Registry No. 1, 92490-07-8; 2, 92490-08-9; 3, 92490-09-0; Ni(COD)$_2$, 1295-35-8; butadiene, 106-99-0; (Z,E)-1,3,6-octatriene, 22038-68-2; (E,E)-1,3,6-octatriene, 22038-69-3.

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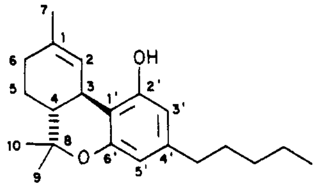
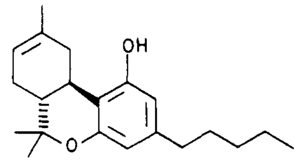
A Novel Approach to the Synthesis of the Cannabinoids

Summary: The primary cannabinoids have been prepared by a novel sequence of reactions from methyl methacrylate and methyl vinyl ketone.

Sir: Marijuana is a complex mixture of many compounds, but the psychotropic activity of this drug is derived principally from the presence of the tetrahydrocannabinols (THC's), *trans*-Δ^1-THC (1) and *trans*-Δ^6-THC (2).[1,2]



1

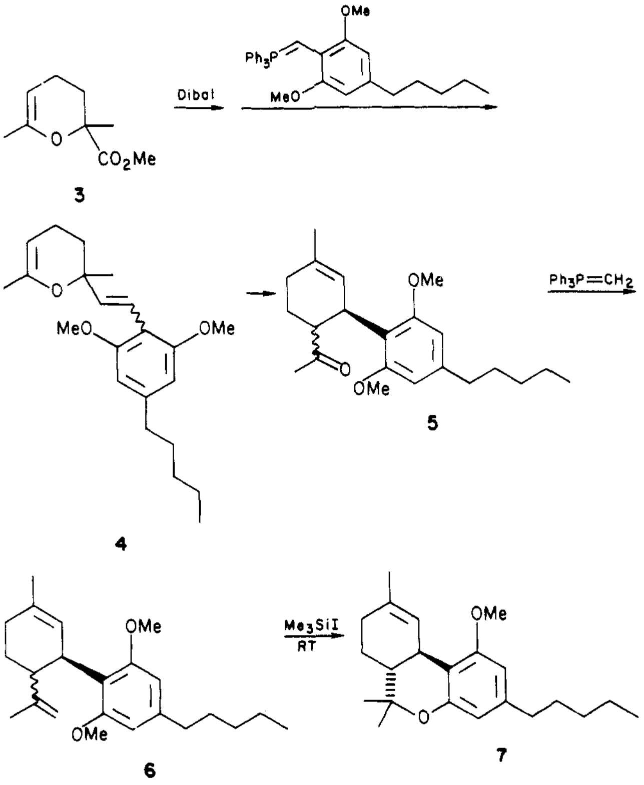


2

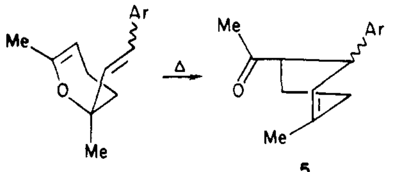
Other physiological activity has been attributed to marijuana,[1a] so that much effort has been expended on the synthesis of the THC's and numerous analogues.[1,3] A particularly effective synthesis of Δ^1-THC should avoid acid because of the facile conversion of Δ^1-THC to Δ^6-THC under acidic conditions.[1,4]

We report a new method for the preparation of *trans*-Δ^1-THC which should be adaptable to the synthesis of numerous analogues as well as large-scale syntheses (see Scheme I). Thus, the substituted dihydropyran 3, available from methyl vinyl ketone and methyl methacrylate,[5] is converted into the diene 4[6] in 67% yield by selective reduction with diisobutylaluminum hydride (Dibal)[8,9] followed by a Wittig reaction[7,9] with a suitable ylide and chromatography on neutral alumina. This product was isolated as a 1:1 mixture of cis and trans isomers.[10]

Scheme I



The key step in the synthesis is a Claisen rearrangement.[11] This is an interesting reaction not only because of the synthetic conversion but also because the reaction must proceed through a boat conformation of the dihydropyran ring (eq 1).[7,9,12] Büchi[7] and Ireland[9] have



4 5 (1)

reported that such rearrangements do occur although the temperatures are high (190–400 °C).[7] Danishefsky[13] observed a related conversion of unsaturated lactone silyl ethers but at much lower temperatures (105 °C).

In view of these literature results, it is most striking that our rearrangement occurs at *room temperature*![14] Indeed, a 94% yield of the ketone 5 is isolated after chromatography on silica gel as a 1:1 mixture of cis and trans iso-

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[1] For excellent reviews, see: (a) Razdan, R. K. "The Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley: New York, 1981; Vol. 4, pp 185–262. (b) Mechoulam, R.; McCallum, N. K.; Burstein, S. *Chem. Rev.* **1976**, *76*, 1.

[2] The monoterpenoid numbering used in *Chemical Abstracts* is followed here.

[3] One of the more recent synthetic efforts is as follows: Richards, R. W.; Rönneberg, H. *J. Org. Chem.* **1984**, *49*, 572.

[4] (a) Taylor, E. C.; Lenard, K.; Shvo, Y. *J. Am. Chem. Soc.* **1966**, *88*, 367. (b) Gaoni, Y.; Mechoulam, R. *Ibid.* **1966**, *88*, 5673.

[5] This can be accomplished by a modification of the procedure of Mundy: Mundy, B. P.; Otzenberger, R. D.; De Bernardis, A. R. *J. Org. Chem.* **1971**, *36*, 2390.

[6] The ^{1}H NMR of diene mixture 4 shows an enol ether vinyl CH at 4.3 ppm and other vinyl CH at 5.4–6.0 ppm in agreement with the reported values for 2-methyl-2-vinyl-3,4-dihydro-2*H*-pyran and analogues prepared by Büchi and Powell.[7] GC/MS shows a parent ion of *m/e* 344 and a base peak of *m/e* 208.

[7] Büchi, G.; Powell, J. E., Jr. *J. Am. Chem. Soc.* **1976**, *92*, 3126.

[8] For example, see: Szantay, C.; Töke, L.; Kolonits, P. *J. Org. Chem.* **1966**, *31*, 1447. Corey, E. J.; Broger, E. A. *Tetrahedron Lett.* **1969**, 1779. Grieco, P. A.; Yokoyama, Y.; Withers, G. P.; Okuniewicz, F. J.; Wang, C.-L. J. *J. Org. Chem.* **1978**, *43*, 4178.

[9] Ireland, R. E.; Aristoff, P. A. *J. Org. Chem.* **1979**, *44*, 4323.

[10] This ratio was based on the integration of the styryl vinyl peaks in the ^{1}H NMR and the relative peak areas upon analysis by capillary GC.

[11] For general reviews of the Claisen rearrangement, see: Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. Rhoads, S. J.; Raulins, N. R. *Org. React. (N.Y.)* **1975**, *22*, 1. Bennett, G. B. *Synthesis* **1977**, 589.

[12] Lutz, R. P.; Roberts, J. D. *J. Am. Chem. Soc.* **1961**, *83*, 2198.

[13] Danishefsky, S.; Funk, R. L.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 6889.

[14] The reaction mixture was allowed to stir in dichloromethane for 48 h. The required time may be considerably less since the compound without a pentyl group rearranges completely in 2 h.

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mers.[15] Related systems also give good yields of Claisen products at room temperature in an apparently stereoselective manner.[17]

The synthesis is completed by a Wittig reaction, deprotection, and ring closure. The Wittig step proceeded to give diene **6**[18] without difficulty in 80% yield after purification on silica gel. Deprotection was attempted with methylmagnesium iodide[16,19] without success; however, trimethylsilyl iodide (Me_3SiI)[20] readily consumed the ether **6** and gave a *single product* (**7**)[21] in 94% yield.[22] Excess Me_3SiI does not affect this product. Removal of the remaining methyl ether is accomplished in 78% yield with excess NaSEt in DMF.[23,24] Thus, the overall yield of *trans*-Δ^1-THC from ester **3** is 37%. Conversion of THC **1** into the more stable isomer **2** was accomplished in 94% yield by using *p*-TsOH in anhydrous ether.[1,4,24]

Additional studies using optically active starting material are in progress as well as the synthesis of various analogues.

Acknowledgment. We gratefully acknowledge the assistance of Jim Spriggle with GC/MS determinations and Robert Zimmermann with ^{13}C NMR analyses.

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[15] Mass spectral analysis of ketone **5** shows the molecular ion at *m/e* 344 and a base peak of *m/e* 43. The acetyl group is also in evidence in the ^1H NMR (δ 2.16) and IR (1715 cm^{-1}). The ratio is based on the relative peak areas from capillary GC analysis of hexane solutions. (The rearrangement does not occur in hexane.) Ketone **5** is a known compound.[16]

[16] Korte, F. Dlugosch, E.; Claussen, U. *Liebigs Ann. Chem.* **1966**, *693*, 165.

[17] These results will be discussed elsewhere.

[18] Diene **6** shows the loss of the carbonyl stretch characteristic of ketone **5** in the IR while mass spectral analysis gives a parent ion of *m/e* 342 and a base peak of *m/e* 287. The ^1H NMR is in accord with the reported values.[19a]

[19] (a) Mechoulam, R.; Gaoni, Y. *J. Am. Chem. Soc.* **1965**, *87*, 3273. (b) Jen, T. Y.; Hughes, G. A.; Smith, H. *J. Am. Chem. Soc.* **1967**, *89*, 4551. (c) Mechoulam, R.; Braun, P.; Gaoni, Y. *Ibid.* **1967**, *89*, 4552; (d) **1972**, *94*, 6159.

[20] Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.

[21] Analysis of ether **7** by MS shows the expected parent ion at *m/e* 328 and a base peak at *m/e* 108. The benzylic (C-3) hydrogen appears at δ 3.15 (d of d, each J = 8 Hz) in the ^1H NMR confirming the trans stereochemistry (e.g., *trans*-Δ^1-THC has a δ 3.15 peak for this hydrogen).[4a]

[22] It is not yet clear where the epimerization of compound **6** occurs, but this conversion is currently under study. A possibly related process is the reaction of *trans*-cannabidiol dimethyl ether with HBr to give 9-bromo-*trans*-hexahydrocannabinol methyl ether.[3]

[23] Feutrill, G. I.; Mirrington, R. N. *Tetrahedron Lett.* **1970**, 1327.

[24] Spectral data are in accord with that published previously.[4]

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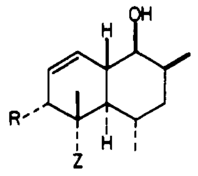
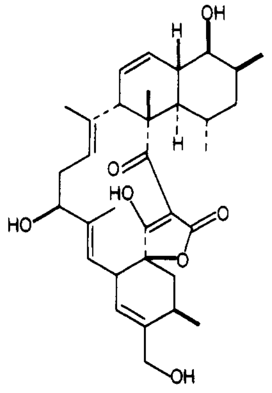
Intramolecular Diels-Alder Cyclization of Conjugated Aldehydes. Synthesis of a Chlorothricolide Intermediate

Summary: Various substituted 2,8,10-undecatrienals have been found to undergo facile intramolecular Diels-Alder cyclization in the presence of dialkylaluminum chlorides to give bicyclo[4.4.0]octahydronaphthalenecarboxaldehydes with high endo selectivity. The method has been applied to the synthesis of a synthetic intermediate related to the macrolide antibiotic aglycon chlorothricolide.

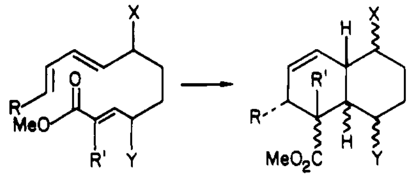
Sir: In the course of studies on the synthesis of kijanolide and related natural products,[1] we wished to prepare hydronaphthalenes related to **1**. Others have explored the highly attractive intramolecular Diels-Alder strategy for direct assemblage of such systems via dienyl acrylic esters such as **2**.[2] Unfortunately, the reaction requires high temperatures and gives rise to a mixture of exo/endo adducts.[2a] Lewis acid catalysis has been successfully employed in **2a**-type systems,[2e] but the approach fails with the isomeric **2b** owing to destructive side reactions.[2a,d]



1a, Z = CO_2R
1b, Z = COR



kijanolide



2a, X = H; Y = OR
2b, X = OR; Y = H

After due consideration of the foregoing results we decided to examine a slight variant of the intramolecular Diels-Alder approach to systems such as **1** by using a conjugated aldehyde as the internal dienophile with Lewis acid catalysis. It was our belief that the aldehyde group would serve as a more effective dienophile activator than an ester, particularly in conjunction with Lewis acids.[3] The aldehyde was also more in line with our projected synthetic use of the adducts. The dramatic improvements engendered through this relatively simple modification prompts this preliminary report of our findings which are potentially applicable to a variety of heretofore unattainable or inefficient intramolecular Diels-Alder cyclizations.

Initial studies were carried out on aldehyde **6**, prepared via selective addition of 4,6-heptadienylmagnesium bromide to isopropyl (*E*)-3-formylpropenoate[4a] along the lines

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[1] Mallams, A. K.; Puar, M. S.; Rossman, R. R.; McPhail, A. T.; MacFarlane, R. D.; Stephens, R. L. *J. Chem. Soc., Perkin Trans. 1*, **1983**, 497-1534. Mallams, A. K.; Puar, M. S.; Rossman, R. R. *J. Am. Chem. Soc.* **1981**, *103*, 3938-3940. Hirayama, N.; Kasai, M.; Shirahata, K.; Ohashi, Y.; Sasada, Y. *Tetrahedron Lett.* **1980**, *21*, 2559-2560. Keller-Schierlein, P. W.; Muntwyler, R.; Pache, W.; Zähner, H. *Helv. Chim. Acta* **1969**, *52*, 127.

[2] (a) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200-5211. (b) Hall, S. E.; Roush, W. R. *J. Org. Chem.* **1982**, *47*, 4611-4621. (c) Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1982**, *47*, 4825-4829. (d) Takeda, K.; Shinagawa, M.; Koizumi, T.; Yoshii, E. *Chem. Pharm. Bull.* **1982**, *30*, 4000-4005. (e) Funk, R. L.; Zeller, W. E. *J. Org. Chem.* **1982**, *47*, 180-182. (f) Burke, S. D.; Powner, T. H.; Kageyama, M. *Tetrahedron Lett.* **1983**, *24*, 4529-4532. (g) Snider, B. B.; Burbaum, B. W. *J. Org. Chem.* **1983**, *48*, 4370-4374. (h) For a recent review, see: Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183-234.

[3] Cf. Branchadell, V.; Oliva, A.; Bertran, J. *Chem. Phys. Lett.* **1983**, *97*, 378-380. Paido, L.; Branchadell, V.; Oliva, A.; Bertran, J. *Theochem.* **1983**, 255-260. Several examples of conjugated aldehydes in thermal intramolecular Diels-Alder additions leading to hydrindane systems have been reported. The stereoselectivity was not high. Roush, W. R.; Peseckis, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6696-6704. Taber, D. F.; Campell, C.; Gunn, B. P.; Chiu, I.-C. *Tetrahedron Lett.* **1981**, *22*, 5141-5144.

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