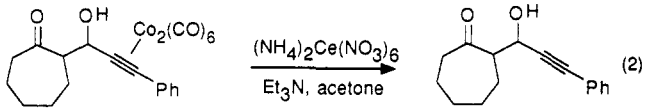
interesting to note that the related coupling reactions of acetylenic acetal complexes $[RC{\equiv}CCH(OR)_2]Co_2(CO)_6$ show a significantly different pattern of selectivity with these same enol derivatives[10] probably reflecting the differing steric and electronic requirements of the OR vs O-Lewis acid groups in the transition state.

Efficient demetalation of the complexes is effected upon their treatment with ceric ammonium nitrate (acetone, Et_3N, 0 °C) as illustrated by the isolation (>95% yield) of aldol 13 from complex 9 (eq 2). The convenient introduction and removal of the directing $Co_2(CO)_6$ unit



(2)

combined with the selectivity of the cobalt-mediated aldol coupling thus provides a unique method for the stereoselective synthesis of acetylenic aldols. Efforts are underway to expand the scope and explore the applications of these reactions in natural products synthesis.

Acknowledgment. We thank Dr. Angel Montana for helpful discussions and Dr. H. Daniel Hodes for some initial experiments. We are grateful for support provided by the National Institutes of Health (Grant GM 34799) and to Pressure Chemical Co. for a gift of cobalt carbonyl.

Supplementary Material Available: Representative synthetic procedures; spectroscopic properties of new compounds; tables of X-ray coordinates, thermal parameters, bond lengths, bond angles, and associated data for *syn*-8; and copies of the ^1H NMR spectra of complexes 7-11 (18 pages). Ordering information is given on any current masthead page.

An Optically Active Terpenic Synthon for Δ^9-Cannabinoids: Synthesis of (−)-11-Hydroxy-Δ^9-tetrahydrocannabinol (THC) and Its 1′,1′-Dimethylheptyl Analogue

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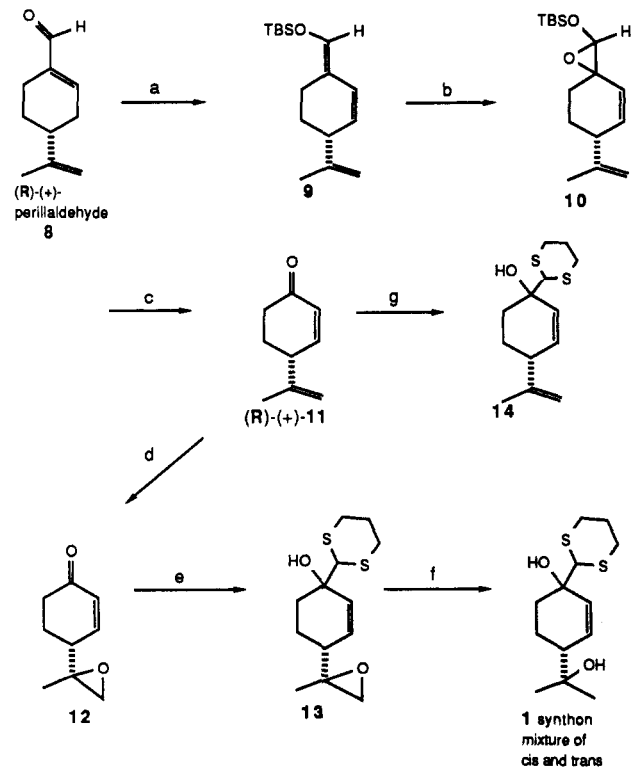
Summary: A facile entry into Δ^9-tetrahydrocannabinoids has been achieved via synthon 1, synthesized from (*R*)-(+)-perillaldehyde in a six-step process (23% overall yield).

Sir: Several years ago we reported[1] an entry into Δ^9-tetrahydrocannabinoids via a terpenic synthon carrying a 1,3-dithiane moiety. The remarkable finding in this approach was that, under acid catalysis formation, the presence of the 1,3-dithiane group effectively inhibited the isomerization of the Δ^9-unsaturation to the thermodynamically more stable Δ^8-position in the THC ring system.[2] In view of the fact that the instability of the Δ^9-unsaturation occurs in metabolites and other derivatives of Δ^9-THCs, this 1,3-dithiane containing synthon had, we felt, great potential for the synthesis of a variety of hitherto inaccessible metabolites.[2] We were unable to exploit the potential of those findings since the optically inactive terpenic synthon would lead to only racemic products.

In recent attempts to overcome this problem, we have been examining various approaches including the use of a readily available, enantiomerically pure terpene precursor to the optically active synthon 1. The recent report, by Tius and Kerr[3] for the synthesis of (*R*)-(+)-perillaldehyde (8) from commercially available (+)-limonene oxide and its conversion to 11-hydroxy-Δ^9-THC (**6a**),[4] a major metabolite of Δ^9-THC, now prompts us to record our findings in this area.

We have found that (*R*)-(+)-perillaldehyde (8, Scheme I, $[\alpha]^{26}_D$ = +128.6° (158 mg/mL, CH_3OH) [lit.[3] $[\alpha]^{19}_D$ = +128.8° ($CHCl_3$)] is an excellent starting terpene for the synthesis of the optically active synthon 1. In our approach, 8 was converted to the epoxy silyl ether **10** via the silyl enol ether **9** using essentially the same reaction conditions reported by Tius and co-workers;[4] however,

Scheme I[a]



[a] (a) TBSOTf, Et_3N, CH_2Cl_2, 0 °C; (b) MCPBA, diethyl ether–aqueous $NaHCO_3$, 25 °C; (c) HF, $NaIO_4$, CH_3CN–H_2O, 25 °C (55% overall for *a*–*c*); (d) MCPBA, CH_2Cl_2, 87%; (e) *n*-BuLi, 1,3-dithiane, THF, 60%; (f) $LiAlH_4$, diethyl ether, 78%; (g) *n*-BuLi, 1,3-dithiane, THF, 90%.

(1) Uliss, D. B.; Handrick, G. R.; Dalzell, H. C.; Razdan, R. K. *J. Am. Chem. Soc.* **1978**, *100*, 2929.

(2) For the dibenzopyran numbering system used in this paper and review of cannabinoid synthesis, see: (a) Razdan, R. K. In *Total Synthesis of Natural Products*; Ap Simon, J., Ed.; John Wiley: New York, 1981; Vol. 4, pp 186–262. (b) Mechoulom, R.; McCallum, N. K.; Burstein, S. *Chem. Rev.* **1976**, *76*, 75.

(3) Tius, M. A.; Kerr, M. A. *Synth. Commun.* **1988**, *18*, 1905.

(4) Tius, M. A.; Gu, X.; Kerr, M. A. *J. Chem. Soc., Chem. Commun.* **1989**, 62.

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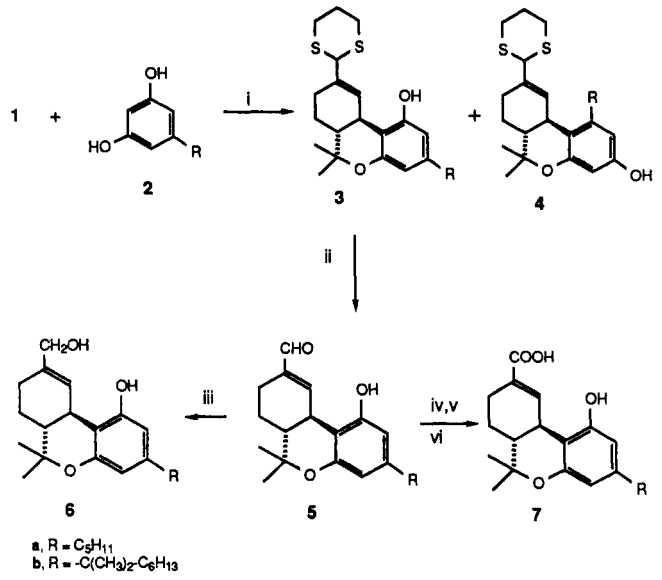
Scheme II[a]



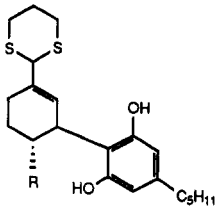
[a] (i) PTSA, benzene; (ii) HgO, $BF_3{\cdot}Et_2O$, 15% H_2O–THF; (iii) $NaBH_4$, EtOH or $LiAlH_4$, diethyl ether; (iv) Ac_2O, py; (v) MnO_2, NaCN, MeOH; (vi) 2 N NaOH, THF.

treatment of the epoxy silyl ether **10** with HF in the presence of $NaIO_4$ in CH_3CN/H_2O at room temperature gave the key intermediate (*R*)-(+)-4-isopropenyl-2-cyclohexen-1-one (**11**, Scheme I, $[\alpha]_D$ = +192.2° (16.2 mg/mL, CH_3OH)). Chromatographic purification was required only of the final product which was obtained in an overall yield of 58% from **8**. As far as we are aware (*R*)-(+)-**11** has not been reported,[5] and our synthesis is in contrast to the procedure of Stevens and Albizati[6] who prepared the enantiomer, (*S*)-(−)-**11**. Treatment of (*R*)-(+)-**11** with *m*-chloroperbenzoic acid in CH_2Cl_2 gave regioselectively the epoxide **12** in 87% yield after flash chromatography (1:1 ethyl acetate/hexanes). The lithium anion of 1,3-dithiane (1 equiv) in THF added regioselectively to the ketone **12** in a 1,2 fashion[1] to give **13**. After purification by flash chromatography (1:1 ethyl acetate/hexanes), **13** was obtained as a mixture of stereoisomers in 60% yield. Reduction with $LiAlH_4$ in diethyl ether followed by flash chromatography (60% ethyl acetate/hexanes) furnished the synthon **1**[7] as a mixture of cis and trans isomers in 78% yield (41% overall from **11**).

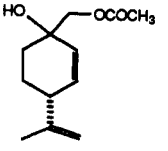
The Δ^9-cannabinoid formation with olivetol (**2a**) in the presence of *p*-toluenesulfonic acid (PTSA) in benzene proceeded to form the Δ^9-THC derivative **3a** and the abnormal product **4a** in similar yields as previously reported (Scheme II).[1] Removal of the 1,3-dithiane masking group of **3a** with HgO and $BF_3{\cdot}Et_2O$ in 15% aqueous THF gave the Δ^9-THC aldehyde **5a**, which was reduced with $LiAlH_4$ in diethyl ether to give the Δ^9-THC metabolite **6a**.[1] After purification by preparative TLC, the pure metabolite **6a**[8] was obtained as a solid (mp 140.5–141.5 °C, $[\alpha]^{26}_D$ = −161.9° (45.9 mg/mL, EtOH) [lit.[9a] $[\alpha]^{26}_D$ = −125° (*c* = 0.26, EtOH)]. Capillary GC (5% methyl phenyl silicone) and high-resolution NMR (400 MHz) clearly showed the absence of any Δ^8-THC isomer.

Having established the utility of the synthon **1** for the synthesis of (−)-**5a** which can be either reduced to the metabolite **6a** or oxidized, as the acetate, to the acid **7a**,[4,9b] we examined the reaction of 5-(1′,1′-dimethylheptyl)resorcinol (**2b**) with **1**. The condensation proceeded very smoothly in the presence of PTSA in benzene at 45 °C for 4 h and gave **3b** in 43% yield after flash chromatography (10% ethyl acetate/hexanes). In this instance no appreciable formation of abnormal product **4b** was observed.[10] Removal of the 1,3-dithiane group was accomplished as in the case of **3a** to give the hitherto unknown aldehyde **5b**[11] ($[\alpha]^{26}_D$ = −205.9° (12.1 mg/mL, EtOH)). $NaBH_4$ reduction of the aldehyde furnished (−)-**6b**[12] ($[\alpha]^{26}_D$ = −149.5° (11.0 mg/mL EtOH)).

As part of this study, we also prepared the 1,3-dithiane adduct of **11**, i.e. **14** (Scheme I), and examined its reaction with olivetol (**2a**) using various acids, e.g. $BF_3{\cdot}Et_2O$, PTSA, CCl_3COOH. In every case the desired cannabinoid **3a** was formed in lower yields (3–4%) compared to the use of **1** (ca. 20%). In each case the first step is the attack of the resorcinol to form the ring-opened intermediate **15** from **1** or **16** from **14** and the difference in yield of the desired product can be attributed to the presence of the tertiary hydroxyl group in **1** which facilitates the subsequent ring-closure step. It should be pointed out that the same isopropenyl group in **14** is present in the synthon **17** used by Tius et al.,[4] but they did not encounter such low yields in the formation of THCs. The reason for these differences among synthons **1**, **14**, and **17** is not clear and is presently under investigation.



15 R = 



17

16 R = 

The 1′,1′-dimethylheptyl analogue (−)-**6b** is expected to be one of the most potent cannabinoids known. Its

(5) We have been privately informed by Prof. S. Agurell and coworkers (Karolinska Institute, Stockholm, Sweden) that they have also synthesized (*R*)-(+)-**11** and will be reporting their findings shortly. We are grateful to these authors for this information.

(6) Stevens, R. V.; Albizati, K. F. *J. Org. Chem.* **1985**, *50*, 632. They converted (*S*)-(−)-perillyl alcohol to (*S*)-(−)-**11** ($[\alpha]^{22}_D$ = −153.8° (10.3 mg/mL, CH_3OH)) in a five step process in 40% overall yield.

(7) ^1H NMR data identical with that of the previously reported racemic compound, ref 1.

(8) ^1H NMR (400 MHz, $CDCl_3$) δ 6.67 (s, 1 H, C*H*=C), 6.25 and 6.11 (2 s, 2 H, Ph *H*), 5.22 (br s, 1 H, PhO*H*), 4.01 (br s, 2 H, CH_2OH), 3.24 (br d, 1 H, *J* = 10.8 Hz, PhC*H*), 2.41 (dd, 2 H, *J* = 8.2, 6.0 Hz, PhCH_2C), 2.25 (m, 2 H, CH_2C=C), 1.95, 1.7, 1.55, 1.4, and 1.25 (5 m, 8 H, $CH_2CH_2CH_2CH_3$, CH_2CH, CH_2OH), 1.40 and 1.10 (2 s, 6 H, $(CH_3)_2CO$), 0.86 (br t, 3 H, *J* = 6.8 Hz, CH_2CH_3).

(9) (a) Inayama, S.; Sawa, A.; Hosoya, E. *Chem. Pharm. Bull.* **1974**, *22*, 1519. (b) Pitt, C. G.; Fowler, M. S.; Sathe, S.; Srivastava, S. C.; Williams, D. L. *J. Am. Chem. Soc.* **1975**, *97*, 3798.

(10) This is presumably due to the steric effect provided by the 1′,1′-dimethyl group, which suppresses the attack of the resorcinol at the 4-position. Similar results have been observed in our laboratories in the synthesis of Δ^8-THC derivatives; See also: Petrzilka, T.; Haefliger, W.; Sikemeier, C. *Helv. Chim. Acta* **1969**, *52*, 1102.

(11) ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1 H, C(O)*H*), 7.95 (d, 1 H, *J* = 1.8 Hz, C=C*H*), 6.45 (d, 1 H, *J* = 1.7 Hz, Ph *H*), 6.33 (d, 1 H, *J* = 1.7 Hz, Ph *H*), 5.34 (br s, 1 H, PhO*H*), 3.54 (m, 1 H, PhC*H*), 2.55 and 2.39 (2 m, 2 H, CH_2C=C), 2.10 (m, 1 H, $CHC(Me)_2O$), 1.8, 1.5, 1.25, and 1.1 (4 m, 12 H, $CH_2CH_2CH_2CH_2CH_2CH_3$ and $CH_2CHC(Me)_2O$), 1.49 and 1.19 (2 s, 6 H, $C(CH_3)_2O$), 1.24 (s, 6 H, $(CH_3)_2CCH_2$), 0.87 (t, 3 H, *J* = 6.9 Hz, CH_2CH_3).

(12) ^1H NMR (400 MHz, $CDCl_3$) δ 6.70 (s, 1 H, C=C*H*), 6.37 (d, 1 H, *J* = 1.7, Ph *H*), 6.24 (d, 1 H, *J* = 1.7, Ph *H*), 5.11 (br s, 1 H, PhO*H*), 4.03 (br s, 2 H, CH_2OH), 3.25 (br d, 1 H, *J* = 11.2 Hz, PhC*H*), 2.27 (m, 2 H, CH_2C=C), 1.98 (m, 1 H, $CHC(CH_3)_2O$), 1.71 (m, 2 H, CH_2CH_2C=C), 1.48, 1.20, and 1.05 (3 m, 11 H, $CH_2CH_2CH_2CH_2CH_2CH_3$ and CH_2OH), 1.43 and 1.11 (2 s, 6 H, $(CH_3)_2CO$), 1.18 (s, 6 H, $(CH_3)_2CCH_2$), 0.83 (t, 3 H, *J* = 6.9 Hz, CH_3CH_2).

counterpart in the Δ^8-THC series was recently synthesized and reported to be extremely active pharmacologically.[13] It is well established that the pharmacological activity in the Δ^8-series parallels that of the naturally occurring Δ^9-THC series.[14] The interest in the synthesis of (-)-**6b** arose because our sequence (Scheme II) allows for easy radiolabeling. Thus treatment of **5b** with tritiated $NaBH_4$ should give tritiated **6b**, which will be used in binding studies of mouse brain homogenates for possible isolation of a THC receptor.

Acknowledgment. This work was carried out with the support of the National Institutes of Drug Abuse (NIDA, Grant No. DA 05488). We are grateful to the Eli Lilly and Co., Indianapolis, for the supply of (1',1'-dimethylheptyl)resorcinol and Prof. J. L. Neumeyer, Northeastern University, for assistance in determination of optical rotations.

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(14) Razdan, R. K. *Pharmacol. Rev.* **1986**, *38*, 75.

S_N2 Reactions of a Carbon Nucleophile with *N*-Aryl-*O*-pivaloylhydroxylamines: A Model for in Vivo Reactions of Carcinogenic Metabolites of Aromatic Amines

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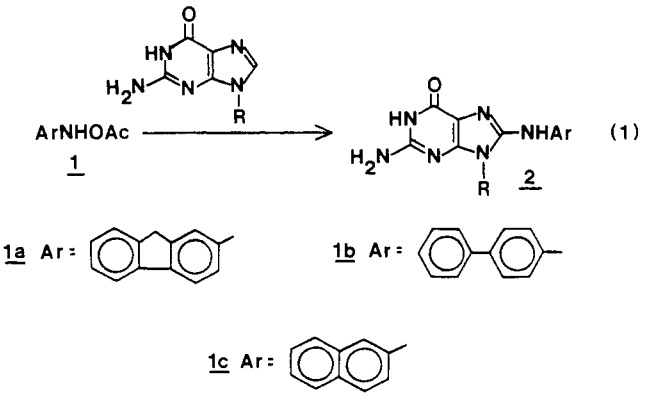
Summary: The reaction of the *N*-aryl-*O*-pivaloylhydroxylamines **3a–c** with *N,N*-dimethylaniline **4** to generate the diphenylamines **5a–c** and **6a–c**, a model for the in vivo reaction of similar esters of carcinogenic *N*-arylhydroxylamines with C-8 of guanosine, proceeds via an S_N2 mechanism.

Sir: *O*-Acetyl-*N*-arylhydroxylamines such as **1a** are putative carcinogenic metabolites of polycyclic aromatic amines, which are thought to be responsible for the characteristic "C-8 adduct", **2**, obtained from a variety of in vivo and in vitro studies of the metabolism of the corresponding amines or hydroxylamines.[1] Recently it has been shown that **1b** and **1c** do indeed react with deoxyguanosine to form the adducts **2b** and **2c** (R = deoxyribose) in low yields in $EtOH/CHCl_3/H_2O$ (eq 1).[2] The mechanism of this reaction has not been investigated, but a nitrenium ion process is often invoked to explain it.[1] Results from our laboratory and others indicate that aryl nitrenium ions rarely, if ever, undergo nucleophilic attack at nitrogen.[3-5] We have investigated the model reaction of the *N*-aryl-*O*-pivaloylhydroxylamines **3** with *N,N*-dimethylaniline, **4**, in MeOH (eq 2) and found that this process has the characteristics of an S_N2 reaction.



(1)

The decomposition of **3** in 3.7 M **4** in dry MeOH at 25 °C yields the diphenylamines **5** and **6** (Table I). Under these conditions **3a** and **3b** undergo complete reaction within 24 h and appear to be quantitatively converted into **5** and **6**. After 24 h under the same conditions ca. 70% of **3c** is recovered unreacted, and correspondingly low yields of **5c** and **6c** are obtained (Table I). At least one other minor unidentified product is detected in the reaction of **3c**.

Table I. Yields of the Diphenylamines 5a–c and 6a–c and Second-Order Rate Constants for the Reaction of 3a–c and 4 in MeOH at 25 °C

	% yields[a]		
ester	5	6	k_2,[b] M^{-1} s^{-1}
3a	72	10	$(1.1 \pm 0.1) \times 10^{-4}$
3b	60	20	$(3.4 \pm 0.2) \times 10^{-6}$
3c	14	6	$(1.8 \pm 0.3) \times 10^{-6}$

[a] Recovered yields after incubation of **3** in 3.7 M **4** in MeOH at 25 °C for 24 h. See supplementary material for details. [b] See supplementary material for details of kinetic methods.

The kinetics of this process were monitored by ^1H NMR spectroscopy in methanol-d_4 under pseudo-first-order conditions for **3a** and **3b** in the concentration range 0.05–0.20 M in **4**, and by UV methods for **3c** at concen-

(1) See for example: King, C. M.; Traub, N. R.; Lortz, Z. M.; Thissen, M. R. *Cancer Res.* **1979**, *39*, 3369–3372. Beland, F. A.; Dooley, K. L.; Jackson, C. N. *Cancer Res.* **1982**, *42*, 1348–1354. Flammang, T. J.; Westra, J. G.; Kadlubar, F. F.; Beland, F. A. *Carcinogenesis* **1985**, *6*, 251–258. Delclos, K. B.; Miller, E. C.; Miller, J. A.; Liem, A. *Carcinogenesis* **1986**, *7*, 277–287. Lai, C. C.; Miller, E. C.; Miller, J. A.; Liem, A. *Carcinogenesis* **1987**, *8*, 471–478.
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(4) Gassman, P. G.; Campbell, G. A. *J. Am. Chem. Soc.* **1971**, *93*, 2567–2569; **1972**, *94*, 3891–3896. Gassman, P. G.; Campbell, G. A.; Frederick, R. C. *J. Am. Chem. Soc.* **1968**, *90*, 7377–7378; **1972**, *94*, 3884–3891. Gassman, P. G.; Granrud, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 1498–1499; **1984**, *106*, 2448–2449.
(5) McClelland, R. A.; Panicucci, R.; Rauth, A. M. *J. Am. Chem. Soc.* **1985**, *107*, 1762–1763.

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