Table VII. Experimental Formal Steric Enthalpies of Esters and Acids Based on Gas-Phase Enthalpies of Formation at 25 °C

compound	formula	ΔH_f (exptl)[a]	SD	ref[b]	ΔH_f (strain free)[c]	SM	ΔH_f (calcd)[d]	FSE- (exptl)[e]	FSE- (expected)
succinic acid	$C_4H_6O_2$	-196.70	0.8	P	-195.85	0.00	-195.85	-0.85	0.00
2,2-dimethylpropanoic acid	$C_5H_{10}O_2$	-117.42	1.6	P	-124.87	0.00	-124.87	7.45	0.00
3-methylbutanoic acid	$C_5H_{10}O_2$	-121.89	1.5	P	-120.25	0.09	-120.16	-1.73	0.00
isopropyl acetate	$C_5H_{10}O_2$	-115.13	0.2	P	-116.48	0.00	-116.48	1.35	0.85
methyl bicyclo[1.1.0]butane-1-carboxylate	$C_6H_8O_2$	-39.34	0.2	P	-102.88	0.00	-102.88	63.54	
methyl cyclobutanecarboxylate	$C_6H_{10}O_2$	-84.92	0.3	P	-108.41	0.00	-108.41	23.49	
adipic acid	$C_6H_{10}O_4$	-206.74	0.6	P	-206.15	0.43	-205.72	-1.02	0.00
methyl 2,2-dimethylpropanoate	$C_6H_{12}O_2$	-122.80	0.3	P	-120.43	0.00	-120.43	-2.37	0.85
methyl 3-methylbutanoate	$C_6H_{12}O_2$	-119.00	1.7	P	-115.81	0.09	-115.72	-3.28	0.85
ethyl 3-methylbutanoate	$C_7H_{14}O_2$	-125.96	2.0	P	-124.17	0.09	-124.08	-1.88	0.85
octanedioic acid	$C_8H_{14}O_4$	-213.89	1.0	P	-216.44	0.86	-215.58	1.69	0.00
2-ethylhexanoic acid	$C_8H_{16}O_2$	-133.72	0.4	P	-138.06	0.81	-137.25	3.53	0.00
isopropyl pentanoate	$C_8H_{16}O_2$	-130.23	0.8	P	-131.40	0.37	-131.03	0.80	0.85
methyl heptanoate	$C_8H_{16}O_2$	-123.30	0.3	P	-124.11	0.80	-123.31	0.01	0.85
propyl pentanoate	$C_8H_{16}O_2$	-127.53	0.4	P	-127.32	0.80	-126.52	-1.01	0.85
sec-butyl butyrate	$C_8H_{16}O_2$	-130.33	1.0	P	-131.40	0.75	-130.65	0.32	0.85
butyl pentanoate	$C_9H_{18}O_2$	-133.89	0.5	P	-132.47	0.97	-131.50	-2.39	0.85
isobutyl pentanoate	$C_9H_{18}O_2$	-135.90	0.9	P	-134.47	0.70	-133.77	-2.14	1.05
sec-butyl pentanoate	$C_9H_{18}O_2$	-137.00	0.5	P	-136.55	0.97	-135.58	-1.42	1.05
homocubane-1-carboxylic acid	$C_{10}H_{10}O_2$[f]	0.60	0.0	O	-115.72	0.00	-115.72	116.32	
methyl homocubane-1-carboxylate	$C_{11}H_{12}O_2$[f]	6.26	1.3	O	-111.28	0.00	-111.28	117.54	
dodecanedioic acid	$C_{12}H_{22}O_4$	-233.48	0.5	P	-237.03	1.29	-235.74	2.26	0.00
dodecanoic acid	$C_{12}H_{24}O_2$	-153.44	0.5	P	-154.28	1.88	-152.40	-1.04	0.00
methyl dodecanoate	$C_{13}H_{26}O_2$	-146.94	0.5	P	-149.84	1.88	-147.96	1.02	0.85
tridecanoic acid	$C_{13}H_{26}O_2$	-157.79	0.6	P	-159.43	2.10	-157.33	-0.46	0.00
methyl tridecanoate	$C_{14}H_{28}O_2$	-151.86	0.7		-154.99	2.10	-152.89	1.03	0.85
tetradecanoic acid	$C_{14}H_{28}O_2$	-165.80	1.0	p	-164.58	2.31	-162.27	-3.53	0.00
methyl tetradecanoate	$C_{15}H_{30}O_2$	-156.91	0.7	P	-160.14	2.31	-157.83	0.92	0.85
pentadecanoic acid	$C_{15}H_{30}O_2$	-167.07	1.1	P	-169.72	2.53	-167.19	0.12	0.00
hexadecanoic acid	$C_{16}H_{32}O_2$	-176.17	1.1	P	-174.87	2.74	-172.13	-4.04	0.00
methyl pentadecanoate	$C_{16}H_{32}O_2$	-162.52	0.7	P	-165.28	2.53	-162.75	0.23	0.85
nonadecanoic acid	$C_{19}H_{38}O_2$	-187.69	1.3	P	-190.31	3.39	-186.92	-0.77	0.00
eicosanoic acid	$C_{20}H_{40}O_2$	-194.17	1.8	P	-195.46	3.70	-191.76	-2.41	0.00

[a-e] See Table II. [f] Reference 9.

equality of c[C_CKH_H_H_] and c[C_CEH_H_H_] and the defined equality of c[C_C_CKH_H_] and c-[C_C_CEH_H_], the above pairs might be presumed to be equal also, and Benson does use equal values. However, the rather meager data seem to fit the assigned values better than equal values.

Synthesis of (±)-11-Nor-9-carboxy-Δ^9-tetrahydrocannabinol: New Synthetic Approaches to Cannabinoids†,[1]

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A completely regioselective synthesis of (±)-11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (1), a principal human metabolite of Δ^9-tetrahydrocannabinol (2), has been carried out in seven steps and 14% overall yield from apoverbenone (9) and the bis-MOM ether of olivetol. Condensation of 9 with the aryllithium derived from the bis-MOM ether of olivetol gives an unstable tertiary allylic alcohol that undergoes oxidative rearrangement to give enone 42. Reaction of 42 with acid results in hydrolysis of the MOM ethers and cyclization to benzopyranone 21. Conversion to MOM ether 39 followed by Li/NH_3 reduction and trapping of the enolate with *N*-phenyltriflimide gives vinyl triflate 40 plus the isomer with a cis ring fusion. Palladium-catalyzed carboxylation, hydrolysis of the MOM ether, and separation from cis acid 41 gives pure 1. Model experiments employing unsubstituted resorcinol derivatives that lead to ester 27 are described, as are a number of alternative approaches to acid 1.

Introduction

Cannabis sativa (marijuana) has been employed for many centruies as a medicinal agent and in social and religious rituals.[3] In contemporary society the illicit use of marijuana as a recreational drug has led to the development of methods to ascertain if an individual has been using the drug. The most widely used test procedures

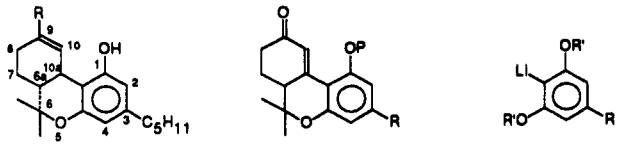
† Dedicated to the memory of Dr. Ulrich Weiss.

(1) For a preliminary communication describing the synthesis of acid 1, see: Huffman, J. W.; Zhang, X.; Wu, M.-J., Joyner, H. H. *J. Org. Chem.* **1989**, *54*, 4741.

(2) To whom inquiries regarding the crystallographic studies should be directed.

0022-3263/91/1956-1481$02.50/0

Chart I



1 R = CO_2H
2 R = CH_3
3 R = CH_2OH

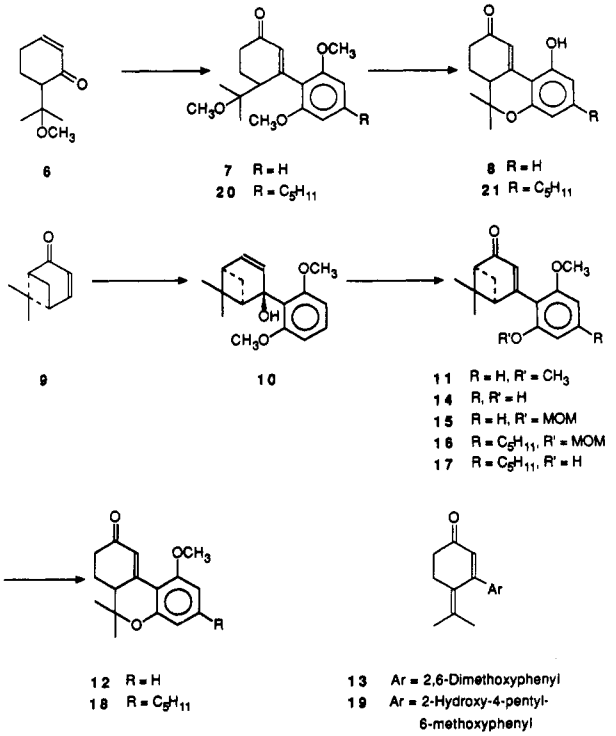
4

5

employ immunoassay techniques that detect the presence in body fluids (usually urine) of 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (9-carboxy-Δ^9-THC, 1), a principal human metabolite of Δ^9-tetrahydrocannabinol (Δ^9-THC, 2)[4] (Chart I). In addition to acid 1 and other human metabolites of THC there is considerable current interest in synthetic analogues of THC in which cannabimimetic effects are minimized and therapeutic effects are enhanced.[5]

Although there is considerable forensic interest in acid 1, the only reported synthesis of this important THC metabolite was presented several years ago and entails the sequential oxidation of alcohol 3 to the corresponding aldehyde followed by further oxidation to 1.[6] The overall yield is low and alcohol 3, itself a THC metabolite, is prepared by a multistep sequence from THC.[6,7] A number of alternative syntheses of 3 have been described; however, most suffer from a lack of regioselectivity in the initial acid-catalyzed condensation of olivetol and an aliphatic unit.[6,7] A second complicating factor in the synthesis of cannabinoids in general is the instability of the Δ^9 relative to the Δ^8 isomer.[8] Syntheses of 11-oxygenated cannabinoids in which the double bond is introduced by elimination invariably afford a preponderance of the Δ^8 isomer.[7a,9] In order to overcome these problems, we now describe a new synthetic approach to the tricyclic cannabinoid nucleus, which leads to intermediates that have been converted to racemic 11-oxygenated Δ^9-cannabinoids with complete regioselectivity. This synthesis also avoids the troublesome oxidation of alcohol 3 and/or the corresponding aldehyde to carboxylic acid 1.

Scheme I



6

7 R = H
20 R = C_5H_{11}

8 R = H
21 R = C_5H_{11}

9

10

11 R = H, R' = CH_3
14 R, R' = H
15 R = H, R' = MOM
16 R = C_5H_{11}, R' = MOM
17 R = C_5H_{11}, R' = H

12 R = H
18 R = C_5H_{11}

13 Ar = 2,6-Dimethoxyphenyl
19 Ar = 2-Hydroxy-4-pentyl-6-methoxyphenyl

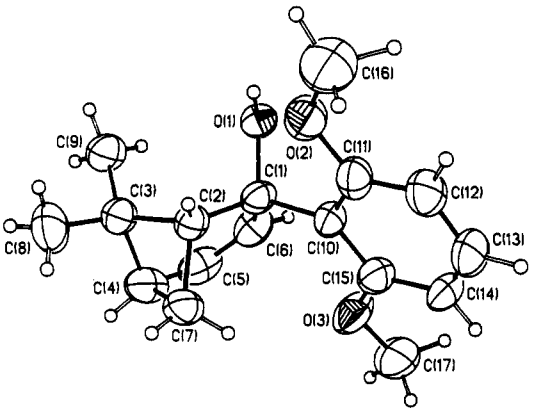


Figure 1. ORTEP structure of **10**.

It was envisioned that a protected tricyclic enone (4) would serve as a key intermediate and that the 10,10a olefin would be used to generate the requisite trans ring fusion and 9,10 double bond. Enones similar to 4 (P = H, R = n-C_5H_{11} or $C(CH_3)_2(CH_2)_5CH_3$) have been prepared by groups at Hoffman-La Roche and Eli Lilly, respectively, using the classical von Pechmann condensation of a substituted resorcinol with an α-acetylglutaric ester.[10] While this synthesis is reasonably efficient in the two cases reported, it is limited to the preparation of enones 4 in which R is sufficiently large to preclude condensation ortho to R. Also, this synthesis leads to racemic materials and in our hands the base-catalyzed cyclization of the initial von

(3) Mechoulam, R. In *Cannabinoids as Therapeutic Agents*; Mechoulam, R., Ed.; CRC Press: Boca Raton, FL, 1986; pp 1–19.

(4) (a) Hawks, R. L., Ed. "The Analysis of Cannabinoids in Biological Fluids", NIDA Research Monograph 42, National Institute on Drug Abuse: Rockville, MD, 1982. This monograph describes a number of analytical procedures for human metalbolites of THC and a concise summary of the human metabolism of THC. (b) Williams, P. L.; Moffat, A. C. *J. Pharm. Pharmacol.* **1980**, *32*, 445. (c) Law, B.; Mason, P. A.; Moffat, A. C.; Glendle, R. J.; King, L. J. *Ibid.* **1984**, *36*, 289. (d) The numbering system depicted for 1 is that based on the dibenzopyran ring system. An alternative system based on the monoterpene unit is also used for cannabinoids.

(5) In particular ocular effects, the antiemetic and analgesic properties of THC analogues have been examined. For a recent review see the entire volume cited in ref 3.

(6) (a) Pitt, C. G.; Fowler, M. S.; Srivastava, S. C.; Williams, D. L. *J. Am. Chem. Soc.* **1975**, *97*, 3798. (b) Tius et al. (Tius, M. A.; Gu, X.; Kerr, M. A. *J. Chem. Soc., Chem. Commun.* **1989**, 62) have recently modified this synthesis but do not present yield data.

(7) (a) Pitt, C. G.; Hauser, F.; Hawks, R. G.; Sathe, S.; Wall, M. E. *J. Am. Chem. Soc.* **1972**, *94*, 8578. (b) Razdan, R. K.; Uliss, D. B.; Dalzell, H. C. *Ibid.* **1973**, *95*, 2361. (c) Uliss, D. B.; Hendrick, G. R.; Dalzell, H. C.; Razdan, R. K. *Ibid.* **1978**, *100*, 2929. This synthesis has recently been adapted to the synthesis of optically active THC metabolites and analogues: Siegel, C.; Gordon, P. M.; Razdan, R. K. *J. Org. Chem.* **1989**, *54*, 5428. We thank Dr. Razdan for a prepublication copy of the manuscript, which mentions the preparation of acid 1 but presents no details. (d) Lander, N.; Ben-Zvi, Z.; Mechoulam, R.; Martin, B.; Nordqvist, M.; Agurell, S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 8. For general reviews of cannabinoid synthesis see: (e) Razdan, R. K. In *The Total Synthesis of Natural Products*; Ap Simon, J., Ed.; John Wiley: New York, 1981; Vol. 4, pp 186–262. (f) Mechoulam, R.; McCallum, N. K.; Burstein, S. *Chem. Rev.* **1976**, *76*, 75.

(8) Dalzell et al. (Dalzell, H. C.; Uliss, D. B.; Handrick, G. R.; Razdan, R. K. *J. Org. Chem.* **1981**, *46*, 949) find that acid-catalyzed equilibration of Δ^8- or Δ^9-THC gives a 97/3 mixture of Δ^8 to Δ^9 isomer.

(9) (a) Schwartz, A.; Madan, P. *J. Org. Chem.* **1986**, *51*, 5463. (b) Ap Simon, J. W.; Collier, T. L.; Guiver, M. D. *Can. J. Chem.* **1982**, *60*, 2804.

(10) (a) Farneholtz, K. E.; Lurie, M.; Kierstead, R. W. *J. Am. Chem. Soc.* **1966**, *88*, 2079; **1967**, *89*, 5934. We thank Dr. Alan Schwartz and Mr. Pradeep Madan for the gift of a quantity of an advanced intermediate for the Roche synthesis of 8 and detailed procedures for the preparation of 8. (b) Archer, R. A.; Blanchard, W. B.; Day, W. A.; Johnson, D. W.; Lavagnino, E. R.; Ryan, C. W.; Baldwin, J. E. *J. Org. Chem.* **1977**, *42*, 2277.

Pechmann product has presented difficulties. In order to circumvent these problems, we envisioned an alternative approach to enones 4 in which an appropriately substituted aryllithium (5) is condensed with an alicyclic ketone.

This synthetic methodology was developed originally by using the aryllithium derived from 1,3-dimethoxybenzene (5, R = H, R′ = CH_3). The reasons for these model experiments were threefold: first, resorcinol derivatives are much less expensive than those of olivetol (5, R = n-C_5H_{11}); second, this approach will lead to cannabinoid analogues lacking the pentyl side chain, which are very difficult to obtain by traditional methods; and, third, from a practical standpoint, the ^1H NMR spectra of these compounds are less complex than those that have the aliphatic side chain.

Results and Discussion

Two conceptually similar but somewhat different approaches to enone 4 (R = H) were explored. The first method employed reaction of substituted cyclohexenone 6 (Scheme I) with (2,6-dimethoxyphenyl)lithium to give an unstable tertiary alcohol, which underwent oxidative rearrangement with Jones' reagent to give enone 7.[11] Cyclohexenone 6 was prepared in 75% yield by Mukaiyama alkylation,[12] using 2,2-dimethoxypropane, of the trimethylsilyl enol ether of cyclohexenone.[13] Reaction of enone 7 with boron tribromide provided phenolic enone 8. The best overall yield of 8 from cyclohexenone was 19%; however, this was not reproducible. In particular, both Mukaiyama product 6 and enone 7 are quite labile and the average yield for this sequence was in the range of 10%.

An alternative, and far more satisfactory, approach to the requisite tricyclic enone was via condensation of a (dialkyoxyaryl)lithium (5, R = H) with the readily available monoterpene derivative (+)-apoverbenone (9).[14] Accordingly, reaction of enone 9 with (2,6-dimethoxyphenyl)lithium gave tertiary allylic alcohol 10. The structure of 10 was confirmed and the stereochemistry established by X-ray crystallography (Figure 1). Oxidative rearrangement of tertiary allylic alcohol 10 using PCC gave enone 11. Although it was anticipated that acid treatment of 11 would proceed with opening of the cyclobutane ring and cyclization to 12, with demethylation, the only isolable product was dienone 13.[15] On the assumption that the reaction conditions (HOTs/$CHCl_3$, reflux) were not stringent enough to effect demethylation, the synthesis was modified to employ phenol 14 as the substrate for formation of 12. This was accomplished by using the aryllithium derived from the MOM ether of 3-methoxyphenyl, which was condensed with ketone 9 and oxidized by using PCC to provide 15.

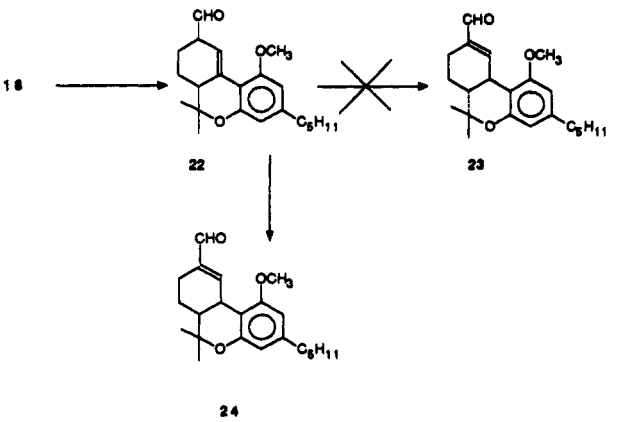
The MOM ether of 15 proved to be surprisingly difficult to hydrolyze with mild acid but was efficiently cleaved with $(CH_3)_3SiBr$ at 0 °C[16] to give 14. Treatment of 14 with 1 equiv of toluenesulfonic acid in refluxing chloroform[10b] gave protected tricyclic enone 12 in 84% yield. The cyclization could also be effected in satisfactory yield, although quite slowly, by either Nafion NR 50 or Amberlyst 15 resin. The overall yield of 12 by this procedure was 56%, based on apoverbenone, which permits the convenient preparation of gram quantities of this material. Unfortunately enone 12 prepared by this route is racemic, although the precursor is optically active. Racemization may occur via hydride shifts during the acid-catalyzed cyclization although it is more probable that enolization of the product is responsible. Enone 12 could also be prepared by methylation of 8; however, the overall yield is not competitive with the synthesis from apoverbenone.

With the development of an efficient synthesis of enone 12, the sequence was extended to the series in which the n-pentyl side chain was present on the aromatic nucleus. Reaction of ketone 9 with the requisite aryllithium and oxidation gave enone 16. Cleavage of the MOM ether with $(CH_3)_3SiBr$, or more economically with pyridinium p-toluenesulfonate in methanol or 2-butanone,[17] gave phenol 17.

Although the relatively small-scale model synthesis of 12 proceeded smoothly, some problems were encountered in preparative-scale syntheses of tricyclic enone 18. In particular, variable amounts of phenolic dienone 19 were obtained and it was ultimately found that the optimum conditions for the rearrangement of 17 to 18 required the presence of ethanol. Using toluenesulfonic acid in chloroform, dried over 3A molecular sieves or chloroform to which a small amount of ethanol had been added provided an 86% yield for this conversion. With rigorously dried chloroform (4A molecular sieves, followed by distillation) an 81% yield of 19 was obtained. In the absence of an external nucleophile the cation obtained by opening of the cyclobutane ring apparently undergoes deprotonation rather than reaction with the phenolic hydroxyl. In the presence of ethanol it appears probable that the cation undergoes an S_N1 reaction to give an intermediate with a structure similar to 20, which is cyclized via a second, intramolecular S_N1 reaction. Enone 19 is probably not an intermediate in the formation of 18 because attempted cyclization of 19 gave as the only isolable product 3-(2-hydroxy-6-methoxy-4-pentylphenyl)cyclohexenone, which apparently arises via a retroaldol reaction.

Enone 18 was also prepared, although in poor overall yield, from 6 via 3-arylcyclohexenone 20 and phenol 21.

Scheme II



(11) (a) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682. (b) Majetich et al. (Majetich, G.; Condon, S.; Hull, K.; Ahmad, S. *Tetrahedron Lett.* **1989**, *30*, 1033) describe the oxidative rearrangement of dienols using PDC.

(12) Ishida, A.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1161.

(13) Girard, C.; Conia, J. M. *Tetrahedron Lett.* 1973, 2767.

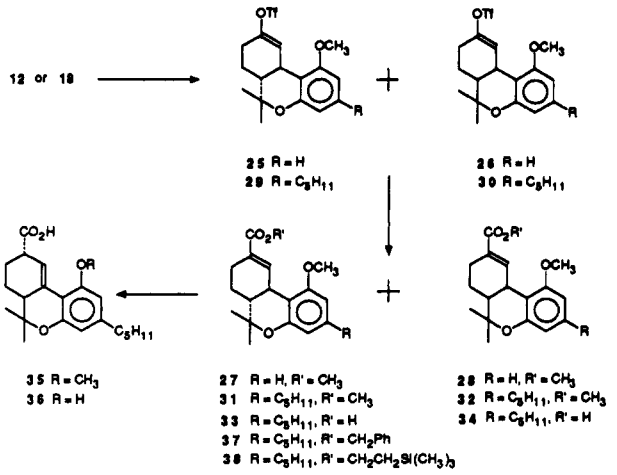
(14) Grimshaw, J.; Grimshaw, J. T.; Juneja, H. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 50. In our hands (+)-apoverbenone prepared by this procedure is usually contaminated with up to 10% of nopinone. The (−)-β-pinene (Aldrich) used as starting material has an optical purity of approximately 90%.

(15) For other examples of the rearrangement of pinene derivatives in the synthesis of cannabinoids, see refs 7e, 10b, and Mechoulam, R.; Lander, N.; Srebnik, M.; Brewer, A.; Segal, M.; Feigenbaum, J. J.; Jarbe, T. U. C.; Consroe, P. In "Structure–Activity Relationships of the Cannabinoids"; Rapaka, R. S., Makriyannis, A., Eds.; NIDA Research Monograph 79, National Institute on Drug Abuse: Rockville, MD, 1987; pp 15–30.

(16) Hanessian, S.; Delorme, D.; Dufresne, Y. *Tetrahedron Lett.* **1984**, *25*, 2515.

(17) Monti, H.; Leandri, G.; Klos-Rinquet, M.; Carriol, C. *Synth. Commun.* **1983**, *13*, 1021.

Scheme III



Phenol **21** was identical with a sample prepared by the Roche procedure.[10a]

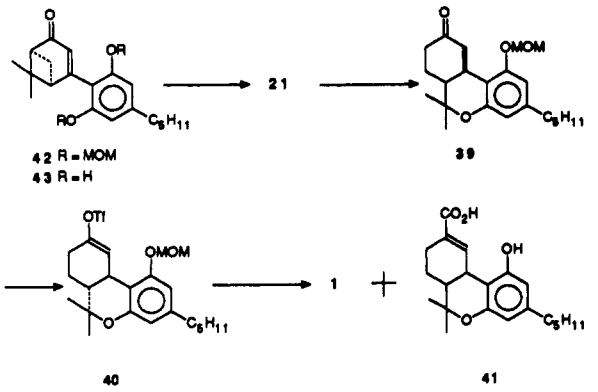
With the development of an efficient method for the synthesis of tricyclic enone **18**, attention was directed toward the introduction of a carbonyl substituent at C-9. The initial synthetic plan was the reaction of **18** with a formyl anion equivalent to generate aldehyde **22** (Scheme II), which on treatment with mild acid would isomerize to conjugated aldehyde **23** with the presumably more stable trans ring fusion. Subsequent oxidation of the aldehyde and demethylation under mild conditions was to afford acid **1**.

Reaction of **18** with either the Magnus reagent derived from (chloromethyl)trimethylsilane[18] or the lithio derivative of (methoxymethyl)diphenylphospine oxide,[19] followed by acid treatment of the initially formed epoxysilane or enol ether, gave an unsaturated aldehyde. However, the NMR spectrum clearly indicated that this aldehyde was that with a cis ring fusion (**24**) rather than the desired trans isomer **23**. In particular the *gem*-dimethyl resonances appeared at δ 1.20 and 1.41, which is in the range expected for the unnatural *cis*-cannabinoid.[20]

Since it was apparent that this approach would not afford the requisite trans isomer, an alternative approach in which the stereochemistry at the ring fusion was generated prior to functionalization at C-9 was explored. Since it is known that Li/NH_3 reduction of enone **21** provides predominantly the saturated ketone with a trans ring fusion,[10a] an approach via dissolving metal reduction of protected enone **18** in which the derived enolate was trapped with *N*-phenyltriflimide[21] was investigated.

Initial exploration of this approach was carried out by using enone **12**, which lacked the *n*-pentyl side chain. Reduction with Li/NH_3 followed by trapping the enolate with *N*-phenyltriflimide provided an approximately 3/1 mixture of trans and cis vinyl triflates **25** and **26** (Scheme III) in a combined yield of 84%. The mixture was separated by simple crystallization and the stereochemistry assigned on the basis of the chemical shifts of the *gem*-dimethyls.[20] Reaction of the mixture of stereoisomeric vinyl triflates with carbon monoxide and methanol using palladium catalysis[22] gave a mixture of trans (**27**) and cis (**28**) esters, which could be separated by preparative TLC.

Scheme IV



Extension of this methodology to enone **18** provided an inseparable mixture of triflates **29** and **30** in a ratio of approximately 3/1 and 84% yield, which was converted to methyl esters **31** and **32** in 82% yield. Since the stereoisomers were again inseparable by conventional chromatography, the mixture was subjected to basic hydrolysis to provide a 1/3 mixture of acids **34** and **35**, which was separated by careful chromatography. Although it was initially assumed that the major product was trans Δ^9-acid **33**, the ^1H NMR chemical shift of H-10 appears at δ 7.36 rather than in the vicinity of δ 8.00 as found for ester **31**. The minor product showed the spectral data expected for cis acid **34**. An authentic sample of Δ^9-acid **33** contaminated with **34** was prepared by employing a modification of the carbonylation procedure, which employed triethylammonium formate.[22a] Acid **33** prepared by this procedure showed the expected ^1H NMR signal for H-10 at δ 7.97. Obviously basic hydrolysis of ester **31** proceeds with rearrangement, presumably of the double bond, to provide an isomer of acid **33**. There was a formal possibility that this product was the Δ^8 acid although it is difficult to propose a reasonable mechanism for this transformation. Also, the ^1H NMR spectral data for the Δ^8 isomer of acid **1**[9a] are not similar to those of the hydrolysis product and the mass spectrum of the hydrolysis product did not show the strong peak resulting from a retro-Diels–Alder reaction, which is characteristic of a Δ^8-cannabinoid.[23] A more plausible structure is that of a Δ^{10} acid (**35**) that arises by base-catalyzed isomerization of the double bond into conjugation with the aromatic ring, a reaction reminiscent of the paspalic acid to lysergic acid isomerization.[24] A number of unsuccessful methods were investigated to effect the cleavage of ester **31** to acid **33**, which included LiI in pyridine or DMF (complex mixtures), K_2CO_3/CH_3OH or Me_3SiCl, NaI/CCl_4 (no reaction) and MeLi or BuLi, Se/THF (gave acid **36**). Benzyl ester **37** was prepared, but it could neither be hydrogenolyzed under mild conditions nor hydrolyzed without rearrangement. Attempted cleavage of the methyl ether of acid **33** using sodium thiopropoxide[25] gave only rearranged acid **36**, which could also be prepared in a similar manner from **35**. Attempted preparation of the 2-trimethylsilyl ethyl

(18) Burford, C.; Cooke, F.; Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1977**, *99*, 4536; *Organometallics* **1982**, *1*, 893.
(19) Earnshaw, C.; Wallis, C. J.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3099.
(20) Uliss, D. B.; Razdan, R. K.; Dalzell, H. C.; Handrick, G. R. *Tetrahedron* **1977**, *33*, 2055. For trans isomers the resonances for the *gem*-dimethyls appear at approximately δ 1.05 and 1.37.
(21) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.
(22) (a) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109. (b) Cheney and Paquette (Cheney, D L.; Paquette, L. A. *J. Org. Chem.* **1989**, *54*, 3334) have used this reaction in a synthetic approach to the isocedranes.
(23) Irayama, S.; Sawa, A.; Hosoya, E. *Chem. Pharm. Bull.* **1976**, *24*, 2209.
(24) (a) Troxler, F. *Helv. Chim. Acta* **1968**, *51*, 1372. (b) Kobel, H.; Schreier, E.; Rutschmann, J. *Ibid.* **1964**, *47*, 1052.
(25) (a) Sher, F. T.; Berchtold, G. A. *J. Org. Chem.* **1977**, *42*, 2569. (b) Feutrill, G. I.; Mirrington, R. N. *Aust. J. Chem.* **1971**, *25*, 1731.

ester **38** failed. Although these results were disappointing in terms of the synthesis of acid **1**, they do provide an entry to the rare group of Δ^{10}-tetrahydrocannabinoids.

Since it was possible to effect the carboxylation of triflates **29** and **30** to acids **33** and **34**, but not possible to cleave the methyl ether of **33** to afford acid **1**, it appeared that a less robust protecting group for the phenolic oxygen would prove advantageous. To this end the Roche phenol (**21**) was converted to MOM ether **39** (Scheme IV). Reduction with Li/NH_3 and reaction of the enolate with *N*-phenyltriflimide proceed smoothly and in excellent yield (98%) to provide a mixture of stereoisomeric triflates (**40**, only trans isomer depicted). This unstable mixture of triflates was subjected to Pd-catalyzed carboxylation to afford a mixture of the MOM ethers of **1** and cis acid **41** in 74% yield. Mild hydrolysis of the mixture of MOM ethers using pyridinium *p*-toluenesulfonate in 2-butanone **21**[17] provided an 83% yield of a mixture of acids **1** and **41**. Although the mixture could not be separated by chromatography, simple crystallization of the mixture provided pure racemic **1**, the ^1H NMR spectrum of which was identical with those of authentic samples. Acid **41** was obtained by concentration of the mother liquors.[26]

Initially enone **21** was prepared by demethylation (NaSPr) of **18**; however, a more efficient approach involved the reaction of apoverbenone (**9**) with the aryllithium derived from the bis-MOM ether of olivetol (**5**, R = C_5H_{11}, R^1 = MOM). Oxidation of the derived tertiary allylic alcohol provided a 79% yield of enone **42** based on apoverbenone. Although very careful hydrolysis of the bis-MOM ether of **42** to phenol **43** could be effected, **43** was very difficult to purify, sensitive to air oxidation, and invariably contaminated with **21**. In practice it was considerably more efficient to carry out the hydrolysis of the MOM ethers using toluenesulfonic acid in ethanol to afford enone **21** directly in 78% yield from **42**.

The synthesis sequence outlined in Scheme V provides (±)-11-nor-Δ^9-THC-9-carboxylic acid (**1**) in seven steps and an overall yield of 14% from apoverbenone and the bis-MOM ether of olivetol.

Experimental Section

Melting points were determined on a Kofler hot stage and are uncorrected. IR spectra were obtained as neat films between salt plates, as KBr pellets, or as solutions in $CHCl_3$. ^1H NMR spectra were recorded at 60, 90, or 200 MHz, using $CDCl_3$, unless otherwise noted, as the solvent. Mass spectral analyses were performed at 70 eV. Ether and tetrahydrofuran (THF) were distilled from Na–benzophenone ketyl immediately before use: diisopropylamine, CH_2Cl_2, and DMF were distilled from calcium hydride, all under an atmosphere of N_2. Commercially available (Aldrich) solutions of methyllithium in ether and *n*-butyllithium in hexane were titrated with 1,3-diphenyl-2-propanone tosylhydrazone as indicator, prior to use.[27] All reactions were carried out under an atmosphere of N_2 or Ar. All compounds containing the intact pinane ring system are optically active and have the configuration depicted in Schemes I and IV. All other compounds are racemic.

6-(1-Methoxy-1-methylethyl)-2-cyclohexen-1-one (6). To a solution of 7.65 g (40 mmol) of $TiCl_4$ and 11.4 g (40 mmol) of $Ti(O\text{-}i\text{-}Pr)_4$ in 250 mL of dry CH_2Cl_2 at −50 °C was added a solution of 6.00 g (35.7 mmol) of the trimethylsilyl enol ether of cyclohexenone[13] and 4.58 g (44 mmol) of 2,2-dimethoxypropane in 20 mL of dry CH_2Cl_2. After being stirred for 1 h at −50 °C, the mixture was quenched with aqeuous K_2CO_3. The organic layer was dried (Na_2SO_4) and after removal of solvent, the crude product was chromatographed on silica gel using 15% ethyl acetate–hexane as eluent to afford 4.50 g (75%) of **6**: IR (neat) 1660, 1600 cm^{-1}; ^1H NMR δ 1.42, 1.80 (s, 3 H each), 2.00–3.00 (m, 5 H), 3.18 (s, 3 H), 5.95 (dt, 1 H, J = 11 Hz, 2 Hz), 6.90 (m, 1 H); MS m/z (rel intensity) 168 (1), 136 (21), 93 (11), 73 (100). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.30; H, 9.55.

3-(2,6-Dimethoxyphenyl)-4-(2-methoxy-2-methylethyl)-2-cyclohexen-1-one (7). A mixture of 3.32 g (24 mmol) of 1,3-dimethoxybenzene in 24 mL of THF and 15 mL of 1.6 M *n*-BuLi was heated at reflux for 2 h. After cooling to 0 °C, 3.36 g (20 mmol) of enone **6** was added, and the solution was stirred for 30 min at 0 °C and then warmed to room temperature. After stirring for 18 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The combined ether extracts were washed with water, dried (Na_2SO_4), and concentrated to give the crude adduct. Without further purification, the alcohol was dissolved in 20 mL of acetone, and 10 mL of 1 M Jones' reagent was added dropwise at 0 °C. The solution was allowed to warm to room temperature and stirred for an additional 30 min. Isopropyl alcohol was added to destroy the excess oxidant and the volatile solvent was evaporated. The green residue was taken up in water and extracted with ether. The ether layer was washed with saturated aqueous $NaHCO_3$ and brine and dried (Na_2SO_4). After removal of solvent, the residue was chromatographed on silica gel using 25% EtOAc–hexanes as eluent to afford 2.53 g (42%) of enone **7** as an unstable viscous oil, which could not be further purified without extensive decomposition: ^1H NMR δ 1.04, 1.20 (s, 3 H each), 3.03 (s, 3 H), 3.81 (s, 6 H), 6.12 (s, 1 H), 6.63 (d, 2 H, J = 8 Hz), 7.30 (t, 1 H, J = 8 Hz); MS m/z (rel intensity) 232 (24), 204 (2), 189 (6), 161 (8), 84 (13), 73 (100).

1-Hydroxy-6,6a,7,8-tetrahydro-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one (8). To a stirred solution of 0.304 g (1 mmol) of enone **7** in 5 mL of dry CH_2Cl_2 at −78 °C was added dropwise 2.25 g (9 mmol) of BBr_3. The reaction mixture was warmed to room temperature and stirred for 7 h. The mixture was poured into ice water, saturated with NaCl, and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), and after removal of solvent, the residue was chromatographed on silica gel using 50% ethyl acetate–hexanes as eluent to afford 0.146 g (60%) of **8** as a yellow solid. Recrystallization from EtOAc gave pure **8**, mp 251–253 °C: ^1H NMR δ 1.17, 1.50 (s, 3 H each), 6.42, 6.68 (d, 2 H, J = 8 Hz), 7.18 (t, 1 H, J = 8 Hz), 8.05 (d, 1 H, J = 2 Hz). Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.62; H, 6.62.

2-(2,6-Dimethoxyphenyl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-ol (10). A mixture of 0.610 g (4.41 mmol) of 1,3-dimethoxybenzene and 2.1 mL of 2.2 M *n*-BuLi in 5 mL of THF was stirred at room temperature for 3 h. After cooling to 0 °C, a solution of 0.500 g (3.68 mmol) of (+)-apoverbenone (**9**)[14] in 4 mL of THF was added dropwise, and the reaction mixture was stirred for 18 h at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The ether extracts were washed with water and dried (Na_2SO_4), and the solvent was evaporated to give the crude adduct as an off white solid, which was recrystallized from hexanes to give 0.724 g (72%) of **10**, which was homogeneous to TLC. Further recrystallization from hexanes gave the analytical sample, mp 147–148 °C: $[\alpha]^{22}_D$ +116.9° (*c* 0.175 in $CHCl_3$); IR (KBr) 3548, 2937, 1589 cm^{-1}; ^1H NMR δ 1.21, 1.34 (s, 3 H each), 1.57 (d, J = 9.0 Hz, 1 H), 1.60 (s, 1 H), 2.14 (q, J = 11.6, 5.8 Hz, 1 H), 2.26, 2.67 (m, 1 H each), 3.80 (s, 6 H), 4.71 (s, 1 H), 6.00, 6.14 (m, 1 H each), 6.58 (d, 2 H, J = 8.2 Hz), 7.16 (t, 1 H, J = 8.4 Hz); MS (CI) m/z (rel intensity) 275 (6), 274 (13), 257 (66), 215 (100). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.15; H, 8.00.

4-(2,6-Dimethoxyphenyl)-6,6-dimethylbicyclo[3.3.1]hept-3-en-2-one (11). Crude alcohol **10**, prepared from 0.42 g (3 mmol) of 1,3-dimethoxybenzene, 3 mL of 1.4 m *n*-Bu Li, and 0.34 g (2.5 mmol) of **9**, was treated with Jones' reagent as described in the preparation of **7** to give 0.27 g (40%) of enone **11** as a yellow oil, which crystallized on standing. Recrystallization from hexanes–ether gave pure **11**: mp 101–102 °C, $[\alpha]^{22}_D$ −103.4° (*c* 0.175 in $CHCl_3$); IR (KBr) 1635 cm^{-1}; ^1H NMR δ 1.18, 1.50 (s, 3 H each), 2.35 (d, 1 H, J = 9 Hz), 3.75 (s, 6 H), 5.93 (br s, 1 H), 6.50 (d, 2 H, J = 8 Hz), 7.20 (t, 1 H, J = 8 Hz); MS m/z (rel intensity) 272 (100), 273 (16), 257 (23), 229 (38), 202 (82), 187 (21), 161 (22), 151 (23), 138 (24), 115 (20). Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.90; H, 7.40.

(26) Tius and Gu (Tius, M. A.; Gu, X-q. *J. Chem. Soc., Chem. Commun.* **1989**, 1171) report the synthesis of **41** but present neither physical nor spectral properties.

(27) Lipton, M. F.; Sorensen, C. M.; Sadler, A. C.; Shapiro, R. H. *J. Organomet. Chem.* **1980**, *186*, 155.

4-(2-Methoxy-6-(methoxymethoxy)phenyl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (15). To a stirred solution of 1.88 g (11.2 mmol) of the MOM ether of 3-methoxyphenol[28] in 20 mL of THF was added at 25 °C 7 mL of 1.6 M *n*-butyllithium. After being stirred for 3 h, the reaction mixture was cooled to 0 °C, and 1.52 g (11.2 mmol) of (+)-apoverbenone (**9**) in 20 mL of THF was added dropwise over 30 min. The resulting solution was allowed to warm to room temperature, stirred for 18 h, and quenched with saturated aqueous NH_4Cl. After extraction with ether, the ether layer was washed with brine, dried (Na_2SO_4), and concentrated to afford the crude tertiary allylic alcohol. Without purification the alcohol was dissolved in 10 mL of dry CH_2Cl_2 and added dropwise to a solution of 4.8 g of PCC in 30 mL of CH_2Cl_2. After being stirred for 2 h, the reaction mixture was diluted with 40 mL of ether and the solution was decanted from the black residue. The residue was washed well with ether and the combined ether washings were washed with 5% aqueous NaOH, 5% aqueous HCl, and saturated aqueous $NaHCO_3$. After drying (Na_2SO_4), the solvent was removed to give 2.73 g of crude product, which was purified by chromatography to give 2.34 g (77%) of enone **15** as a yellow oil: IR (neat) 1650 cm^{-1}; ^1H NMR δ 1.52, 1.20 (s 3 H each), 2.37 (d, 1 H, J = 9 Hz), 2.69–3.02 (m, 3 H), 3.43 (s, 3 H), 3.77 (s, 3 H), 5.13 (s, 2 H), 5.99 (br s, 1 H), 6.59, 6.75 (d, 1 H each, J = 8 Hz), 7.22 (t, 1 H, J = 8 Hz); MS m/z (rel intensity) 302 (31), 257 (78), 215 (23), 189 (21), 45 (100). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.36; H, 7.38.

4-(2-Methoxy-6-hydroxyphenyl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (14). To a stirred solution of 1.88 g (6.2 mmol) of MOM ether **15** in 50 mL of dry CH_2Cl_2 containing 4A molecular sieves at −30 °C was added 3.8 g (24.8 mmol) of $(CH_3)_3SiBr$ dropwise with a syringe over 30 min. The solution was stirred for 1 h at −30 °C and then for 9 h at 0 °C. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with ether. The ether layer was dried (Na_2SO_4) and evaporated to give a yellow solid, which was recrystallized from ethyl acetate to give 1.39 g (87%) of pure **14**: mp 172–174 °C; $[\alpha]^{25}_D$ −109.5° (*c* 1.15 in $CHCl_3$); IR (KBr) 3240, 1628 cm^{-1}; ^1H NMR δ 1.53, 1.15 (s, 3 H each), 2.28 (d, 1 H, J = 9 Hz), 2.65–3.05 (m, 3 H), 3.74 (s 3 H), 6.06 (br s, 1 H), 6.26 (br s, 1 H), 6.48, 6.58 (d, 1 H each, J = 8 Hz), 7.08 (t, 1 H, J = 8 Hz); MS m/z (rel intensity) 259 (10), 243 (28), 215 (61), 202 (30), 188 (100), 173 (32), 161 (21), 147 (32), 137 (26.5). Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02: Found: C, 74.35; H, 7.04.

1-Methoxy-6,6a,7,8-tetrahydro-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one (12). A mixture of 0.72 g (2.8 mmol) of **14** and 0.532 g (2.8 mmol) of *p*-toluenesulfonic acid in 60 mL of $CHCl_3$ was heated at reflux for 24 h. After being cooled to room temperature, the mixture was extracted with ether, and the ether layer was washed with 10% aqueous $NaHCO_3$ and water and dried (Na_2SO_4). Evaporation afforded a yellow oil, which was chromatographed to give 0.60 g (84%) of pure racemic enone **12** as a pale yellow oil, which crystallized on standing. Recrystallization from hexanes–ether gave pure **12**: mp 94–96 °C; IR (neat) 1645 cm^{-1}; NMR δ 1.52, 1.16 (s, 3 H each), 3.92 (s, 3 H), 6.50 (m, 2 H) 7.22 (t, 1 H, J = 8.21 Hz), 7.42 (br s, 1 H); MS m/z (rel intensity) 258 (100), 259 (16), 243 (66), 215 (68), 201 (39), 187 (16); HRMS calcd for $C_{16}H_{18}O_3$ 258.1264, found 258.1256.

B. To a solution of 0.132 g (0.51 mmol) of **14** in 15 mL of $CHCl_3$ was added 0.108 g of Amberlyst 15 resin, and the mixture was stirred at reflux for 80.5 h. The resin was filtered off, the solvent was evaporated, and the residue was chromatographed to give 0.113 g (86%) of material identical with that decribed in part **A**.

C. Reaction of 0.134 g (0.52 mmol) of enone **14** in 8 mL of $CHCl_3$ with 0.214 g of pretreated Nafion NR 50[29] for 162 h at reflux and isolation of the product as described in **B** gave 0.091 g (68%) of material identical with that described above.

D. To a solution of 0.060 g (0.245 mmol) of enone **8** in 3 mL of dry acetone was added 0.84 g of K_2CO_3 and 0.42 mL of Me_2SO_4, and the mixture was stirred at reflux under N_2 for 12 h. The solution was filtered and the acetone evaporated to leave a brown oil, which was purified by preparative TLC to give 0.050 g (79%) of enone **12** identical with that described above.

1-Methoxy-3-(methoxymethoxy)-5-pentylbenzene. To a stirred solution of 6.88 g (35.5 mmol) of 3-methoxy-5-pentylphenol[30] and 9.20 g (71.0 mmol) of diisopropylethylamine in 90 mL of dry CH_2Cl_2 was added dropwise 3.8 mL (53 mmol) of chloromethyl methyl ether. The resulting soution was stirred for 12 h at ambient temperature. The mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and brine, and dried (Na_2SO_4). Evaporation and distillation afforded 6.60 g (78%) of product: bp 115–120 °C (0.25 mm); ^1H NMR δ 0.89 (t, 3 H, J = 7 Hz), 2.54 (t, 2 H, J = 7 Hz), 3.48 (s, 3 H), 3.75 (s, 3 H), 5.12 (s, 2 H), 6.43, 6.45, 6.47 (s, 1 H each); MS m/z (rel intensity) 239 (11), 238 (63), 196 (22), 182 (100), 152 (67), 151 (17), 150 (38), 137 (12), 121 (14), 91 (15), 77 (17). Material prepared by this procedure was invairably contaminated with traces of 1,3-dimethoxy-5-pentylbenzene.

4-(2-Methoxy-4-pentyl-6-(methoxymethoxy)phenyl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (16). The preparation of **16** was carried out by using the procedure employed for **15**. From 3.83 g (16.1 mmol) of the MOM ether of 3-methoxy-5-pentylphenol and 2.20 (16.1 mmol) of (+)-apoverbenone (**9**), there was obtained 4.86 g (81%) of **16** as an oil:[31] IR (neat) 1676, 1607, 1576, 1459 cm^{-1}; ^1H NMR δ 0.90 (t, 3 H, J = 7 Hz), 1.51, 1.18 (s, 3 H each), 2.24 (d, 1 H, J = 9 Hz), 2.55 (t, 2 H, J = 7 Hz), 3.44 (s 3 H), 3.76 (s, 3 H), 5.12 (s, 2 H), 5.99 (s, 1 H), 6.42, 6.60 (s, 1 H each): MS m/z (rel intensity) 373 (7), 372 (32), 328 (26), 327 (100), 285 (23), 259 (33), 245 (10), 115 (12), 45 (75). Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16, H, 8.66. Found: C, 73.92; H, 8.68.

4-(2-Methoxy-4-pentyl-6-hydroxyphenyl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (17). A. Reaction of 4.38 g (11.8 mmol) of **16** with 6.5 mL of $(CH_3)_3SiBr$ under the conditions used for the preparation of **14** gave 3.50 g (91%) of phenol **17** as a thick oil: IR (neat) 3250, 1640, 1605 cm^{-1}; ^1H NMR δ 0.89 (t, 3 H, J = 7 Hz), 1.17, 1.51 (s, 3 H each), 3.70 (s, 3 H), 6.02 (br s, 1 H), 6.21, 6.35 (s, 1 H each).

B. A solution of 1.006 g (2.7 mmol) of MOM ether **16** and 6.76 g (27 mmol) of pyridinium *p*-toluenesulfonate in 30 mL of methanol was heated at reflux for 18 h. The reaction mixture was cooled to room temperature and the solvent was removed at reduced pressure. The residue was triturated with 20 mL of ether and the solids were filtered off and washed with ether. The combined ether extracts were concentrated to dryness and chromatographed on silica gel to give 0.807 g (91%) of material identical with that described in part **A**. Similar results were obtained with use of 2-butanone as the reaction solvent.

1-Methoxy-3-pentyl-6,6a,7,8-tetrahydro-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one (18). A. A solution of 0.174 g (0.53 mmol) of phenol **16** and 0.101 g (0.53 mmol) of *p*-toluenesulfonic acid monohydrate in 15 mL of $CHCl_3$ that had been distilled and stored over 3A molecular sieves was heated at reflux for 26 h. After being cooled to room temperature, the mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$ and brine, and dried over ($MgSO_4$). After removal of the solvent, the crude product was chromatographed on silica gel to give 0.150 g (86%) of racemic enone **18** as a thick oil: IR (neat) 1640 cm^{-1}; ^1H NMR δ 0.89 (t, 3 H, J = 7 Hz), 1.14, 1.49 (s, 3 H each), 2.54 (t, 2 H, J = 7 Hz), 3.87 (s, 3 H), 6.31, 6.35 (s, 1 H each), 7.38 (d, 1 H, J = 2 Hz); MS m/z (rel intensity) 328 (100), 329 (23), 313 (533), 285 (34), 272 (33); HRMS calcd for $C_{21}H_{28}O_3$ 328.2088, found 328.2036.

B. Reaction of 0.174 g (0.53 mmol) of enone **17** with 0.101 g (0.53 mmol) of *p*-toluenesulfonic acid in 15 mL of $CHCl_3$, to which 3 drops of ethanol had been added, under the above conditions gave 0.150 g (86%) of **18** identical with that described in part **A**.

C. To a solution of 0.052 g (0.213 mmol) of phenol **21** in 3 mL of dry acetone were added 0.73 g of K_2CO_3 and 0.36 mL of Me_2SO_4, and the mixture was stirred at reflux for 20 h. The solution was filtered and the acetone evaporated to leave a brown oil, which

(28) Yagoub, A. K.; Iskander, G. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1043.

(29) For activation, 5.0 g of Nafion NR 50 resin was stirred at reflux in 20 mL of distilled water for 2 h. The water was decanted and the resin was stirred with 20 mL of 25% aqueous HNO_3 for 5 h at room temperature. The resin was filtered off, washed with distilled water until the filtrate was neutral, and dried in vacuo for 26 h at 106 °C.

(30) Kurth, H-J.; Kraatz, U.; Korte, F. *Chem. Ber.* **1976**, *109*, 2164.

(31) The enantiomer of **16**, $[\alpha]^{25}_D$ +65.3° (*c* = 1.0, $CHCl_3$), was prepared from (−)-apoverbenone (*ent*-**9**) by the same procedure. (−)-Apoverbenone was prepared from (+)-β-pinene (Harwood, L. M.; Julia, M. *Synthesis* **1980**, 456) by the procedure in ref 4.

was purified by chromatography on silica gel to give 0.041 g (75%) of **18** identical with that described above.

3-(2-Hydroxy-6-methoxy-4-pentylphenyl)-4-isopropylidenecyclohex-2-enone (19). When the reaction described in part **A** was carried out on 1.64 g (5.0 mmol) of **17** in 120 mL of $CHCl_3$, dried over 4A molecular sieves and carefully distilled, using 0.97 g (5.1 mmol) of *p*-toluenesulfonic acid, there was obtained after chromatography on silica gel 1.33 g (81%) of dienone **19**, which gave crystals, mp 129–130 °C, from hexane–ethyl acetate: ^1H NMR δ 0.89 (t, 3 H, J = 7 Hz), 1.91, 2.18 (s, 3 H each), 3.77 (s, 3 H), 6.17, 6.29, 6.47 (br s, 1 H each); MS (CI) m/z (rel intensity) 329 (100), 328 (12), 327 (5). Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.62; H, 8.60.

In an attempt to convert dienone **19** to enone **18**, a solution 0.176 g (0.53 mmol) of **19** and 0.102 g of *p*-toluenesulfonic acid in 12 mL of ethanol was heated at reflux for 48 h. The solvent was removed and the residue was slurried with water and ether. The phases were separated and the aqueous suspension was extracted with ether. The combined ether extracts were washed with water, dried, and evaporated to give a viscous oil. Chromatography on silica gel gave 0.076 g (50%) of 3-(2-hydroxy-6-methoxy-4-pentylphenyl)-2-cyclohexen-1-one as an off-white solid, mp 85–87 °C: ^1H NMR (acetone-d_6) δ 0.89 (t, J = 6.9 Hz, 3 H), 3.77 (s, 3 H), 5.86 (s, 1 H), 6.43 (s, 2 H); MS (CI) m/z (rel intensity) 289 (100), 288 (20). Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.88; H, 8.41.

1,3-Bis(methoxymethoxy)-5-pentylbenzene. To a stirred solution of 10.0 g (55.6 mmol) of olivetol and 15.8 g (122.0 mmol) of diisopropylethylamine in 100 mL of dry CH_2Cl_2 was added dropwise 17.0 g (222 mmol) of chloromethyl methyl ether. This solution was stirred for 16 h at room temperature, diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Concentration and distillation afforded 13.6 g (91%) of the bis-MOM ether of olivetol: bp 159–162 °C (2 mmHg); ^1H NMR δ 0.86 (t, 3 H, J = 7 Hz), 2.50 (6, 2 H, J = 8 Hz), 3.48 (s, 6 H), 5.14 (s, 4 H), 6.52 (s, 2 H), 6.47 (s, 1 H); MS m/z (rel intensity) 269 (18), 268(98), 226 (30), 213 (13), 212 (100), 182 (32), 180 (29), 166 (19), 152 (22), 150 (19), 136 (21), 121 (10), 108 (10), 91 (15), 77 (11).

4-(2,6-Bis(methoxymethoxy)-4-pentylphenyl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (42). To 2.17 g (8.1 mmol) of the bis-MOM ether of olivetol was added 8.1 mmol of *n*-BuLi in hexane at 25 °C. The reaction mixture was stirred at ambient temperature for 3 h and a solution of 1.10 g (8.1 mmol) of (+)-apoverbenone (**9**) in 20 mL of THF was added. The reaction was stirred at room temperature for 18 h, quenched with saturated aqueous NH_4Cl, and extracted with ether. The ether extracts were washed with brine and dried (Na_2SO_4), and the solvent was removed to afford a yellow oil. The crude product was dissolved in 15 mL of CH_2Cl_2 and added to 3.9 g of PCC in 25 mL of CH_2Cl_2. After being stirred for 2 h at room temperature, the mixture was diluted with 50 mL of ether, and the solvents were decanted from the precipitated solids. The organic phase was washed with 5% aqueous NaOH, 10% aqueous HCl, and brine and dried (Na_2SO_4), and the solvent was removed to give the crude product, which was purified by MPLC using ether–hexane mixtures to give 2.58 g (79%) of pure enone **42** as a thick oil: ^1H NMR δ 0.90 (t, 3 H, J = 7 Hz), 1.21, 1.52 (s, 3 H each), 3.43 (s, 6 H), 5.13 (s, 4 H), 5.99 (s, 1 H), 6.66 (br s, 2 H), MS (CI) m/z (rel intensity) 403 (100), 371 (72), 357 (16), 339 (35), 329 (14), 297 (19), 285 (14). Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.48; H, 8.57.

1-Hydroxy-3-pentyl-6,6a,7,8-tetrahydro-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one (21). A. Reaction of 0.200 g (0.53 mmol) of enone **20** with 1.48 g (5.89 mmol) of BBr_3 under the conditions used for the preparation of **8** gave 0.321 g of a dark blue glass, the ^1H NMR and IR spectra of which indicated that enone **21** was present in the mixture. This material was difficult to purify without decomposition and was converted directly to methyl ether **18**. In a subsequent experiment employing 0.225 g of enone **20**, the crude product was taken up in 1:1 hexane–EtOAc and chromatographed on silica gel to give a deep blue semisolid. This material was dissolved in a small volume of ether and on standing in the freezer gave 0.052 g (28%) of enone **21**, mp 194–198 °C; mixed melting point with a sample prepared by the Roche procedure, 194–196 °C.[10a] The ^1H NMR spectra of both samples were identical.

B. To 0.12 g (5.0 mmol) of NaH (0.200 g of 60% dispersion in mineral oil, washed with dry pentane) suspended in 10 mL of dry DMF at ambient temperature was added, with stirring under N_2, 0.40 mL (4.4 mmol) of 1-propanethiol. After stirring for 10 min, a solution of 0.164 g (0.5 mmol) of enone **18** in 8 mL of DMF was added. The mixture was heated at reflux for 3 h, colled to 0 °C, and cautiously acidified with 10% aqueous HCl. The mixture was extracted with ether, the extracts were dried (Na_2SO_4), and the solvent was removed to afford the crude product, which after chromatography on silica gel gave 0.132 g (84%) of enone **21**, identical with that described in **A**.

C. A solution of 0.138 g (0.34 mmol) of **42** and 0.195 g (1.02 mmol) of *p*-toluenesulfonic acid monohydrate in 7 mL of ethanol was heated at reflux for 18 h. After cooling to room temperature, the solvent was evaporated and the residue taken up in ether. The ethereal solution was washed with successive portions of saturated aqueous $NaHCO_3$, 10% aqueous HCl, and brine dried (Na_2SO_4), and the solvent was removed at reduced pressure. Chromatography on silica gel gave 0.083 g (78%) of **21**, identical with that described above.

1-Methoxy-6a,7,8,10a-tetrahydro-6,6-dimethyl-9-(((trifluoromethyl)sulfonyl)oxy)-6*H*-dibenzo[*b*,*d*]pyrans (25 and 26). To a solution of 0.012 g (1.7 mmol) of Li in 10 mL of liquid NH_3 at −78 °C was added dropwise a solution of 0.102 g (0.40 mmol) of enone **12** in 3 mL of THF. After 10 min, the reaction was quenched by the addition of 2 mL of isoprene and the NH_3 was evaporated in a stream of N_2 and then in vacuo. The solid residue was dissolved in 6 mL of THF and cooled to 0 °C, and a solution of 0.150 g of *N*-phenyltriflimide in 2 mL of THF was added. The reaction was stirred at ambient temperature for 18 h, the solvent was evaporated, and the crude product was purified by preparative TLC to give 0.130 g (84%) of a mixture of cis (**26**) and trans (**25**) triflates. The mixture was separated by crystallization from pentane to give 0.094 g (60%) of *trans*-triflate **25**, mp 97–99 °C, and 0.032 g (20%) of the cis isomer (**26**), mp 76–77 °C. For **25**: ^1H NMR δ 1.09, 1.44 (s, 3 H each), 3.83 (s, 3 H), 6.41, 6.45 (d, 1 H each, J = 8.2 Hz), 6.77 (br s, 1 H), 7.10 (t, 1 H, J = 8.1 Hz); MS m/z (rel intensity) 393 (7), 392 (21), 260 (13), 259 (100). For **26**: ^1H NMR δ 1.28, 1.42 (s, 3 H each), 3.83 (s, 3 H), 6.44 (d, 2 H, J = 8.6 Hz), 6.67 (d, 1 H, J = 5.1 Hz), 7.09 (t, 1 H, J = 8.4 Hz); MS (CI) m/z (rel intensity) 394 (10), 393 (40), 392 (10), 244 (16), 243 (100).

1-Methoxy-6a,7,8,10a-tetrahydro-6,6-dimethyl-9-carbomethoxy-6*H*-dibenzo[*b*,*d*]pyrans (27 and 28). A solution of 0.041 g (0.10 mmol) of the mixture of **25** and **26**, 0.03 mL of Et_3N, 0.00063 g of $Pd(OAc)_2$, 0.0017 g of triphenylphosphine, and 0.19 mL of methanol in 0.42 mL of DMF was purged with carbon monoxide for 5 min and then stirred under a carbon monoxide atmosphere for 9 h. The reaction mixture was poured into water and extracted with ether. The ether extracts were dried (Na_2SO_4), and the solvent was removed to give the crude product, which was purified by preparative TLC to give 0.025 g (80%) of trans ester **27**: mp 152–154 °C; ^1H NMR δ 1.09, 1.44 (s, 3 H each), 3.54 (dd, 1 H, J = 3.0 Hz, 11.1 Hz), 3.73, 3.97 (s, 3 H each), 6.46 (d,d, 2 H, J = 1.8 Hz, 8.1 Hz), 7.08 (t, 1 H, J = 8.3 Hz), 7.84 (d, 1 H, J = 1.9 Hz). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.10; H, 7.48. There was also obtained 0.005 g (16%) of cis ester **28**: mp 129–130 °C; ^1H NMR δ 1.30, 1.38 (s, 3 H each), 3.73, 3.86 (s, 3 H each), 6.44 (d, 2 H, J = 8.1 Hz), 7.07 (t, 1 H, J = 8.1 Hz), 7.73 (br d, 1 H, J = 4.9 Hz); HRMS calcd for $C_{18}H_{22}O_4$ 302.1518, found 302.1515.

1-Methoxy-3-pentyl-6a,7,8,10a-tetrahydro-6,6-dimethyl-9-carbomethoxy-6*H*-dibenzo[*b*,*d*]pyrans (31 and 32). The reduction of enone **18** was carried out in the same manner as that described for the preparation of triflates **25** and **26**. From 0.539 g (1.64 mmol) of enone **18** in 8 mL of THF and 0.034 g (4.93 mmol) of Li in 50 mL of liquid NH_3 there was obtained after treatment with 1.17 g (3.28 mmol) of *N*-phenyltriflimide in 7 mL of THF and chromatography on silica gel, 0.640 g (84%) of a mixture of triflates **29** and **30**. For **29**: ^1H NMR δ 0.90 (t, 3 H, J = 7 Hz), 1.09, 1.41 (s, 3 H each), 2.51 (t, 2 H, J = 7 Hz), 3.81 (s, 3 H), 6.28, 6.32 (s, 1 H each), 6.66 (d, 1 H, J = 4 Hz). For **30**: ^1H NMR δ 0.90 (t, 3 H, J = 7 Hz), 1.25, 1.38 (s, 3 H each), 3.81 (s, 3 H), 6.28, 6.32 (s, 1 H each), 6.78 (br s, 1 H). This mixture could not be separated and was used in the succeeding step without further purification. Reaction of 0.349 g of this mixture of triflates with

CO and methanol was carried out by using the procedure employed for reactions of triflates **25** and **26** to give, after chromatography on silica gel, 0.230 g (82%) of a 3/1 mixture of esters **31** and **32**, which could not be separated and was hydrolyzed directly. For **31**: ^{1}H NMR δ 0.89 (t, 3 H, J = 7 Hz), 1.09, 1.43 (s, 3 H each), 2.51 (t, 2 H, J = 7 Hz), 3.72, 3.86 (s, 3 H each), 6.29 (br s, 2 H), 7.82 (br s, 1 H). For **32**: ^{1}H NMR δ 0.89 (t, 3 H, J = 7 Hz), 1.29, 1.38 (s, 3 H each), 2.51 (t, 2 H, J = 7 Hz), 3.72, 3.86 (s, 3 H each), 6.29 (br s, 2 H), 7.74 (br s, 1 H); MS m/z (rel intensity): 372 (54), 357 (80), 341 (15), 329 (12), 316 (11), 314 (18), 313 (100), 301 (12), 297 (13), 245 (14).

1-Methoxy-3-pentyl-6a,7,8,9-tetrahydro-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran-9-carboxylic Acid (35). A solution of 8 mL of methanol and 2.5 mL of 10% aqueous KOH was heated at reflux for 30 min while argon was bubbled through the solution. A solution of 0.161 g (0.43 mmol) of a mixture of esters **31** and **32** was added and the reaction was heated at reflux for 4 h. After cooling to ambient temperature, the mixture was acidified with 10% aqueous HCl and extracted with ether. The extracts were washed with brine and dried over ($MgSO_4$), and the solvent was removed to give the crude product. Chromatography on silica gel and elution with benzene–acetone mixtures gave 0.092 g (59%) of acid **35**: mp 172–174 °C; ^{1}H NMR (acetone-d_6) δ 0.90 (t, 3 H, J = 7 Hz), 1.14, 1.49 (s, 3 H each), 3.87 (s, 3 H), 6.31, 6.35 (br s, 1 H each), 7.36 (s, 1 H); MS (CI) m/z (rel intensity) 359 (100), 358 (63), 343 (81); HRMS calcd for $C_{22}H_{30}O_4$ 358.2144, found 358.2139.

Further elution with the same solvent system gave 0.030 g (19%) of cis acid **34**: mp 170–172 °C: ^{1}H NMR δ 0.89 (t, 3 H, J = 7 Hz), 1.29, 1.38 (s, 3 H each), 3.86 (s, 3 H), 6.29, 6.31 (s, 1 H each), 7.98 (br s, 1 H).

1-Methoxy-3-pentyl-6a,7,8,10a-tetrahydro-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran-9-carboxylic Acid (33). A mixture of 0.087 g (0.188 mmol) of the mixture of triflates **29** and **30** described above, 0.06 mL of Et_3N, 0.0015 g of $Pd(OAc)_2$, and 0.004 g of triphenylphosphine in 1.5 mL of DMF was stirred for 15 min in a carbon monoxide atmosphere. A solution of 2 mL of Et_3N and 02 mL of formic acid in 1 mL of DMF was added, and the mixture was stirred in a carbon monoxide atmosphere for 18 h. The reaction was quenched by stirring with 5% aqueous HCl and extracted with ether. The ether extracts were dried ($MgSO_4$) and the solvent was removed to give the crude product. Chromatography on silica gel afforded 0.042 g (62%) of acid **33**, contaminated with cis isomer **34**, which was used without further purification: ^{1}H NMR δ 0.89 (t, 3 H, J = 7 Hz), 1.10, 1.14 (s, 3 H each), 3.55 (br d, 1 H, J = 8.4 Hz), 3.56 (s, 3 H), 6.29 6.31 (s, 1 H each), 7.97 (br s, 1 H); MS m/z (rel intensity) 358 (50), 344 (28), 343 (67), 313 (100), 298 (17). The NMR signals at δ 1.29 and 1.38 (s) characteristic of the cis isomer were also present.

1-Hydroxy-3-pentyl-6a,7,8,9-tetrahydro-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran-9-carboxylic Acid (36). A. Reaction of 0.041 g (0.11 mmol) of acid **35** with sodium thiopropoxide from 0.068 g of NaH and 0.13 mL of 1-propanethiol in 5 mL of DMF as described for the preparation of **21**, but with heating at 120 °C for 12.5 h, gave, after chromatography on silica gel, 0.033 g (84%) of acid **36**: mp 191–194 °C; ^{1}H NMR (acetone-d_6) δ 0.88 (t, 3 H, J = 6.71), 1.09, 1.37 (s, 3 H each), 3.28 (m, 1 H), 6.13, 6.28 (d, 1 H each, J = 1.47 Hz) 7.29 (br s 1 H); MS (CI) m/z (rel intensity) 345 (100), 344 (38), 329 (21).

B. Reaction of 0.029 g (0.08 mmol) of the mixture of acids **33** and **34** with sodium thiopropoxide from 0.028 g (1.15 mmol) of NaH and 0.08 mL of 1-propanethiol in 4 mL of DMF under the conditions described in part **A** gave 0.021 g (75%) of acid **36**, mp 193–195 °C, identical with that described above.

1-(Methoxymethoxy)-3-pentyl-6,6a,7,8-tetrahydro-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one (39). To a stirred solution of 1.34 g (4.26 mmol) of enone **21** and 1.5 mL of diisopropylethylamine in 15 mL of CH_2Cl_2 was added dropwise 0.53 g (6.6 mmol) of chloromethyl methyl ether. The mixture was stirred at ambient temperature for 18 h, then diluted with CH_2Cl_2, and washed successively with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and brine. After drying (Na_2SO_4) the solvent was removed and the crude product was chromatographed on silica gel to give 1.49 g (92%) of pure **39** as a thick oil: ^{1}H NMR δ 0.89 (t, 3 H, J = 7 Hz), 1.15, 1.50 (s, 3 H each), 3.50 (s, 3 H), 5.27 (s, 2 H), 6.41, 6.56 (br s, 1 H each), 7.37 (d, 1 H, J = 2.2 Hz); MS m/z (rel intensity) 358 (92), 343 (42), 326 (45), 311 (52), 299 (16), 283 (34), 270 (100), 255 (35); HRMS calcd for $C_{22}H_{30}O_4$ 358.2144, found 358.2145.

(±)-1-Hydroxy-3-pentyl-6aβ,7,8,10aα-tetrahydro-6,6-dimethyl-9-carboxy-6*H*-dibenzo[*b*,*d*]pyran (11-Nor-9-carboxy-Δ^9-tetrahydrocannabinol, 1). To a solution of 0.007 g (1 mmol) of Li in 10 mL of liquid NH_3 was added dropwise a solution of 0.090 g (0.25 mmol) of MOM ether **39** in 2 mL of THF. After 5 min the excess Li was destroyed with isoprene and the NH_3 was evaporated, initially under a stream of dry N_2, and finally at 40 °C in vacuo for 10 min. The residue was dissolved in 4 mL of THF, and a solution of 0.178 g (0.5 mmol) of *N*-phenyltriflimide in 2 mL of THF was added. The mixture was allowed to warm to room temperature and stirred for 18 h. After removal of the solvent the crude product was chromatographed on silica gel to give 0.122 g (98%) of pure (TLC) triflate (3/1 mixture of cis and trans) as a pale yellow oil, which decomposed in a few days even when stored under N_2 in the freezer: ^{1}H NMR, trans isomer (**40**) δ 0.89 (t, 3 H, J = 7 Hz), 1.10, 1.43 (s, 3 H each), 3.46 (s, 3 H), 5.20 (s, 2 H), 6.35, 6.49 (br s, 1 H each), 6.85 (br s, 1 H); cis isomer δ 0.89 (t, 3 H, J = 7 Hz), 1.30, 1.41 (s, 3 H each), 3.46 (s, 3 H), 5.20 (s, 2 H), 5.20 (s, 2 H), 6.35, 6.49 (br s, 1 H each), 6.68 (d, 1 H, J = 5.6 Hz).

A mixture of 0.122 g (0.24 mmol) of the mixture of triflate **40** and the corresponding cis isomer, 0.06 mL (0.429 mmol) of Et_3N, 0.0015 g (0.0075 mmol) of $Pd(OAc)_2$, and 0.004 g (0.015 mmol) of triphenylphosphine in 2.5 mL of DMF was stirred under a carbon monoxide atmosphere for 25 min. A solution of 0.15 mL of 96% formic acid in 0.65 mL of DMF was added slowly, and the reaction mixture was stirred for 18 h at 25 °C under a carbon monoxide atmosphere. The reaction was quenched by stirring with 5 mL of 5% aqueous NaOH for 0.5 h, acidified with 10% aqueous HCl, and extracted with ether. The ether extracts were washed with brine and dried ($MgSO_4$), and the solvent was removed to give the crude product. Chromatography on silica gel and elution with benzene–acetone mixtures gave 0.070 g (74%) of a mixture of the MOM ethers of acids **1** and **41**, which was used without further purification.

A solution of 0.070 g (0.18 mmol) of this mixture and 0.657 g (2.61 mmol) of anhydrous pyridinium *p*-toluenesulfonate in 7.5 mL of 2-butanone was heated at reflux for 18 h.[17] The reaction mixture was cooled and the solvent removed at reduced pressure. The residue was slurred with 20 mL of ether, and the solids were filtered off and washed with ether. The solvent was evaporated, and the residue was chromatographed on silica gel, using benzene–acetone mixtures to give 0.052 g (83%) of a mixture of acids **1** and **41**. Crystallization from pentane–acetone gave 0.022 g (35%) of pure 9-carboxy-THC (**1**), mp 202–205 °C (lit.[6a] mp 205–207 °C for the (−) enantiomer): ^{1}H NMR δ 0.80 (t, 3 H, J = 7 Hz), 1.12, 1.44 (s 3 H each), 3.39 (br d, 1 H, J = 10.9 Hz), 6.14, 6.28 (s, 1 H each), 8.13 (s, 1 H). This spectrum is identical with spectra of authentic samples provided by Dr. A. Schwartz, Hoffman-La Roche, and H. Seltzman, Research Triangle Institute. MS (CI) m/z (rel intensity): 359 (100), 358 (63), 343 (81).

Concentration of the combined mother liquors from several experiments provided acid **41**, mp 174–176 °C, after recrystallization from cyclohxane–ethyl acetate: ^{1}H NMR (DMSO-d_6) δ 0.84 (t, 3 H, J = 7.0 Hz), 1.18, 1.28 (s, 3 H each), 3.61 (br s, 1 H), 6.01, 6.16 (d, 1 H each, J = 1.4 Hz), 7.72 (d, 1 H, J = 4.3 Hz); MS m/z (rel intensity) 345 (43), 344 (100), 329 (60), 326 (19), 309 (87), 288 (30); HRMS calcd for $C_{21}H_{28}O_4$ 344.1987, found 344.1986.[26]

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Registry No. (±)-**1**, 104874-50-2; (±)-**6**, 122700-11-2; (±)-**7**, 130799-41-6; (±)-**8**, 130799-42-7; (+)-**9**, 35408-03-8; **10**, 130799-43-8; **11**, 130799-44-9; (±)-**12**, 130799-45-0; **14**, 130799-46-1; **15**, 130799-47-2; **16**, 122700-14-5; **17**, 122700-20-3; (±)-**18**, 122700-13-4; **19**, 130799-48-3; (±)-**20**, 122700-12-3; (±)-**21**, 16849-41-5; (±)-**25**, 130799-50-7; (±)-**26**, 130799-51-8; (±)-**27**, 130799-52-9; (±)-**28**,

130799-53-0; (±)-**29**, 130799-54-1; (±)-**30**, 130799-55-2; (±)-**31**, 130856-19-8; (±)-**32**, 130856-20-1; (±)-**33**, 130799-56-3; (±)-**34**, 130799-57-4; (±)-**35**, 130799-58-5; (±)-**36**, 130799-59-6; (±)-**39**, 122700-15-6; (±)-**40**, 122700-16-7; (±)-*cis*-**40**, 122700-22-5; (±)-**41**, 122797-75-5; (±)-**42**, 122722-23-0; cyclohexenone trimethylsilyl enol ether, 54781-19-0; 1,3-dimethoxybenzene, 151-10-0; 3-methoxyphenol MOM ether, 57234-28-3; 1-methoxy-3-(methoxymethoxy)-5-pentylbenzene, 80393-04-0; 3-methoxy-5-pentylphenol, 41408-15-5; 3-(2-hydroxy-6-methoxy-4-pentylphenyl)-2-cyclohexen-1-one, 130799-49-4; 1,3-bis(methoxymethoxy)-5-pentylbenzene, 94450-80-3; olivetol, 500-66-3.

Supplementary Material Available: Summary of structural details, tables of atomic coordinates, bond lengths, bond angles, and anisotropic thermal parameters for **10**, summary of X-ray analysis of **10**, experimental details for **13** and **24**, and ^{1}H NMR spectra of **7**, **12**, **17**, **18**, **25**, **26**, **28**, **35**, **36**, **39**, **41**, 1-methoxy-3-(methoxymethoxy)-5-pentylbenzene, and 1,3-bis(methoxymethoxy)-5-pentylbenzene (23 pages). Ordering information is given on any current masthead page.

Palladium-Catalyzed Cross-Coupling of β-(Methanesulfonyl)oxy Enones with Organostannanes

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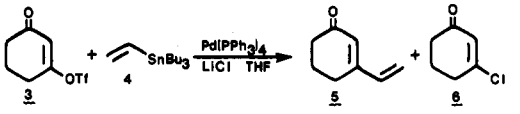
β-(Methanesulfonyl)oxy enones, derived from 1,3-diones, cross-couple with vinylstannanes in 50-80% yields when a substoichiometric amount of $Pd(PPh_3)_4$ and stoichiometric lithium bromide are used. Phenyltributylstannane affords low yields of cross-coupled product. Tetrabutyltin, tributyltin hydride, and ethynyltributyltin do not couple under the reaction conditions. The reaction is proposed to involve in situ formation of the β-bromo enone, oxidative addition to the Pd(0) catalyst, transmetalation, and reductive elimination to afford cross-coupled products. The analogous enol phosphates undergo coupling in low yields, the major product resulting from regeneration of the 1,3-dione.

Palladium-catalyzed carbon-carbon bond-forming reactions have become common methodology for synthetic organic chemists.[1] The chemistry is usually performed under mild conditions, with good tolerance for functionality on the substrates. The ability to couple a wide variety of electrophiles such as organoiodides, bromides, and triflates with nucleophiles (exemplified by organozincs, cuprates, and organotins) in the presence of a catalytic amount of palladium complexes provides new routes into organic compounds. An electrophile that has been little exploited in this field is the methanesulfonate (mesylate) group. We wish to report our success in the coupling of β-mesyloxy enones with vinyl- and allylstannanes in the presence of a palladium(0) catalyst.

Results and Discussion

During a project directed toward the total synthesis of C-ring oxygenated steroids, the need arose for the synthesis of a fully conjugated dienone that was constrained to an *all-Z* geometry. 1-Acetyl-2-vinylcyclohexene (**1**) was chosen as a model for these studies. The synthesis of β-substituted enones from 1,3-diones traditionally involves protection as the β-alkoxy analogue, reaction with a Grignard reagent and then acidic workup.[2] Synthesis of dienone **1** was envisioned to follow Weiler's more recent two-step conversion of 1,3-diones into β-substituted enones.[3] Reaction of 2-acetyl-1-cyclohexanone with diethyl chlorophosphate in the presence of sodium hydride afforded the thermodynamic phosphate **2**. However, treatment of phosphate **2** with bromomagnesium divinylcopper did not afford any of the desired product.

β-(Trifluoromethanesulfonyl)oxy (trifloxy) enones are known to undergo oxidative addition reactions with palladium(0).[4] Reaction conditions for the coupling of β-trifloxy enones with organostannanes were developed in analogy with the known palladium-catalyzed cross-coupling of vinyl triflates with organostannanes in the presence of stoichiometric LiCl.[5,6] Treatment of triflate **3** with vinyltributylstannane (**4**) in the presence of 3 equiv of LiCl and 5 mol % of $Pd(PPh_3)_4$ afforded a 1:1 mixture of the vinyl-substituted product **5** along with 3-chlorocyclohex-2-en-1-one (**6**). All attempts to achieve cross-coupling of



3 **4** **5** **6**

independently prepared[8] chloro enone **6** with vinyltin **4** failed. Michael addition of chloride therefore acts to remove starting material from the reaction and lowers yields of cross-coupled products. Palladium-catalyzed reaction of **3** with **4** in the absence of LiCl returned starting materials. Formation of chloro enone **6** suggested that LiCl was not an acceptable stabilizing halide[6,7] for the cross-coupling of β-sulfonyloxy enones and that a more reactive halide, such as bromide,[1] would be required.

Because the β-position of an enone is activated toward oxidative addition, the corresponding (methanesulfonyl)-oxy (mesyloxy) enone should react in a manner analogous

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