## STEREOSPECIFIC TOTAL SYNTHESIS OF $(+)-\epsilon$ - AND $(-)-\gamma_2$ -CADINENE<sup>1,2</sup>

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Abstract—(+)- $\epsilon$ -Cadinene (1) and (-)- $\gamma_2$ -cadinene (2) have been synthesized from the enol ether ketone 3 via the methylene ketone 4. These two stereospecific total syntheses confirm the structures assigned to these sesquiterpenes and represent the first preparation by totally synthetic methods of any of the widespread group of cadinanes in their native state.

The substance originally known as  $\epsilon$ -cadinene was first isolated from ylang ylang oil in 1954 and was initially thought to possess a trans decalin system.<sup>3-5</sup> The structure of this sesquiterpene was revised by Westfelt<sup>6,7</sup> who converted  $\epsilon$ -cadinene, under mild conditions, to muurolene dihydrochloride (5). This conversion indicated that the ring junction in the sesquiterpene was actually cis. Westfelt pointed out that the conversion of a muurolane (possessing a cis decalin system) to a cadinane (possessing a trans decalin system) occurred readily by epimerization at C<sub>2</sub> during certain reactions if conditions were not carefully controlled. This type of an epimerization had resulted in the initial erroneous assignment of stereochemistry at C<sub>9</sub> for  $\epsilon$ -cadinene. Since the name "cadinene" is convertionally used for cadalenic sesquiterpenes with a trans ring junction, Westfelt suggested that the name of this cis sesquiterpene be changed to  $\epsilon$ -muurolene. The sesquiterpene with the trans ring junction which was now called  $\epsilon$ -cadinene, was prepared by Westfelt, from a partially directed dehydrohalogenation of (-)-cadinene dihydrochloride (6). The properties of  $\epsilon$ -cadinene (1a) were shown to be markedly different from the cis analog  $\epsilon$ -muurolene (7).<sup>6,7</sup>



7 5 6 7a: Enantiomer 6a: Enantiomer

Since Westfelt's elegant work, the isolation of both enantiomeric forms of  $\epsilon$ -cadinene from various plant sources have been reported.<sup>8a,b,c</sup> However, a detailed description in the literature of the natural product is still lacking. The properties of the synthetic  $\epsilon$ -cadinene described in this paper are in good agreement with Westfelt's  $\epsilon$ -cadinene from (-)-cadinene dihydrochloride.

In the case of  $\gamma_2$ -cadinene, there are again few reports on the isolation of this compound.9-11 Kartha et al. initially obtained  $(-)-\gamma_2$ -cadinene from North Indian vetiver oil, and on the basis of spectral and chemical evidence, assigned structure 2 to this compound.<sup>9</sup> The synthesis of  $(\pm)$ - $\gamma_2$ -cadinene has been carried out by Kelly and Eber,<sup>12</sup> and the properties of the synthetic  $(-)-\gamma_2$ -cadinene described below are in excellent agreement with the properties reported by the above authors for the racemic compound. There remains some discrepancy however, in the rotation we obtained for the synthetic material and that reported by Kartha et al.9 for the natural product. Trivedi et al.<sup>11</sup> have reported that  $(-)-\gamma_2$ -cadinene co-occurs with the isomeric  $(-)-\gamma$ -cadinene (8) in North Indian vetiver oil, and that the separation of these two isomeric cadinenes can be accomplished by elaborate argentic chromatography. Since  $(-)-\gamma$ -cadinene is strongly levorotatory  $(-116^\circ, -145^\circ)$ ,<sup>11</sup> the co-occurrence of a small amount of this compound with  $(-)-\gamma_2$ -cadinene may account for the relatively high rotation reported  $(-40^{\circ})^{9}$  for the latter. In the present work the rotation found for the synthetic cadinene was  $-4.9^{\circ}$ . The isolation of  $(-)-\gamma_2$ -cadinene from the same botanical source, i.e. from the oil of Vetiveria zizanioides L. (Nash) for purposes of further comparison is presently in progress.

In previous papers on cadinane chemistry, the synthesis of a key intermediate, the *cis* enol ether ketone 3, and its conversion to (+)-cadinene dihydrochloride (6a) have been described.<sup>13,14</sup> In our work directed toward the muurolane and cadinane series, we found that epimerization at C<sub>9</sub> occurred readily during the mildest conditions required for a Wittig reaction on the *cis* enol ether ketone 3. The reaction conditions were determined by using 2-methylcyclohexanone (9) as the model compound, since the ketone group in the latter should be hindered approximately to the same extent as the ketone group in compound 3.

The model ketone 9 was converted in good yield to the corresponding olefin 10 using the method of Greenwald *et al.*<sup>15</sup> with the following modifications: Methylene-triphenylphosphorane was prepared as described<sup>15</sup> by the reaction of triphenylmethylphosphonium bromide with dimethyl sulfunyl carbanion. During the preparation of the latter compound from sodium hydride and dimethyl sulfoxide, however, the volume of hydrogen evolved was measured quantitatively. This allowed the determination of the amount of carbanion present. In order to prevent



any base catalyzed enolization, care was taken at this point, to avoid the presence of excess base (carbanion, or possibly sodium hydride). A slight excess of the phosphonium salt was therefore used. Since it is reported that the yield of Wittig reactions on polyfunctional compounds improves upon increasing the ratio of ylid to ketone,<sup>16</sup> the Wittig reaction on the enol ether ketone **3** was run in the presence of excess (28%) ylid. Under these conditions, a 95% conversion of the starting ketone to the corresponding olefin **11** was accomplished. This compound, without further purification, was converted by acid hydrolysis to the methylene ketone **4**. The latter, after purification, indicated from its ORD curve (see octant diagram below) that it possessed a *trans* ring junction.



tWe are grateful to Dr. J. A. Marshall for bringing this work to our attention.

<sup>‡</sup>The epimerization-addition in the Wittig reaction has since been observed with some frequency, for example as reported by Huffman and Mole,<sup>20</sup> and Heathcock and Radcliffe.<sup>21</sup> If the non-epimerized olefin is the desired product, utilizing methylenetriphenylphosphorane in olefin synthesis from enolizable ketones does not seem satisfactory. As McMurry and Von Beroldingen point out,<sup>19</sup> the method of Sowerby and Coates<sup>22</sup> seems best suited for the olefination of sensitive ketones. If the latter method<sup>22</sup> proceeds with retention of the *cis* configuration in the case of enol ether 3, a possible route to the synthesis of the compounds in the muurolane system will be opened.

Acid hydrolysis of the enol ether functions is rapid, and it was found in a preliminary experiment that the reaction of cyclohexyl vinyl ether with dilute acid in ethanolic solution was exothermic and went to completion at room temperature within the first few minutes. In another experiment the stability of the terminal methylene group was tested under the hydrolytic conditions mentioned above. The model compound used in this case was 2-methylmethylenecyclohexane (10). It was found that no bond migration took place when the olefin 10 was treated with dilute acid in ethanol. Assuming, therefore, that no epimerization at C<sub>9</sub> took place during the conversion of the methylene enol ether 11 to the corresponding methylene ketone 4, we concluded that the Wittig reaction on enol ether 3 proceeded with initial epimerization followed by addition.

When these results were reported in communication form,<sup>1,2</sup> we were unaware that this type of epimerization in the Wittig reaction had been observed previously. Marshall *et al.*<sup>18</sup> had also observed this phenomenon during a sequence of reactions directed toward the stereoselective total synthesis of certain sesquiterpenes of the eudesmane type<sup>†</sup>: the Wittig reaction of the *cis* decalone 12 proceeded with the initial epimerization at the ring junction to yield the *trans* olefin 13.

Marshall *et al.* suggested that enolization leading to epimerization might be caused by the solvent (dimethyl sulfoxide), or alternatively, might be catalyzed by the enolate itself. We suggested in our case that epimerization could be initiated by a small amount of ylid, which by extracting a proton, would yield the enolate anion 14.<sup>17</sup> The latter, in turn would catalyze the fast epimerization to a *trans* decalin system (15). This mechanism is similar to the one proposed recently by McMurry and Von Beroldingen<sup>19</sup> who suggest that the ylid itself is the epimerizing agent.<sup>‡</sup>

The nature of the ring junction of the methylene ketone 4 was further confirmed in the next step when the Wittig reaction on the latter yielded  $\epsilon$ -cadinene (1) and not  $\epsilon$ -muurolene (7a). The synthetic  $\epsilon$ -cadinene had properties similar to those reported for  $\epsilon$ -cadinene by Westfelt,<sup>6.7</sup> and yielded (+)-cadinene dihydrochloride (6a). The same sesquiterpene was prepared, for purposes of



comparison, from the known crystalline *trans* diketone  $16^{13.14}$  by a double Wittig reaction. The two synthetic compounds were found to be identical.

The ease of epimerization at C<sub>9</sub> to yield the more stable trans decalin system was observed earlier in this work during an attempted synthesis of muurolene dihydrochloride. Thus we found that treatment of the enol ether ketone 3 with methyllithium in ether vielded the methyl carbinol 17 which was cleaved under very mild conditions to the keto-alcohol 18. Diol 19 obtained from a second methyllithium reaction on 18 gave only cadinene dihydrochloride when treated under the very mild conditions developed by Westfelt to minimize epimerization at C<sub>9</sub> in this step.7 Although it is known that even under these specific conditions partial epimerization from the muurolane to the cadinane analogue does occur, Westfelt has shown that in such cases the original stereochemistry is largely retained in the dihydrochloride product, and that furthermore each of the two dehydrochlorides can be recognized readily in the presence of the other by their distinctive IR spectra<sup>7</sup> (Experimental). Since in our case no trace of the characteristic IR absorption of muurolene dihydrochloride could be detected in the product, while crude or at any stage in its purification, it follows that the inversion took place in the methyllithium reaction itself. Because the natural (-)-cryptone used for the relay<sup>13</sup> in the present work is now available only with considerable difficulty we are not in a position to investigate further the mechanism of this inversion.



Inspection of models shows that the reactive  $C_9$ hydrogen in 3 is actually free from any 1,3-diaxial interactions since the flattening of part of the ring A due to the  $\Delta^6$  unsaturation eliminates the axial position at  $C_7$  and forces the potentially axial hydrogen at  $C_5$  into a quasi-axial position. When inversion at  $C_9$  occurs by a base catalyzed mechanism, the base in question can easily approach the  $C_9$  hydrogen which is activated by the adjacent ketone function.

In the sequence of reactions directed toward the synthesis of  $\gamma_2$ -cadinene (2), the *trans* methylene ketone 4 was treated with methyllithium to yield the corresponding methyl carbinol 20. As has been pointed out previously<sup>2,23</sup> the addition of the reagent from the least hindered equatorial side of the ketone function results in the formation of an axial OH group. In agreement with these findings, alcohol 20 upon dehydration yielded as the main olefinic product,  $\gamma_2$ -cadinene. The presence of any  $\epsilon$ -cadinene (1) which would result from the dehydration

of an OH group in the equatorial position was not detected.



In preliminary experiments carried out to determine the conditions for the above dehydration, it was found that the method described by Barton et al.24 was not applicable in our case. These authors prepared 3-methyl-cholest-2ene (21) from 3-methyl-cholestan-3 ( $\alpha$  or  $\beta$ )-ol (22) by treating the alcohol(s) with a mixture of acetic acid and perchloric acid. This dehydration in the A ring of the steroid system to yield the  $\Delta^2$  olefin seemed a good model for the the preparation of  $\gamma_2$ -cadinene from the alcohol 20. We found on model compounds, however, that a secondary reaction, namely the addition of acetate, competed with the dehydration reaction. A second dehydration method was investigated using phosphorous oxychloride in pyridine. This method was also utilized by the above workers in their studies on the 3methylcholestanols (22).24 The main product isolated from a trial run in our case was unchanged alcohol. Our findings for this reaction are in agreement with the results of Iguchi et al.25 who reported that the selective dehydration of diol 23 with phosphorous oxychloride in pyridine left intact the axial C<sub>10</sub> OH group and dehydrated only the equatorial OH group at  $C_1$  to give the olefin 24.



Dehydration in the present work of the methylene alcohol 20 was accomplished with thionyl chloride in pyridine. As has been pointed out, the latter is a stronger dehydrating agent than phosphorous oxychloride.<sup>26</sup> The  $\gamma_2$ -cadinene obtained by this method showed in its NMR spectrum one vinylic proton (other than the two methylene protons) at  $\delta$  5.48 as an unresolved multiplet. This splitting pattern ruled out the possible formation of the less favorable  $\Delta^5$  isomer ( $\gamma$ -cadinene, 8) from the above dehydration.<sup>2</sup>

The synthetic  $\gamma_2$ -cadinene is in the same antipodal form as the natural product from North Indian vetiver oil. This so-called unusual antipodal form<sup>27</sup> is related to (+)cadinene dihydrochloride (**6a**) and is less common among the cadinanes which are generally related to (-)-cadinene dihydrochloride (**6**). The synthetic sesquiterpene from the above dehydration, after purification by argentic layer chromatography, was converted easily to (+)-cadinene dihydrochloride (m.p. and m.m.p. 116-117°;  $[\alpha]_D + 37^\circ$ ).

The above series of transformations afford several new intermediates which are well suited to serve as starting materials for the further synthesis, some under present study, of natural cadinanes, muurolanes, and of the alcohols in this series.

## EXPERIMENTS

All m.ps are uncorrected and were determined on a Kofler hot stage micro block. The IR spectra were determined on a Perkin Elmer 337 double beam spectrophotometer. The NMR spectra were determined on a Varian model 60A instrument in CDCl, with TMS as the internal standard. ORD were determined on a Cary-60 instrument in MeOH and optical rotations were determined in CHCl, on a Perkin-Elmer 141 polarimeter. GLC was carried out on an Aerograph Autoprep model A-700 instrument using He as the carrier gas. Analyses were carried out by Galbraith Laboratories.

2-Methylmethylenecyclohexane 10. The Wittig reaction was run following the method of Greenwald et al.<sup>15</sup> During the generation of the dimethylsulfonyl carbanion from 1.4g (0.06 mol) NaH and 30 ml DMSO, the volume of H<sub>2</sub> given off was 1.3401 (22.8°, 746 mm). To the resulting solution of the carbanion, triphenylmethylphosphonium bromide (22.13 g, 0.06 mol, m.p. 226-228°) was added in 60 ml DMSO. The salt was prepared in turn from triphenylphosphine and MeBr. To the dark red soln of the ylid, 5.4g of 2-methylcyclohexanone (0.05 mol) was added and the mixture was maintained at 50-55° for 15 hr. After the usual work up, evaporation of the solvent yielded a crude product which was distilled under partial vacuum (b.p. 53-54°/63 mm). The corresponding olefin (3.3g, 61%) showed no ketone absorption in the IR:  $\nu_{max}^{CCL_4}$  3090, 1695, 895 cm<sup>-1</sup>;  $\delta$  4.6 (s, 2 H), 1.0 (d, 3 H, J = 6 Hz).

Methylene enol ether 11. The carbonyl 3 was prepared according to Günay<sup>28</sup> and had the following constants:  $\nu_{\text{CCL}}^{\text{CCL}}$  1716, 1751, 1188 cm<sup>-1</sup>;  $\alpha_{310} - 333^{\circ}$  (min);†  $n_D^{21}$  1.5023. The Wittig reaction was run as described above. The carbanion was prepared from 0.760 g NaH (0.031 mol) and 16 ml DMSO. To the resulting soln 11.42 g (0.032 mol) triphenylmethylphosphonium bromide in 32 ml DMSO was added. To this soln of the ylid 4.956 g (0.021 mol) enol ether 3 was added and the reaction was allowed to proceed at 50° for 17 hr. After the usual work up, the crude product isolated (5.2 g) indicated in the IR that there was about 5% unreacted ketone present. The ether 11 ( $\nu_{\text{CCL}}^{\text{CCL}}$  3090, 1660, 1189, 890 cm<sup>-1</sup>) was used in the next step without further purification.

Methylene ketone 4. The ether 11 (5.2 g) was treated with 23 ml 0.5 N 95% ethanolic HCl. A mild evolution of heat was noted. The system was kept under N<sub>2</sub> and stirred at room temp. for 25 min. A 0.5 ml aliquot taken at the end of 5 min indicated in the IR, after the work up, that complete hydrolysis of the enol ether group had taken place. An intense saturated ketone peak appeared at 1715 cm<sup>-1</sup> and the band at 1189 cm<sup>-1</sup> disappeared.

The rest of the compound was isolated by adding an equal amount of water and extracting the aqueous layer several times with pentane. The pentane layers were combined, washed with water, and dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent gave 3.7 g of an orange oil which was distilled (b.p. 114–125°/1.5 mm) prior to gas chromatography (25% Carbowax 20M, 20' × 1/4"). The distillate was found to consist essentially of two components. The main component (ketone 4) was about 80% of the whole product:  $\nu_{max}^{CCl_4}$  3090, 1715, 1800, 1650, 895 cm<sup>-1</sup>; NMR,  $\delta$  4.62 (d, 2 H); 0.92, 0.68 (both doublets, 6 H, J = 6.5 Hz). (Found: C, 81.51 H, 10.86. Calcd for C<sub>14</sub>H<sub>22</sub>O; C, 81.50; H, 10.75%); [ $\alpha$ ]<sub>D</sub> + 21.6°,  $\alpha_{310}$  + 800° (max).

 $\epsilon$ -Cadinene (1) from methylene ketone 4. The Wittig reaction was run as described above. NaH (0.134 g, 0.005 mol) was allowed to react with 4 ml abs DMSO. To this soln of the carbanion 2.0 g (0.005 mol) triphenylmethylphosphonium bromide in 6 ml DMSO was added. The ketone (0.750 g, 0.003 mol) was then added to the resulting soln of the ylid and the reaction was maintained at 50° for 20 hr. After the usual work up, 844.9 mg of a crude product was obtained which was distilled (b.p. 99–100°/2 mm) to yield 488 mg of  $\epsilon$ -cadinene. The gas chromatogram (25% Carbowax 20M, 10' × 1/8") of the latter showed a single, symmetrical peak. The synthetic sesquiterpene had the following constants:  $\nu_{\rm crut}^{\rm crut}cs_2$ 3075, 1790, 1648, 1188, 1140, 1085, 1075, 893, 817, 652, 638 cm<sup>-1</sup>; NMR,  $\delta$  4.75 (m, 4 H), 0.91, 0.62 (both doublets, 3 H, J = 6.5 Hz); [ $\alpha_{\rm 1D}^{\rm ap} + 6.0^{\circ} n_{\rm 1D}^{\rm 22}$  1.5039.

 $\epsilon$ -Cadinene from the trans-diketone 16. The procedure for the Wittig reaction was the same as described above. The ylid was prepared from 0.172 g (0.007 mol) NaH, 5 ml abs DMSO and 2.570 (0.007 mol) triphenylmethylphosphonium bromide. The trans-

diketone 16 (0.500 g, 0.002 mol) was then added and the reaction was allowed to proceed at 50° for 23 hr. After the work up in the usual manner, 521.8 mg of a crude product was obtained which was distilled under vacuum in two batches in a short-path apparatus. The distillate ( $\epsilon$ -cadinene, 429 mg) was purified by gas chromatography (25% Carbowax 20M, 20' × 1/4"): [ $\alpha$ ]<sup>20</sup><sub>D</sub> + 10°, n<sup>22</sup><sub>D</sub> 1.5031. The NMR and IR spectra of the  $\epsilon$ -cadinene prepared by both methods were superimposable. The identity of the sesquiterpenes was further established by coinjection on the gas chromatogram.

Cadinene dihydrochloride (6a) from  $\epsilon$ -cadinene (1).  $\epsilon$ -Cadinene (81.0 mg) was saturated in 0.2 ml anhyd ether with dry HCl at - 18°. The immediate formation of a white solid was noted. The mixture was stored in the refrigerator for 24 hr. At the end of this period the IR spectrum of the mixture showed the presence of some unreacted material. The system was resaturated with HCl and stored in the refrigerator 24 hr more. The crystalline product (61 mg) was recrystallized twice from MeOH and finally from EtOAc to yield pure 6a, m.p. 116-117°, m.m.p. with an authentic sample<sup>14</sup> 116-117°;  $[\alpha]_D^{12}$  + 37.5°.

Hydroxy enol ether 17. A 3-neck flask was fitted with a glass stopper, a reflux condenser, and a dropping funnel. The apparatus was thoroughly dried and flushed with a stream of dry N2. Li wire (10.85 g, 1.56 mol) in 300 ml anhyd ether was allowed to react with MeI (110.07 g, 0.78 mol) in 175 ml anhyd ether. The reaction started instantaneously and was brought to completion by refluxing for 0.5 hr after almost all of the Li had reacted. The ketone 3 (5.00 g, 0.021 mol) in 50 ml anhyd ether was slowly added and the mixture was stirred at room temp. for 15 hr. At the end of this period, the mixture was poured over ice and the organic component was extracted with ether. The ether layer was washed with water containing some Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, and then with water, and was finally dried over  $Na_2SO_4$ . Evaporation of the solvent gave 5.6 g of a yellow oil:  $\nu_{max}^{CCl_4}$  3625 (sharp), 3495 (broad), 1189 cm<sup>-1</sup>. This product (17) was used in the next experiment without further purification.

Keto alcohol 18. The ether 17 (5.6 g) was taken into 40 ml ether and this soln was extracted 50 times with 20 ml portions of a 20% aqueous soln of NaHSO<sub>3</sub>. The combined extract was saturated with solid Na<sub>2</sub>CO<sub>3</sub>·H<sub>2</sub>O. The oily layer which formed was extracted with ether. The ether layer after washing with water and drying over Na<sub>2</sub>SO<sub>4</sub> gave, upon evaporation, 1.6730 g of an oil which showed in the IR no absorption for an enol ether group at 1189 cm<sup>-1</sup>:  $\nu_{max}^{CC_4}$  3627 (sharp), 3489 (broad), 1718 cm<sup>-1</sup>. This product (18) was used in the next experiment without further purification.

Diol 19. MeLi was prepared in anhyd ether as described above from 5.85 g (0.84 mol) Li wire and 60.21 g (0.42 mol) MeI. The carbonyl 18 (1.2 g, 0.005 mol) was added in 15 ml anhyd ether and the mixture was refluxed for 17 hr. The mixture was worked up in the usual way and evaporation of the solvent yielded 1.2720 g of an oil, which showed in the IR a very weak band in the saturated ketone region:  $\nu_{\rm mel}^{\rm CCL_4}$  3612 (sharp), 3480 cm<sup>-1</sup> (broad).

Reaction of diol 19 with HCl and purification of the product by reversed phase partition chromatography. The method described by Westfelt' for the preparation of muurolene dihydrochloride from the natural muurolenes was followed. The diol (380 mg) was dissolved in 0.4 ml anhyd ether and this soln was saturated with dry HCl at  $-23^{\circ}$ . The mixture was stored in the refrigerator overnight. Removal of the solvent yielded 330 mg of a semicrystalline product. Purification was carried out by reversed phase partition chromatography as described by Westfelt for the separation of a mixture of muurolene dihydrochloride and cadinene dihydrochloridei<sup>7</sup> Hexane on PVC was used as the stationary phase and MeOH-water as the mobile phase. PVC (Diamond Alkali Co., Grade 450, 60 g) was shaken with 20 ml hexane in 320 ml 80% aq MeOH satd. with hexane. The column (19 mm × 400 mm) was prepared according to Wickberg.<sup>29</sup>

The crude product (330 mg) was dissolved in a minimum amount of 90% aq MeOH satd. with hexane and applied to the column. The fractions collected were 5 ml each, except for the first five fractions, which were 10 ml each. A total of 110 fractions were collected. The crystalline residues from fractions 20-32 indicated from their m.p. and IR spectra (KBr pellets) that they did not

<sup>&</sup>lt;sup>†</sup>In preliminary work a sample carefully fractionated through a 125-plate column and homogeneous by gc analysis showed  $\alpha_{311}$  – 376° (min). We thank Dr. M. K. Logani for this result.

contain muurolene dihydrochloride. In fact, these fractions contained pure cadinene dihydrochloride (muurolene dihydrochloride has a strong band at  $810 \text{ cm}^{-1}$  where cadinene dihydrochloride has no absorption. The latter has a strong band at  $850 \text{ cm}^{-1}$  where muurolene dihydrochloride does not absorb).<sup>7</sup>

The reaction and purification were repeated with the following modifications' the dihydrochloride was prepared from 200 mg diol as described above and the mixture was recrystallized from 20 to 40 pet ether. Chromatography of the crystalline material (m.p.  $99-115^{\circ}$ ) and of the mother liquor failed to yield any muurolene dihydrochloride. Chromatography of the former yielded pure cadinene dihydrochloride and of the latter yielded an oil and no crystalline material. The oil, as well as the crystalline product showed no absorption in the IR for muurolene dihydrochloride.

Reaction of the diol 19 with HCl failed to proceed under milder conditions  $(-43^{\circ})$ .

Methylene alcohol 20. MeLi was prepared in anhyd ether as described above from 1.414 g (0.20 mol) Li wire and 14.7 g (0.10 mol) MeI. Ketone 4 (700 mg, 0.002 mol) in 42 ml anhyd ether was gradually added to the soln of the organolithium reagent and the mixture was stirred at room temp. for 20 hr. After the hydrolysis and usual work up evaporation of the solvent yielded crude 20 (1.0135 g) which had no absorption in the IR for a saturated ketone group:  $\nu_{max}^{CCL_4}$  3610 (sharp), 3080, 1648, 890 cm<sup>----</sup>. This compound was used in the next experiment without further purification.

 $\gamma_2$ -Cadinene 2. Methylene alcohol 20 (506.7 mg) in 6.4 ml anhyd pyridine was allowed to react with a soln of 0.6 ml SOCl<sub>2</sub> in 2 ml anhyd pyridine at - 17° as described by Smolders.<sup>30</sup> After the work up, removal of the solvent (ether) yielded 500 mg of a crude product. A portion of the latter, after distillation under vacuum, was purified by argentic layer chromatography in the following manner: Brinkmann Silica Gel F-254 preparative plates (layer thickness: 2 mm) were impregnated with AgNO<sub>3</sub> by dipping the plates in a 9.9% soln of AgNO<sub>3</sub> in 40% aq EtOH. The plates were dried in a vacuum oven at room temp. overnight and were stored in a dark desiccator.

The distilled product above (75 mg) was applied as a band and was developed with anhyd benzene. Visualization was accomplished with a UV lamp. The main fraction consisted of  $\gamma_2$ -cadinene (25.8 mg):  $\nu_{max}^{CCL} c^{S_2}$  3080, 1770, 1640, 1390, 1370, 882, 832, 790 cm<sup>-1</sup>; NMR,  $\delta$  5.48 (broad multiplet, 1 H), 4.69, 4.57 (1 H each), 1.67 (s, 3 H), 0.93, 0.73 (both doublets, 3 H, J = 6.5 Hz);  $|\alpha|_{D^2}^{D^2} - 4.9^\circ$ .

Cadinene dihydrochloride (6a) from  $\gamma_2$ -cadinene (2). (-)- $\gamma_2$ -Cadinene (13.4 mg) in a few drops of anhyd ether was saturated with dry HCl at -15°. The crystalline product was recrystallized three times from MeOH to yield pure cadinene dihydrochloride (m.p. and m.m.p. with authentic<sup>14</sup> (+)-cadinene dihydrochloride 116-117°; [ $\alpha$ ]<sub>20</sub><sup>20</sup> + 37°).

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