve the yield of this reaction by varying the reaction conditions were not

successful. It was felt that the ketal functionality. with one of the oxygen atoms necessarily axially oriented (cf. 18a) could be sterically interfering with the approach of the vinyl ketone 7 to the β -carbon atom of the enamine 18 (anti-parallel attack (15)), thus accounting for the low yield of product. Therefore, it was decided to investigate the use of the pyrrolidine enamine of 4-hydroxycyclohexanone (21), which could, presumably, react from a conformation possessing an equatorially oriented hydroxyl group (cf. 21a). Condensation of 21 with the unsaturated ketone 7 was attempted under a variety of conditions and a 40% yield of a mixture of annelated products was finally realized. The crude product was equilibrated (sodium methoxide in methanol) and then subjected to analysis by g.l.c. and spectral methods. The latter revealed that this material consisted of a mixture of hydroxy octalones 22 and 23 in a ratio of approximately 7:3, respectively. The two compounds were readily separated by preparative g.l.c.

It should be noted that both 22 and 23 actually consisted of a mixture of two epimeric

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alcohols. Thus, a careful integration of the p.m.r. spectrum of the major condensation product 22^4 indicated that the two alcohols possessing axial and equatorial hydroxyl groups were present in a ratio of approximately 3:2, respectively. That compound 22 was indeed a mixture of two epimeric alcohols was shown by chromium trioxide – pyridine oxidation (16) of this material, which produced, in 94% yield, the crystalline dione 24. The latter, by means of g.l.c. and spectral analysis, was shown to be homogeneous.

Similarly, a careful analysis of the p.m.r. spectrum of the minor condensation product 23^4 indicated that the epimeric alcohols were present in a ratio of approximately 1:1.

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To obtain additional information regarding the relative stereochemistry (at C_4 and C_{10}) of the major and minor condensation products 22 and 23, it was decided to correlate the former keto alcohol with the previously obtained, and structurally simpler, decalone 14. Since assignment of the stereochemistry of the latter appeared to be on a firm basis, this correlation would provide corroborative support for the proposed stereochemistry of 22 and, by inference, of 23 as well.

Treatment of the hydroxy octalone 22 with methanesulfonyl chloride in pyridine afforded, in 85% yield, the corresponding keto mesylate 25. Reaction of the latter with lithium in liquid ammonia containing some ethanol reduced not only the α , β -unsaturated ketone system (11, 12) but also effected hydrogenolysis of the mesylate functionality (17). Oxidation of the resulting

⁴For the sake of simplicity, this material will subsequently be referred to as one compound. crude product with Jones' reagent (18) produced the saturated, *trans*-fused decalone **14**, identical in every respect with a sample of the compound obtained as described previously.

In order to demonstrate the potential use of octalone 22 as an intermediate for the synthesis of cadinane-type sesquiterpenoids, and to fully confirm the stereochemical assignments outlined above, it was decided to convert 22 into racemic cadinene dihydrochloride (30) (19-22), the stereochemistry of which has been established unambiguously. To this end, octalone 22 was treated with ethanedithiol in the presence of boron trifluoride etherate to afford the dithioketal 26 (see Scheme 4). Desulfurization of the latter with Raney nickel in refluxing ethanol afforded, in 77% yield, the olefinic alcohol 27. Oxidation of 27 with chromium trioxide in pyridine (16) gave, in 89% yield, the keto olefin 28, which in turn was converted, by reaction with methyllithium in ether, into the tertiary alcohol 29 (91% yield). Treatment of the latter compound with anhydrous hydrogen chloride in anhydrous ether at 0° afforded, in 80% yield, racemic cadinene dihydrochloride (30). The latter was identical in every respect with an authentic sample of (+)-cadinene dihydrochloride.5

The enamine annelation approach to the synthesis of cadinane-type and/or related sesquiterpenoids, as outlined above, is attractive in terms of simplicity and efficiency. However, the general scheme does possess disadvantages. One of these is the production, in the annelation reaction itself, of diastereomeric products (22)

⁵We are very grateful to Dr. M. D. Sutherland for a generous sample of (\pm) -cadinene dihydrochloride.

and 23) which must then be separated at an early stage of the overall synthetic sequence. This complication is, however, at least partially offset by the results obtained from the lithiumammonia reduction of the initially formed annelation products. That is, on the basis of the work reported in this paper, it is obvious that the lithium-ammonia reduction of a mixture of octalones 22 and 23 would produce a mixture of the corresponding trans- and cisfused 2-decalones 31 and 32, respectively. Separation at this stage of the synthetic sequence would then provide one with two distinct synthetic precursors, one (31) potentially convertible into cadinane-type sesquiterpenoids and the other (32) potentially convertible into amorphane-type sesquiterpenoids.



Another problem which must as yet be overcome involves the regioselective introduction of olefinic double bonds into various positions of an appropriate synthetic intermediate. For example, conversion of the keto olefin 28 into the natural products δ -cadinene (33) and ω -cadinene (34) would require the introduction of a methyl group at the carbonyl carbon (of 28) and the controlled, regioselective introduction of carbon-carbon double bonds into two distinct positions. We are currently investigating methods for carrying out these transformations in a controlled fashion.

Experimental

General⁶

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> Melting points, which were determined on a Fisher-Johns melting point apparatus, and boiling points are uncorrected. The u.v. spectra were, unless otherwise noted, measured in methanol solution on a Unicam, model SP 800, spectrophotometer. Routine i.r. spectra

were recorded on a Perkin-Elmer model 710 spectrophotometer, while comparison spectra were recorded on Perkin-Elmer models 421 or 457 spectrophotometers. The p.m.r. spectra were, unless otherwise noted, taken in deuteriochloroform solution on Varian Associates spectrometers, A-60, T-60 and/or HA-100 or XL-100. Signal positions are given in the Tiers τ scale, with tetramethylsilane as an internal standard. The multiplicity, integrated peak areas, and proton assignments are indicated in parentheses. High resolution mass spectrometric measurements were carried out on an AEI type MS-9 mass spectrometer. Gas-liquid chromatographic analyses were carried out on Varian Aerograph g.l.c. units, models 700 and/or 90-P. The following columns were employed: column A, 10 ft $\times \frac{1}{2}$ in., 8% FFAP on 60-80 mesh Chromosorb G; column B, $10 \text{ ft} \times \frac{1}{2} \text{ in.}$, 20% Carbowax 20M on 60-80 mesh Chromosorb W; column C, 10 ft × 🛊 in., 30% Carbowax 20M on Chromosorb W. The specific column used, along with the column temperature and carrier gas (helium) flow-rate (in ml/min) are indicated in parentheses. Microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia, Vancouver.

Methyl (E)-4-Methyl-2-pentenoate (9)

Sodium hydride (4.3 g of a 56% dispersion in mineral oil) was added to 50 ml of dry dimethyl sulfoxide and the resulting suspension was slowly heated under a nitrogen atmosphere to 75° and maintained at that temperature until all frothing had ceased (~45 min). The solution was cooled to room temperature and a solution of 18.2 g of trimethylphosphonoacetate in 30 ml of dimethyl sulfoxide was added. The solution was allowed to stir for 10 min and then a solution of 5.76 g of isobutyraldehyde in 30 ml of dimethyl sulfoxide was added dropwise. After the addition was complete, the reaction mixture was allowed to stir for an additional hour. Water was added and the resulting mixture was extracted thoroughly with petroleum ether (b.p. 30-60°). The combined extracts were successively washed with water and brine, and then dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the residue under reduced pressure afforded 6.5 g (65%) of methyl (E)-4-methyl-2-pentenoate, b.p. 65°/10 mm (lit. (23) b.p. 74–75°/46 mm); $n_{\rm D}^{25}$ 1.4309 (lit. (23) $n_{\rm D}^{25}$ 1.4305); i.r. (film) $\lambda_{\rm max}$ 5.8, 6.05 μ ; p.m.r. τ 8.95 (d, 6H, --CH(CH₃)₂, J = 7 Hz), 7.50 (m, 1H, -CH(CH₃)₂), 6.30 (s, 3H, OCH₃), 4.25 (d of d, 1H, H-2, $J_{2,3} = 16$ Hz, $J_{2,4} = 1$ Hz), 3.05 (d of d, 1H, H-3, $J_{2,3} = 16$ Hz, $J_{3,4} = 7$ Hz).

(E)-4-Methyl-2-pentenoic Acid (10)

To a stirred solution of 34 g of potassium carbonate in 200 ml of methanol-water was added 23 g of methyl (E)-4-methyl-2-pentenoate. The reaction mixture was stirred at reflux for 3 h. Most of the methanol was removed under reduced pressure and the residue was diluted with water. The resulting aqueous solution was washed with ether (washings discarded), acidified with dilute hydrochloric acid, and thoroughly extracted with ether. The combined ether extracts were successively washed with water and brine, and dried over magnesium sulfate. Removal of the solvent and distillation of the residue under reduced pressure afforded 17.2 g (82%) of

⁶This general section is applicable to the succeeding, accompanying paper (13), as well as to the present paper.

(*E*)-4-methyl-2-pentenoic acid, b.p. $75^{\circ}/0.6 \text{ mm}$; n_D^{27} 1.4454; u.v. λ_{max} 217 nm (ϵ 3630); i.r. (film) λ_{max} 3.1-4.0 (broad), 5.9, 6.1 μ ; p.m.r. τ 8.95 (d, 6H, --CH(CH₃)₂), J = 6.5 Hz), 7.25-7.8 (m, 1H, --CH(CH₃)₂), 4.2 (d of d, 1H, H-2, $J_{2,3} = 15.5$ Hz, $J_{2,4} = 1.5$ Hz), 2.9 (d of d, 1H, H-3, $J_{2,3} = 15.5$ Hz, $J_{3,4} = 6.5$ Hz), -2.15 (s, 1H, --CO₂H).

Anal. Calcd. for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 62.85; H, 8.76.

(E)-2-Methyl-3-hepten-5-one (7)

Finely cut lithium wire (25.8 g) was added to 600 ml of anhydrous ether under nitrogen. To the resulting stirred mixture was added dropwise a solution of 120 ml of ethyl bromide (previously distilled from calcium hydride) in 300 ml of anhydrous ether. During the addition the reaction mixture was kept at -10° by application of an external Dry Ice-acetone cooling bath. After the addition was complete the solution was warmed to 0° , kept at this temperature for 1 h, filtered under nitrogen, and used immediately.

A solution of 32 g of (E)-4-methyl-2-pentenoic acid in 540 ml of anhydrous ether was cooled to -78° (Dry Ice - acetone) and 600 ml of the previously prepared ethyllithium solution was added dropwise. After the addition was complete, the white slurry was allowed to stir at -78° for an additional hour. The cooling bath was removed and stirring was continued until a clear solution resulted. The latter was poured into rapidly stirred, ice-cold 1 N hydrochloric acid. The resulting mixture was thoroughly extracted with ether. The combined ether extracts were washed successively with dilute ammonium hydroxide, water, and brine and then dried over magnesium sulfate. The solvent was removed by careful distillation through a Vigreaux column at atmospheric pressure. Fractional distillation of the residue under reduced pressure yielded 17 g (92%, based on unrecovered starting material) of (E)-2-methyl-3hepten-5-one (7), b.p. 54°/10 mm; u.v. λ_{max} 221 nm (a quantitative u.v. spectrum was not obtained, since the material contained a small amount of the corresponding β , γ -unsaturated ketone); i.r. (film) λ_{max} 5.98, 6.14 μ ; p.m.r. τ 8.90 (d, 6H, --CH(CH₃)₂, J = 7 Hz), 8.95 (t, 3H, $-CH_2CH_3$, J = 7 Hz), 7.45 (q, 2H, $-CH_2$ -CH₃, J = 7 Hz), 3.98 (d of d, 1H, H-4, $J_{4,5} = 16$ Hz, $J_{4,6} = 1.5$ Hz), 3.20 (d of d, 1H, H-5, $J_{4,5} = 16$ Hz, $J_{5,6} = 6$ Hz).

Anal. Calcd. for C₈H₁₄O: C, 76.19; H, 11.11. Found: C, 76.10; H, 11.12.

Preparation of Octalones 12 and 13

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A mixture of 6 g (0.02 mol) of the pyrrolidine enamine of cyclohexanone (11) and 2.6 g (0.02 mol) of (E)-2methyl-3-hepten-5-one (7) was stirred under nitrogen at 60° for 40 h. Anhydrous dioxan (12 ml) was added and the reaction mixture was refluxed overnight. To the resulting solution was added 1 ml of glacial acetic acid, 2 ml of water, and 0.5 g of anhydrous sodium acetate and refluxing was continued for 4 h. The cooled reaction mixture was diluted with water and the resulting mixture was extracted thoroughly with ether. The combined ether extracts were washed successively with water, dilute hydrochloric acid, water, and brine and then dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the residual material under reduced pressure afforded 3.5 g (83%) of a pale yellow oil, b.p. 100°/0.2 mm. This material was shown by g.l.c. to consist of a 7:3 mixture of octalones 12 and 13, respectively. Separation of the two components was accomplished by preparative g.l.c. (column A, 200°, 86). The major octalone 12 exhibited u.v. λ_{max} 249 nm (ϵ 13 600); i.r. (film) λ_{max} 6.0, 6.15 μ ; p.m.r. τ 9.21, 9.11 (d, d, 6H, --CH(CH₃)₂, J = 7 Hz), 8.26 (s, 3H, vinyl CH₃).

Mol. Wt. Calcd. for $C_{14}H_{22}O$: 206.167. Found (high resolution mass spectrometry): 206.166.

The minor octalone **13** exhibited u.v. λ_{max} 249 nm (ε 13 400); i.r. (film) λ_{max} 6.0, 6.1 μ ; p.m.r. τ 9.11 (d, 6H, --CH(CH₃)₂, J = 6 Hz), 8.26 (s, 3H, vinyl CH₃).

Mol. Wt. Calcd. for $C_{14}H_{22}O$: 206.167. Found (high resolution mass spectrometry): 206.166.

Lithium–Ammonia Reduction of Octalone 12

To 150 ml of liquid ammonia (distilled from sodium metal) was added 200 mg of finely cut lithium wire. After the lithium had dissolved, a solution of the octalone 12 (450 mg) in 25 ml of anhydrous ether was added dropwise over a period of 30 min. The reaction mixture was allowed to stir for an additional 1.5 h and then ammonium chloride was added to discharge the blue color. The ammonia was allowed to evaporate under a slow stream of nitrogen and the residual material was diluted with water. The resulting mixture was extracted thoroughly with ether. The combined ether extracts were washed successively with water, dilute hydrochloric acid, water, and brine and then dried over anhydrous magnesium sulfate. Removal of the ether, followed by distillation of the residual material under reduced pressure gave 350 mg (78%) of the trans-fused decalone 14, b.p. 125°/0.6 mm. Analysis of the product by g.l.c. (column B, 215°, 110) revealed the presence of only one component. An analytical sample of 14 exhibited i.r. (film) λ_{max} 3.42, 3.51, 5.85 µ; p.m.r. τ 9.23, 9.13 (d, d, 6H, $-CH(CH_3)_2$, J = 7 Hz), 8.99 (d, 3H, secondary $CH_3, J = 6.5 Hz).$

Anal. Calcd. for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.48; H, 11.31.

Lithium-Ammonia Reduction of Octalone 13

The lithium-ammonia reduction of the octalone 13 was carried out via a procedure identical with that described above. From 150 mg of 13 there was obtained 115 mg (75%) of the *cis*-fused decalone 16. Analysis of the product by g.l.c. (column B, 215°, 110) showed the presence of only one component. An analytical sample exhibited i.r. (film) λ_{max} 3.45, 5.85 µ; p.m.r. τ 9.13, 9.09 (d, d, 6H, --CH(CH₃)₂, J = 6 Hz), 9.02 (d, 3H, secondary CH₃, J = 6.5 Hz).

Mol. Wt. Calcd. for $C_{14}H_{24}O$: 208.183. Found (high resolution mass spectrometry): 208.182.

Hydrogenation of Octalone 13

A solution of 100 mg of the octalone 13 in 10 ml of freshly distilled ethyl acetate was hydrogenated at atmospheric pressure and room temperature over 10 mg of 10% palladium-on-charcoal. Distillation of the crude product under reduced pressure afforded 96 mg (92%) of a colorless oil, b.p. 125°/0.6 mm. This material was subjected to epimerization with sodium methoxide in refluxing methanol. The resulting product was shown



to contain 98% of one component by g.l.c. analysis (column B, 180°, 100). An analytical sample of this material exhibited i.r. and p.m.r. spectra identical with those of the *cis*-fused decalone 16, obtained as described above.

Preparation of Octalones 19 and 20

A solution of l g of the pyrrolidine enamine of 4.4ethylenedioxycyclohexanone (18) (24) and 500 mg of (E)-2-methyl-3-hepten-5-one (7) in 4 ml of dry dioxan was refluxed for 48 h. A solution of 0.2 g of sodium acetate in 1.1 ml of acetic acid - water (1:2) was added and refluxing was continued for 1.5 h. The cooled reaction mixture was then diluted with water and thoroughly extracted with ether. The combined ether extracts were successively washed with water, aqueous sodium carbonate, water, and brine and then dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the residue under reduced pressure gave 121 mg (8%) of a viscous oil, b.p. 150°, 0.1 mm. Gas-liquid chromatographic analysis (column A, 180°, 85) revealed that this material consisted of a mixture of two compounds, in a ratio of 4:1. Analytical samples were collected by preparative g.l.c. The major compound, octalone 19, exhibited u.v. λ_{max} 243 nm (ϵ 13 000); i.r. (film) λ_{max} 6.05 μ ; p.m.r. τ 9.18, 9.08 (d, d, $6H, -CH(CH_3)_2, J = 6.5 Hz), 8.23 (s, 3H, vinyl CH_3),$ 6.06 (s, 4H, --OCH₂CH₂O--).

Mol. Wt. Calcd. for $C_{16}H_{24}O_3$: 264.172. Found (high resolution mass spectrometry): 264.172.

The minor isomer, octalone 20, exhibited u.v. λ_{max} 243 nm (ϵ 18 900); i.r. (film) λ_{max} 6.01, 6.15 μ ; p.m.r. τ 9.08, 9.06 (d, d, 6H, -CH(CH₃)₂, J = 6.0 Hz), 8.23 (s, 3H, vinyl CH₃), 6.06 (s, 4H, -OCH₂CH₂O--).

Mol. Wt. Calcd. for $C_{16}H_{24}O_3$: 264.172. Found (high resolution mass spectrometry): 264.172.

Preparation of Hydroxy Octalones 22 and 23

A solution of 18 g of 4-hydroxycyclohexanone (25) and 20.7 ml of pyrrolidine in 234 ml of benzene was refluxed under a Dean-Stark water separator until no further separation of water occurred. The benzene and excess pyrrolidine were removed under reduced pressure (0.1 mm) to yield a crude, crystalline enamine, i.r. (Nujol) λ_{max} 3.0, 6.1 μ . To this material was added 13.5 g of (E)-2-methyl-3-hepten-5-one (7) and the resulting mixture was stirred at 50° for 17 h. At this time, the i.r. spectrum of an aliquot showed the absence of absorptions due to the vinyl ketone. Hence, an additional 5 g of the vinyl ketone 7 was added and stirring was continued for an additional 19 h. Dry dioxan was then added and the resulting solution was refluxed for 16 h. A solution of 5 g of sodium acetate in acetic acid water (30 ml, 1:2) was added and refluxing was continued for 4 h. The cooled reaction mixture was diluted with water and thoroughly extracted with ether. The combined ether extracts were washed successively with water, dilute hydrochloric acid, water, and brine and dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the residue under reduced pressure gave 14 g (40%) of a colorless oil, b.p. 200°/0.1 mm. This material was shown by g.l.c. analysis (column C, 215°, 170) to be a mixture of two components in a ratio of approximately 3:2. Subjection of this mixture to epimerizing conditions (150 ml of

2 *M* sodium methoxide in methanol, reflux 12 h) changed this ratio to 7:3, respectively. The two components were separated by preparative g.l.c. (column C, 230°, 110). The major octalone (22) exhibited u.v. λ_{max} 248 nm (ϵ 10 900); i.r. (CHCl₃) λ_{max} 2.75, 2.9, 6.05 µ; p.m.r. τ 9.16, 9.07 (d, d, 6H, --CH(CH₃)₂, *J* = 6.5 Hz), 8.23 (s, 3H, vinyl CH₃), 6.15, 5.82 (unresolved multiplets, 1H, --CHOH).

Mol. Wt. Calcd. for $C_{14}H_{22}O_2$: 222.162. Found (high resolution mass spectrometry): 222.162.

The minor octalone (23) exhibited u.v. λ_{max} 247 nm (ϵ 9300); i.r. (CHCl₃) λ_{max} 2.75, 2.9, 6.05, 6.15 μ ; p.m.r. τ 9.07, 9.04 (d, d, 6H, --CH(CH₃)₂, J = 6 Hz), 8.26 (s, 3H, vinyl CH₃), 6.10, 5.78 (unresolved multiplets, 1H, --CHOH).

Mol. Wt. Calcd. for $C_{14}H_{22}O_2$: 222.162. Found (high resolution mass spectrometry): 222.162.

Preparation of Dione 24

A solution of 60 mg of chromium trioxide in 1.5 ml of dichloromethane containing 0.09 ml of pyridine was allowed to stir at room temperature for 15 min. To this solution was added a solution of 30 mg of octalone 22 in 0.5 ml of dichloromethane. The resulting reaction mixture was allowed to stir at room temperature for 25 min and was then diluted with 8 ml of ether. The ether layer was washed with water and brine and dried over anhydrous magnesium sulfate. Removal of the ether afforded 28 mg (94%) of the dione 24, m.p. 108–110°. This material showed one peak on g.l.c. analysis (column A, 180°, 86) and exhibited u.v. λ_{max} 247 nm (ϵ 13 000); i.r. (CHCl₃) λ_{max} 5.85, 6.05, 6.15 µ; p.m.r. τ 9.20, 9.07 (d, 6H, --CH(CH₃)₂, J = 6.5 Hz), 8.12 (s, 3H, vinyl CH₃).

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.28; H, 9.18.

Conversion of Hydroxy Octalone 22 into Decalone 14

To a solution of 225 mg of octalone 22 in 6 ml of dry pyridine at 0° was added 0.15 ml of methanesulfonyl chloride. The reaction mixture was allowed to stir at room temperature for 3.5 h. Ice was added, the mixture was allowed to stir for an additional 10 min, and then was thoroughly extracted with ether. The combined ether extracts were washed with water, dilute sulfuric acid, dilute aqueous sodium bicarbonate, and brine and dried over anhydrous magnesium sulfate. Removal of the solvent afforded 280 mg (85%) of the crude oily methanesulfonate derivative 25, i.r. (film) λ_{max} 6.0, 7.45, 8.55 μ .

A solution of this material in 1.8 ml of absolute ethanol was added dropwise to a solution of 1.35 g of lithium in 50 ml of liquid ammonia (distilled from sodium metal) at -78° . The mixture was stirred at -78° for 1 h and then at -33° for 1.5 h. Additional ethanol was added until the blue color disappeared. The liquid ammonia was allowed to evaporate, water was added to the residue, and the resulting mixture was thoroughly extracted with ether. The combined ether extracts were washed with water and brine and dried over anhydrous magnesium sulfate. Removal of the solvent gave 160 mg of a mixture of alcohols. This material was dissolved in 12 ml of acetone (distilled from potassium permanganate) and to the resulting solution was added standard chromic acid solution (18) until the orange color persisted. The orange color was discharged by addition of isopropyl alcohol and the solvent was removed under reduced pressure. The residue was diluted with water and the mixture was thoroughly extracted with ether. The combined ether extracts were washed with water and brine and dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the residue under reduced pressure afforded 136 mg (85%) of the decalone 14, b.p. 125°/0.6 mm. This material showed one peak on g.l.c. analysis (column B, 215°, 110) and exhibited spectra (i.r., p.m.r.) identical with those of an authentic sample of the *trans*-fused decalone 14.

Preparation of the Dithioketal 26

To a cold (0°) , stirred mixture of 3.6 g of octalone 22 and 3.0 ml of ethanedithiol was added 1.4 ml of boron trifluoride etherate. The solution was allowed to warm to room temperature and then stirred for an additional 1 h. After dilution with water, the reaction mixture was thoroughly extracted with chloroform. The combined chloroform extracts were washed with water and brine and dried over anhydrous magnesium sulfate. Removal of the solvent gave 5.2 g of crude material. A benzene solution of the latter was filtered through a short column of Woelm activity I neutral alumina (20 g). The alumina column was eluted with additional benzene. Concentration of the filtrate gave a crystalline solid which, upon recrystallization from ether afforded 3.2 g (66%) of the dithioketal 26, m.p. $105-110^{\circ}$; i.r. (Nujol) λ_{max} 3.0, 6.1 μ ; p.m.r. τ 9.21, 9.02 (d, d, 6H, $-CH(CH_3)_2$, J = 7 Hz), 8.07 (s, 3H, vinyl CH₃), 6.67 (m, 4H, -SCH₂CH₂S-), 6.54, 5.86 (unresolved multiplets, 1H.

Mol. Wt. Calcd. for $C_{16}H_{26}OS_2$: 298.142. Found: (high resolution mass spectrometry): 298.144.

Preparation of Alcohol 27

To a solution of 700 mg of the dithioketal **26** in 100 ml of absolute ethanol was added 10 g of commercial Raney nickel. The mixture was refluxed for 5 h, cooled, and filtered through a bed of Celite. The filtrate was concentrated and the residual oil was distilled under reduced pressure to afford 350 mg (77%) of the alcohol **27**, b.p. 120°/0.25 mm; i.r. (film) λ_{max} 3.0, 6.0 µ; p.m.r. τ 9.23, 9.09 (d, d, 6H, --CH(CH₃)₂, J = 6.5 Hz), 8.40 (s, 3H, vinyl CH₃), 6.36, 5.85 (unresolved multiplets, 1H,

-CHOH).

Mol. Wt. Calcd. for $C_{14}H_{24}O$: 208.183. Found (high resolution mass spectrometry): 208.183.

Preparation of Octalone 28

To an ice-cold solution of 720 mg of chromium trioxide in 18 ml of anhydrous pyridine was added a solution of 350 mg of alcohol 27 in 9 ml of anhydrous pyridine. The solution was allowed to stir at room temperature for 40 h. The reaction mixture was poured into stirred anhydrous ether. Celite was added and the mixture was filtered. The filtrate was thoroughly washed with water and brine and dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the oily residue under reduced pressure yielded 307 mg (89%) of a colorless oil, b.p. 130°/0.35 mm. This product was shown to be homogeneous by g.l.c.

(column B, 180°, 85). An analytical sample exhibited i.r. (film) $\lambda_{max} 5.85 \mu$; p.m.r. τ 9.21, 9.05 (d, d, 6H, ---CH(CH₃)₂, J = 6.5 Hz), 8.36 (s, 3H, vinyl CH₃).

Mol. Wt. Calcd. for $C_{14}H_{22}O$: 206.167. Found (high resolution mass spectrometry): 206.168.

Preparation of Alcohol 29

A solution of 230 mg (1.06 mmol) of octalone 28 in 30 ml of anhydrous ether was cooled to 0°. To this solution was added, dropwise, 2 ml of 2.16 M methyllithium (4.32 mmol) in ether. After the addition was complete the solution was allowed to stir for 2 h at room temperature and was then poured into a mixture of ice and water. The ether layer was separated and washed with water and brine and dried over anhydrous magnesium sulfate. The solvent was removed and the residual oil was distilled under reduced pressure to afford 224 mg (91%) of a viscous oil, b.p. 130°/0.25 mm. This oil was shown by g.l.c. analysis (column C, 200°, 110) to contain one major component along with trace amounts of unidentified material. The major component, obtained by preparative g.l.c., was a white crystalline substance, m.p. 79–80°; i.r. (Nujol) λ_{max} 3.0, 6.1 µ; p.m.r. τ 9.21, 9.07 (d, d, 6H, --CH(CH₃)₂, J = 6.5 Hz), 8.81 (s, 3H, tertiary CH₃), 8.37 (s, 3H, vinyl CH₃).

Mol. Wt. Calcd. for $C_{15}H_{26}O$: 222.198. Found (high resolution mass spectrometry): 222.198.

Preparation of (\pm) -Cadinene Dihydrochloride (30)

A solution of 100 mg of the crystalline alcohol 29 in 10 ml of anhydrous ether was cooled to 0°. Dry hydrogen chloride gas was bubbled into the solution. At the end of 15 min, the gas flow was stopped and the solution was stirred for an additional hour. The ether was removed under reduced pressure to afford 100 mg (80%) of crystalline (\pm)-cadinene dihydrochloride (30). An analytical sample was obtained by recrystallization from *n*-hexane-methanol to afford white crystals, m.p. 104.5-106°. This sample showed no depression of melting point on admixture with an authentic sample of (\pm)-cadinene dihydrochloride and its i.r. spectrum was superimposable with that of the authentic sample; i.r. (Nujol), λ_{may} 3.45, 6.95, 8.75, 11.75 u.

i.r. (Nujol), λ_{max} 3.45, 6.95, 8.75, 11.75 µ. Anal. Calcd. for $C_{13}H_{26}Cl_2$: C, 65.01; H, 9.39. Found: C, 64.75; H, 9.52.

Financial support from the National Research Council of Canada and a National Research Council of Canada Studentship (to W.M.P.) are gratefully acknowledged.

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