tion of a quinol and an (alkylamino)phenol) is energetically more favorable than is transamination. The mechanistic discrepancy between the enzymatic reaction and the model reaction may arise from the fact that the *o*-quinone cofactor in *mammalian copper-containing amine oxidases* is TOPA and not PQQ. But in any case, it can be said that the novel structure of PQQ, *pyrroloquinoline quinone*, contributes to the catalytic efficiency in the amine oxidation. Simple *o*-quinones, like phenanthrenequinone, do not display any catalytic activity at all in the related aerobic oxidation of amines. As Bruice et al. have reported,[11a] the presence of a pyridine nucleus in PQQ facilitates the nucleophilic addition of amines to the C(5) quinone carbon atom and stabilizes the carbinolamine intermediate thus formed by intramolecular hydrogen bonding.[11a] The presence of an acidic pyrrole proton is also very important for intramolecular general base catalysis to operate, as is indicated in Scheme III. The significance of the *pyrroloquinoline quinone* structure is now being further investigated by using indolequinone and quinolinequinone analogues of PQQ.

**Acknowledgment.** This study was supported in part by a Grant-in-Aid for Co-operative Research (No. 01303007) from the Ministry of Education, Science, and Culture of Japan, to which our thanks are due. We also thank Mr. Seiji Nakajima (Workshop of Osaka University) for his help in the experiments.

**Registry No.** 1, 74447-88-4; 1 $H_2$, 102408-71-9; 2, 128031-21-0; 2 $H_2$, 128031-23-2; 3, 128031-22-1; 4, 136342-75-1; 5 (isomer 1), 136342-76-2; 5 (isomer 2), 136342-77-3; 5 $H_2$, 136342-78-4; 6, 116451-41-3; 7, 136342-79-5; $PhCH_2NH_2$, 100-46-9; $PhCH_2NMe_2$, 103-83-3; $PhCH(Me)NH_2$, 98-84-0; $PhCH_2NHMe$, 103-67-3; $PhCH(Ph)NH_2$, 91-00-9; PhCHO, 100-52-7; $PhC(O)CH_3$, 98-86-2; $Ph_2CO$, 119-61-9; *p*-$MeOC_6H_4CH_2NH_2$, 2393-23-9; *p*-$ClC_6H_4CH_2NH_2$, 104-86-9; *p*-$MeC_6H_4CH_2NH_2$, 104-84-7; $PhCD_2NH_2$, 15185-02-1; $PhCH_2N{=}CHPh$, 780-25-6; *tert*-butylamine, 75-64-9; *n*-propylamine, 107-10-8; *N*-methylpropylamine, 627-35-0; cyclopropylamine, 765-30-0; *n*-hexylamine, 111-26-2; cyclohexylamine, 108-91-8; methylhydrazine, 60-34-4; *N,N*-dimethylpropylamine, 926-63-6; triethylamine, 121-44-8.

# Synthesis of Racemic and Optically Active $\Delta^9$-Tetrahydrocannabinol (THC) Metabolites

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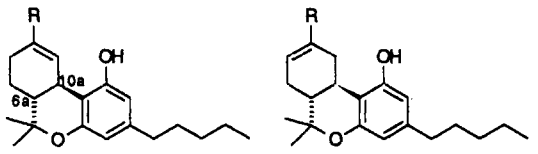
The preparation of racemic and optically active $\Delta^9$-THC metabolites is described from synthon **13**. Racemic synthon **13** is prepared in four steps (46%) from Danishefsky's diene. Optically active synthon **13** is prepared from perillaldehyde via the enone **22** in six steps (23% yield). Alternatively, nopinone can be converted to **13** in three steps (50% yield) via a cyclobutane ring cleavage. The acid-catalyzed condensation of **13** with olivetol (**6a**) and subsequent conversion to 11-hydroxy and 9-carboxyl $\Delta^9$-THC metabolites **2a** and **4a** is described, as well as the preparation of 1′,1′-dimethylheptyl THC analogues **2b**, **3b**, and **4b** from 5-(1′,1′-dimethylheptyl)resorcinol (**6c**).

## Introduction

Although *Cannabis Sativa* (marijuana) has been used for centuries and its active constituent, $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC, **1a**, Chart I),[1] was identified and synthesized many years ago, until recently very little was known about its mode of action. The recent reports of isolations of possible cannabinoid receptors,[2] as well as cannabinoid-like activity in "nonclassical" compounds (e.g., H-CP-55940),[3] have lead to a renewed interest in $\Delta^9$-THC's structure–activity relationships (SAR) as well as receptor(s) identification. Because of the extremely active pharmacology of some THC metabolites,[4] they seem ideal targets for radiolabelled binding and SAR studies.

Chart I




| $\Delta^9$-THCs | $\Delta^8$-THCs |
|---|---|
| **1a**; R = $CH_3$ | **1b**; R = $CH_3$ |
| **2a**; R = $CH_2OH$ | **2b**; R = $CH_2OH$ |
| **3a**; R = CHO | **3b**; R = CHO |
| **4a**; R = COOH | **4b**; R = COOH |

In addition, the continued illicit use of marijuana, as well as present concern over drug abuse, have lead to the development of methods to determine accurately marijuana use by individuals. One of the main metabolic pathways of $\Delta^9$-THC (**1a**) is hydroxylation at the allylic C-11 position followed by oxidation to the 11-nor-9-carboxy-$\Delta^9$-THC (**4a**). This compound is then excreted as the glucuronide in urine.[5] Metabolite **4a** is used as an internal standard in various analytical procedures to unequivocally confirm its presence in biological fluids. It has, therefore, gained

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

(2) (a) Devane, W. A.; Dysarz, F. A., III; Johnson, M. R.; Melvin, L. S.; Howlett, A. C. *Mol. Pharmacol.* **1988**, *34*, 605. (b) Matsuda, L. A.; Lolait, J.; Brownstein, M. J.; Young, A. C.; Bonner, T. I. *Nature* **1990**, *346*, 561. (c) Herkenham, M.; Lynn, A. B.; Little, M. D.; Johnson, M. R.; Melvin, L. S.; DeCosta, B. R.; Rice, K. C. *Proc. Natl. Acad. Sci.* **1990**, *87*, 1932.

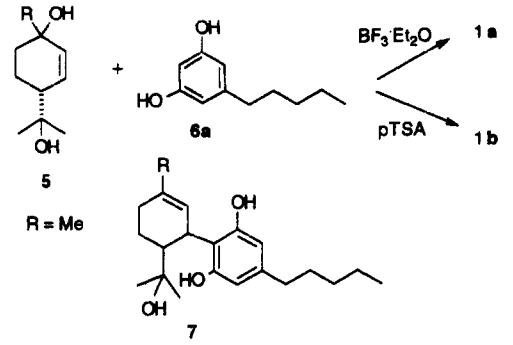
(3) (a) Little, P. J.; Compton, D. R.; Johnson, M. R.; Melvin, L. S.; Martin, B. R. *J. Pharmacol. Exp. Ther.* **1988**, *247*, 1046. (b) Martin, B. R.; Compton, D. R.; Thomas, B. F.; Prescott, W. R.; Little, P. J.; Razdan, R. K.; Johnson, M. R.; Melvin, L. S.; Mechoulam, R.; Ward, S. *J. Neuroscience and Biochemical Rev.*, in press.

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

(5) Agurell, S.; Halldin, M.; Lindgren, J.; Ohlsson, A.; Widman, M. *Ibid.* **1986**, *38*, 21.

0022-3263/91/1956-6865$02.50/0 

**Scheme I**



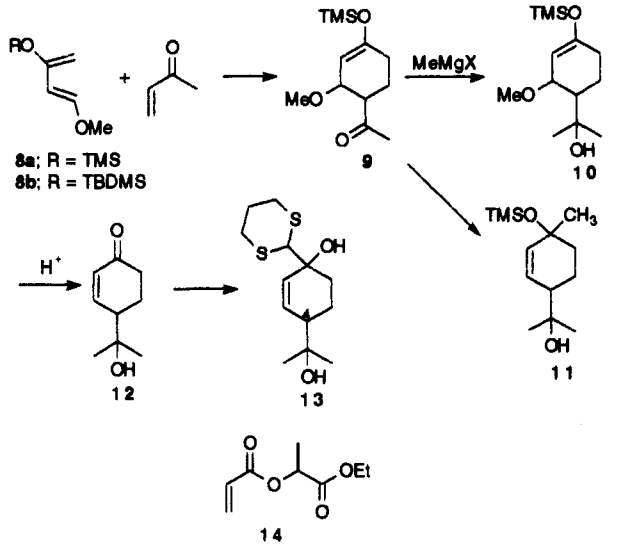

considerable forensic importance and is used in various detection kits to ascertain the use of marijuana by individuals. For all of these reasons, there is increased interest in the synthesis of cannabinoids, especially metabolites of $\Delta^9$-THC and analogues.

Earlier syntheses of the metabolites of **1a** used $\Delta^9$-THC as the starting material, but all suffered from two major problems. Firstly, $\Delta^9$-THCs readily isomerize to the less potent $\Delta^8$-THC isomers and it is known that treatment of **1a** with acid catalysis leads to a 97/3 mixture of $\Delta^8$ to $\Delta^9$ isomers **1b**/**1a**.[6] Secondly, the THC skeleton itself is sensitive to oxidative conditions and leads to complicated mixtures upon oxidative metabolite preparations. These two problems led to extremely low yields (<5%) in earlier syntheses of $\Delta^9$-THC metabolites.[7] Several recent syntheses of $\Delta^9$-THC metabolites have been reported. Tius et al.[8] have reported a novel synthesis of alcohol **2a** which does not address the double-bond isomerization difficulties. A new approach to acid **4a** by Huffman et al.[9] avoided both these problems but gave racemic product as well as a cis/trans mixture (6a,10a) which had to be separated. The same group has subsequently solved the problem of racemization.[10] We now describe in detail our efforts to circumvent these problems in the synthesis of optically active $\Delta^9$-THC metabolites.

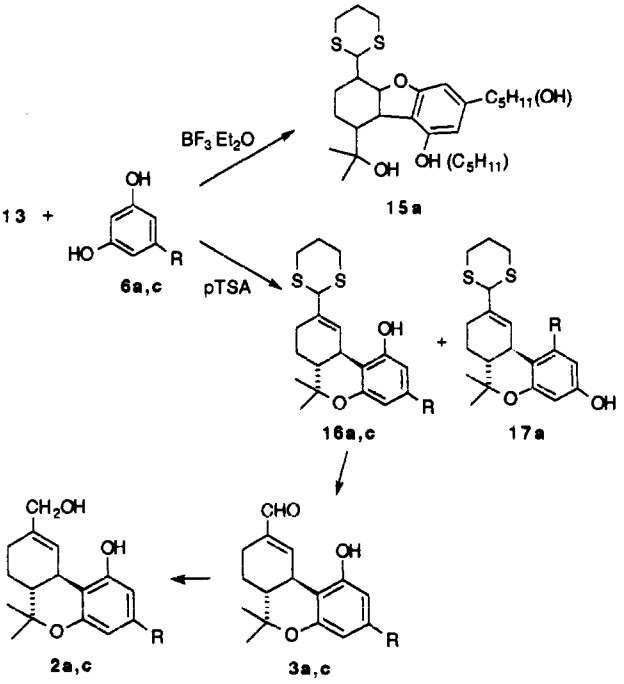
Our approach is based on the use of monoterpene, *p*-menth-2-ene-1,8-diol (**5**) used to synthesize both $\Delta^9$- and $\Delta^8$-THCs (Scheme I).[11] We envisioned that replacement of the allylic methyl group (R) of **5** with the dithiane protecting group would lead to an efficient route to 11-oxo metabolites that would avoid harsh oxidative conditions. Interestingly, by introducing the dithiane moiety into the THC structure the isomerization of the $\Delta^9$ double bond was also inhibited.

**Racemic Synthesis of $\Delta^9$-THC Metabolites.**[12] The racemic terpenic synthon **13** was easily prepared in four steps from Danishefsky's diene[13] (**8a**, Scheme II). The

**Scheme II**




**Scheme III**



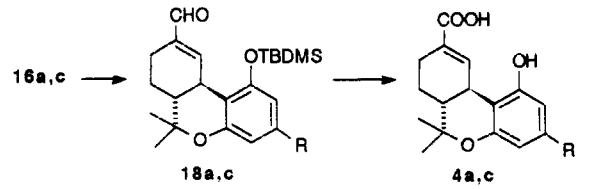

**a**, R = $C_5H_{11}$
**c**, R = -$C(CH_3)_2$-$C_6H_{13}$

crude adducts **9**,[13] from the Diels–Alder reaction of **8a** with methyl vinyl ketone, were treated with $CH_3MgI$ to afford a mixture of the cis and trans isomers **10**. Interestingly, a large excess of the Grignard led to **11**, presumably via a $S_n2'$ displacement of the methoxyl group.[14] Careful hydrolysis (see Experimental Section) of **10** gave the enone **12** without dehydration. The lithium anion of 1,3-dithiane added in a 1,2 fashion to **12** and yielded the desired terpenic synthon (±)-**13** as a 4:1 mixture of isomers. The relative configuration of these isomers was not identified, and the mixture could be used as such in subsequent steps.

To our surprise, the condensation of (±)-**13** with **6a** (Scheme III) using our method[11b] developed for the syn-

(6) Dalzell, H. C.; Uliss, D. B.; Handrick, G. R.; Razdan, R. K. *J. Org. Chem.* **1981**, *46*, 949.
(7) (a) Pitt, C. G.; Fowler, M. S.; Sathe, S.; Srivastava, S. C.; Williams, D. L. *J. Am. Chem. Soc.* **1975**, *97*, 3798. (b) Pitt, C. G.; Hauser, F.; Hawks, R. L.; Sathe, S.; Wall, M. E. *J. Am. Chem. Soc.* **1972**, *94*, 8578. (c) Razdan, R. K.; Uliss, D. B.; Dalzell, H. C. *J. Am. Chem. Soc.* **1973**, *95*, 2361. (d) Inayama, S.; Sawa, A.; Hosoya, E. *Chem. Pharm. Bull. Jpn.* **1974**, *22*, 1519.
(8) Tius, M. A.; Gu, X.; Kerr, M. A. *J. Chem. Soc., Chem. Commun.* **1989**, 62.
(9) (a) Huffman, J. W.; Zhang, X.; Wu, M. J.; Joyner, H. H. *J. Org. Chem.* **1989**, *54*, 4741. (b) Huffman, J. W.; Zhang, X.; Wu, M. J.; Joyner, H. H.; Pennington, W. T. *Ibid.* **1991**, *56*, 1481.
(10) Huffman, J. W.; Joyner, H. H.; Lee, M. D.; Jordan, R. D.; Pennington, W. T. *Ibid.* **1991**, *56*, 2081.
(11) (a) Handrick, G. R.; Uliss, D. B.; Dalzell, H. C.; Razdan, R. K. *Tetrahedron Lett.* **1979**, 681. (b) Razdan, R. K.; Dalzell, H. C.; Handrick, G. R. *J. Am. Chem. Soc.* **1974**, *96*, 5860.
(12) For a preliminary communication describing the synthesis of racemic **13**, see: Uliss, D. B.; Handrick, G. R.; Dalzell, H. C.; Razdan, R. K. *J. Am. Chem. Soc.* **1978**, *100*, 2929.
(13) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.
(14) A reviewer suggested that magnesium halide acting as a Lewis acid may be assisting in the conjugate addition of the methyl to **9** to give **11**.

**Scheme IV**




a, R = $C_5H_{11}$
c, R = $-C(CH_3)_2-C_6H_{13}$

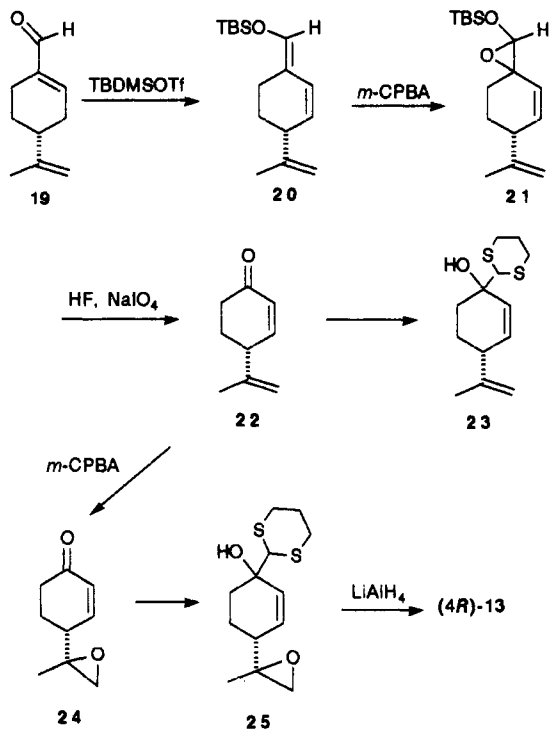
thesis of $\Delta^9$-THC did not form the desired THC adduct **16a**. The reaction of **13** with olivetol (**6a**) and $BF_3 \cdot Et_2O$ gave, as the major product, a compound tentatively assigned as benzofuran **15a**. Presumably, **15a** is formed by an intramolecular attack by the phenolic oxygen on the double bond in preference to the desired displacement of the tertiary hydroxyl in intermediate **7** (R = 1,3-dithianyl). As will be discussed later, formation of **15a** is dependent upon the acid catalyst used and possible "activation" of the double bond by the dithiane moiety.

The condensation of the synthon (±)-**13** with **6a** catalyzed by *p*-toluenesulfonic acid (pTSA) did produce the desired product, **16a**. The acid reaction gave a mixture of "normal" (±)-**16a** (20%) and "abnormal" **17a** (30%). As both the cis and trans isomers of (±)-**13** gave the same product mixture, a common carbonium ion intermediate is probably involved. Significantly, only the $\Delta^9$-isomers were formed; no isomerization to the $\Delta^8$-THC isomer was observed. The $\Delta^8$ isomer of **16a**, prepared from **3b** and propane-1,3-dithiol in the presence of $BF_3 \cdot Et_2O$, did not isomerize to **16a** when treated with pTSA in refluxing benzene. This eliminates the possibility that the $\Delta^9$ isomer is more stable in these dithiane adducts. It appears that the 1,3-dithiane group in **16** destabilizes an incipient carbonium ion at $C_9$, contrary to the known stabilization of carbocations by $\beta$-sulfur groups,[15] and thereby prevents isomerization between $\Delta^9$ and $\Delta^8$ isomers. This may be caused by electronic effects such as (i) competitive formation of a sulfonium ion adjacent to $C_9$ or (ii) diminution of hyperconjugative stabilization (as a result of the substitution of sulfur for hydrogen at $C_{11}$). The THC metabolite precursor (±)-**16a** was easily transformed to the racemic metabolite (±)-**3a** by removal of the 1,3-dithiane masking group with HgO and $BF_3 \cdot Et_2O$. Reduction gave the $\Delta^9$-THC metabolite (±)-**2a**.

Having established the utility of the synthon (±)-**13**, we examined its reaction with 5-(1′,1′-dimethylheptyl)resorcinol (**6c**).[16] The 1′,1′-dimethylheptyl THC analgues are known to be much more active than natural THCs and are therefore interesting targets. The condensation proceeded very smoothly in the presence of pTSA and gave (±)-**16c** (43% yield). In this instance no appreciable formation of abnormal product was observed. 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 the synthesis of $\Delta^8$-THC derivatives.[11,17] Compound (±)-**16c** was converted to the hiterto unknown aldehyde ±-**3c** and the alcohol (±)-**2c** as in the case of (±)-**16a**.

Both THC metabolite precursors (±)-**16a,c** were also converted to the acid derivatives (Scheme IV). Thus,

**Scheme V**



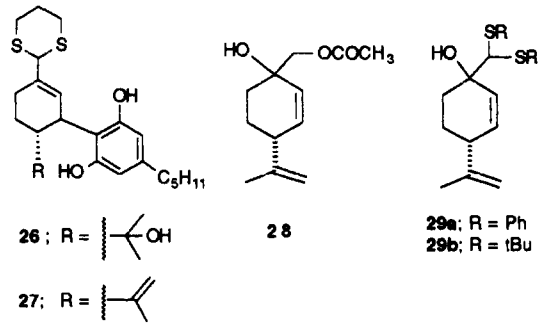

(±)-**16a** was converted to (±)-**18a** by silylation followed by hydrolysis of the dithiane group with MeI/$K_2CO_3$. If the hydrolysis was done with HgO and $BF_3 \cdot Et_2O$, ca. 30% of the product mixture was the deprotected phenol **3a**. (±)-**16c** was converted to (±)-**18c** by silylation and hydrolysis with HgO and $BF_3 \cdot Et_2O$ because, in this case, the product mixture contained only ca. 10% of **3c**. Both (±)-**18a** and (±)-**18c** were converted to the acids (±)-**4a** and (±)-**4c** using $NaClO_2$ in the presence of the HOCl scavanger, 2-methyl-2-butene, followed by hydrolysis of the silyl group, according to our previously described procedure.[18]

**Optically Active Synthesis of $\Delta^9$-THC Metabolites.**[19] Originally, it was thought that the synthesis of optically active synthon **13** could be achieved by an asymmetric Diel–Alder reaction. It was envisioned that the $TiCl_4$-mediated reaction of **8a** with the chiral dieneophile **14** (Scheme II), developed by Helmchen et al.,[20] would result in an adduct that could be transformed to (4*R*)-**13** in the same manner described for the racemic synthesis. Unfortunately, the use of a Lewis acid (either $TiCl_4$ or $SnCl_4$) resulted in decomposition of diene **8a** without any Diels–Alder products. We reasoned that steric hindrance might retard decomposition and therefore prepared diene **8b**,[21] replacing the TMS group of **8a** with a TBDMS group. Unfortunately, **8b** also decomposed when reacted with **14** in the presence of $TiCl_4$. These results were not anticipated because $TiCl_4$ is commonly used in the reaction of **8a** with aldehydes.[13] We were also unsuccessful in resolving the diastereomeric *O*-methyl mandelate esters of racemic alcohol **12**.

In view of the above, we chose to synthesize an optically active synthon from an optically pure starting material.

(15) Block, E. *Reactions of Organosulfur Compounds*; Academic: New York, 1978; Chapter 4.
(16) Dominianni, S. J.; Ryan, C. W.; DeArmitt, C. W. *J. Org. Chem.* **1977**, *42*, 344.
(17) See also: Petrzilka, T.; Haefliger, W.; Sikemeier, C. *Helv. Chim. Acta* **1969**, *52*, 1102.
(18) Siegel, C.; Gordon, P. M.; Razdan, R. K. *Synthesis*, in press.
(19) For preliminary communications describing the synthesis of optically active **13**, see: Siegel, C.; Gordon, P. M.; Razdan, R. K. *J. Org. Chem.* **1989**, *54*, 5428. Gordon, P. M.; Siegel, C.; Razdan, R. K. *J. Chem. Soc., Chem. Commun.* **1991**, 693.
(20) Poll, T.; Sobczak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Lett.* **1985**, *26*, 3095.
(21) Danishefshy, S. J. *Aldrichimica Acta* **1986**, *19*, 59.

**Chart II**



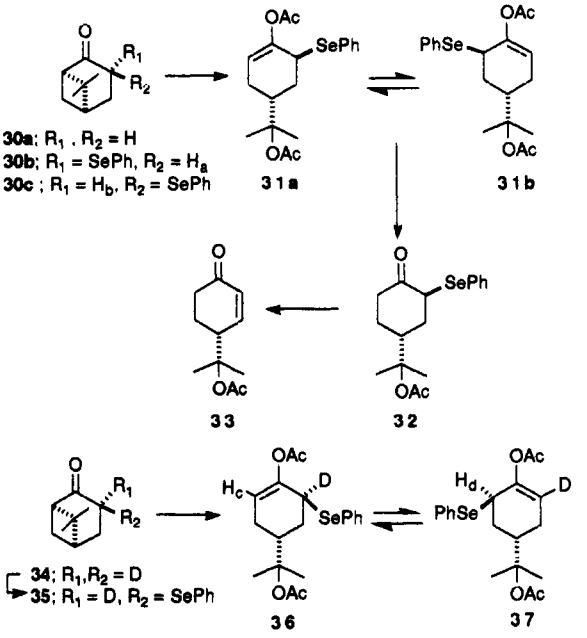

(*R*)-(+)-Perillaldehyde (**19**) was synthesized by a slight modification of the procedure of Tius and Kerr,[22] starting from commercially available (+)-limonene oxide. In our approach, **19** (Scheme V) was converted to the epoxy silyl ether **21** via **20**. We found that if the epoxidation of **20** was not stopped immediately after initial disappearance of the starting material (TLC), a byproduct,[8] arising from the addition of the *m*-chlorobenzoate ion to the epoxide, is formed. It could be converted to **22** by modifying the conditions in the next reaction (longer reaction time). Treatment of **21** with HF in the presence of $NaIO_4$ gave the key intermediate (*R*)-(+)-4-isopropenyl-2-cyclohexen-1-one (**22**). If this process was carried out in two steps (HF hydrolysis followed by oxidative cleavage with periodate), the yield was substantially lower due to the instability of the intermediate hydroxy aldehyde. As long as the hydrolysis was carried out in the presence of $NaIO_4$ the yield was ca. 60% from **19**. As expected, the lithium anion of 1,3-dithiane added to the ketone **22** in a 1,2 fashion to give **23** as a mixture of stereoisomers.

We examined the reaction of **23** with olivetol (**6a**) using various acids, e.g., $BF_3{\cdot}Et_2O$, pTSA, and $CCl_3COOH$. In every case, the desired cannabinoid **16a** was formed in lower yields (3–4%) compared to the use of **13** (ca. 20%). The major product was tentatively identified as the dehydrated analogue of **15a**. In each case, the first step is the attack of the resorcinol to form the ring-opened intermediate **26** or **27** (Chart II) and the difference in yield of the desired product can be attributed to the presence of the tertiary hydroxyl group in **26** which appears to facilitate the subsequent ring closure step. It should be pointed out that the same isopropenyl group present in **27** is also present in both *p*-mentha-2,8-dien-1-ol[17] and the synthon **28** used by Tius et al.,[8] for the formation of THCs. To date, the reason(s) for these differences among synthons **13**, **23**, and **28** is unclear. They could be due to an "activation" by the dithiane of the adjacent double bond in **27**, possibly by internal delivery of the acid (proton or $BF_3{\cdot}Et_2O$) from an initially formed sulfonium ion. Surprisingly, it appears that the 1,3-dithiane group inhibits $\beta$-carbonium ion formation, preventing $\Delta^9 \rightarrow \Delta^8$ isomerization, but seems to promote the $\gamma$-carbonium ion to give benzofuran products. This finding is unexpected, as normally sulfur stabilizes $\beta$- over $\gamma$-carbocations through the favored formation of three- over four-member sulfonium rings.[15] In the hope of decreasing benzofuran formation by steric hindrance, we increased the size of the aldehyde protecting group by synthesizing synthons **29a** and **29b**. However, these synthons did not increase the yield of the desired THC.

With the knowledge that the tertiary hydroxyl group was important, we decided to synthesize optically active **13**. Treatment of (*R*)-(+)-**22** (Scheme V) with *m*-CPBA, gave,

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

**Scheme VI**




regioselectively, the epoxide **24** in 87% yield. The lithium anion of 1,3-dithiane added regioselectively to the ketone **24** in a 1,2 fashion to give **25** as a mixture of stereoisomers (60% yield) which after reduction, furnished the synthon (4*R*)-**13** as a mixture of cis and trans isomers in 78% yield (41% overall from **22**). As with racemic **13**, the $\Delta^9$-cannabinoid formation with **6a** in the presence of pTSA, gave the $\Delta^9$-THC derivative (−)-**16a** and the abnormal product **17a**. Transformation to the $\Delta^9$-derivatives (−)-**2a**, (−)-**3a**, and (−)-**4a** was accomplished as described in the racemic series. In the 1′,1′-dimethylheptyl series (−)-**2c**, (−)-**3c**, and (−)-**4c** were also prepared. The enantiomeric purity of (−)-**2a** and (−)-**2c** was shown to be ≥99.5% by Marciniak, Charalambous, and Markriyannis.[23] They established this through the $^1H$ NMR spectra of the respective Mosher's[24] diesters for each enantiomer. Similarly (−)-limonene oxide was transformed to (4*S*)-**13** which led to metabolites (+)-**2c**, (+)-**3c**, and (+)-**4c** as described above for the (−) series.[18,19]

Finally, we also developed a shorter route to optically active synthon **13**. Our approach is based on the elegant work of Yoshikoshi et al.,[25] who reported the cyclobutane ring cleavage of (+)-3-methylnopinone, in high yield using $BF_3{\cdot}OEt_2/Zn(OAc)_2$, with almost no loss of stereochemical integrity. **30c** (Scheme VI) was prepared along with the cis isomer **30b** (20%) by treatment of (1*R*-(+)-nopinone (**30a**) with LDA followed by phenylselenyl bromide.[26] The stereochemistry of **30b** and **30c** was established by NOE studies. For **30b**, a NOE enhancement (4.5%) was observed between $H_a$ and the bridge methylene hydrogen cis to it. For isomer **30c**, a NOE enhancement (1%) between $H_b$ and one of the methyl groups of the geminal pair was observed. When compound **30b** was subjected to Yoshikoshi conditions,[25] the major product formed, **31** (70%), displayed a very low optical rotation value ($[\alpha]^{22}_D = -0.96°$

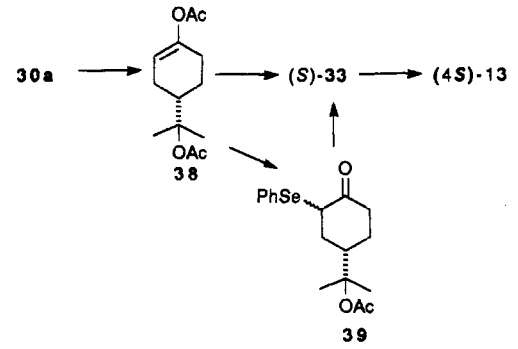
(23) These authors have informed us that the paper relating details on the synthesis, the NMR assignments, and the analyses will be published separately.

(24) Mosher, H. S.; Dale, J. A. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(25) (a) Kato, M.; Kamat, V. P.; Tooyama, Y.; Yoshikoshi, A. *J. Org. Chem.*, **1989**, *54*, 1536. (b) Kato, M.; Watanabe, M.; Vogler, B.; Tooyama, Y.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1990**, 1706.

(26) For the kinetic-controlled alkylation of nopinone to give exclusively *trans*-2-methylnopinone, see: Konopelski, J. P.; Djerassi, C. *J. Org. Chem.* **1980**, *45*, 2297.

**Scheme VII**




($c$ = 0.0396, MeOH). Base hydrolysis of the enol acetate functionality in compound **31** followed by an oxidation/elimination[27] sequence gave, via **32**, the enone (*S*)-**33** (40% yield, $[\alpha]^{22}_D$ = −0.62° ($c$ = 0.0567, MeOH). This was in contrast with the value of $[\alpha]^{22}_D$ = +58.76° ($c$ = 0.0573, MeOH) obtained for (*R*)-**33**. The latter was prepared from **24** by treatment with (i) $LiAlH_4$, (ii) PCC, and (iii) $Ac_2O$/DMAP/pyr. The observed optical rotation of (S)-**33** prepared above corresponds to an enantiomeric excess of only 1% and an almost complete loss of optical purity from the starting nopinone. The loss in optical activity was demonstrated to be due to a [1,3] shift of the phenylselenide group (**31a** ↔ **31b**) by deuterium labeling experiments (Scheme VI). Ketone **35**, prepared from labeled ketone **34**,[28] under Yoshikoshi conditions[25] gave a mixture of **36** and **37** in a ratio (by $^1H$ NMR integration of protons $H_c$ and $H_d$) of 1.17:1, clearly demonstrating the allyl phenylselenide shift presumably via a [1,3] sigmatropic rearrangement. Although this kind of 1,3-shift of allylic selenides[29] and racemization by allylic rearrangement of similarly constituted allylic esters[30] had been documented, this constitutes an interesting case of racemization in allylic selenides.

A shorter route was found to proceed *without* racemization (Scheme VII). Using the above conditions, **30a** was converted to **38** in good yield (70–85%). Treatment of **38** with allyl ethyl carbonate catalyzed by $Pd(OAc)_2$, bis(diphenylphosphino)ethane, and $n$-$Bu_3SnOMe$[31] gave the enone (*S*)-**33**. Compound (*S*)-**33** was determined to be 94% optically pure by comparison with (*R*)-**33**. This indicated no loss of optical purity from the starting nopinone.[32] Alternately, the enol acetate **38** was converted to the phenylseleno ketone **39** using silver trifluoroacetate and phenylselenyl bromide.[26] Following the oxidation/elmination sequence[27] **39** gave **33**. Reaction of an excess of 2-lithio-1,3-dithiane with enone **33** and subsequent $LiAlH_4$ reduction gave the desired terpenic synthon (4*S*)-**13** (82%, 46–59% overall yield from nopinone). Similarly, (1*S*)-(−)-nopinone was converted to (*R*)-**38** and to the corresponding synthon (4*R*)-**13**. Synthon (4*S*)-**13** was transformed to THC metabolites (+)-**2c**, (+)-**3c**, and (+)-**4c** without any loss in optical purity from the starting nopinone.

In summary, efficient processes are now at hand for the conversion of either limonene oxide (via perillaldehyde) or nopinone to the synthon **13**, which can be transformed into various $\Delta^9$-THC metabolites in both the (+) and (−) series. The pharmacological activity of these THC metabolites is showing interesting results. Tritiated (−)-**2c**, prepared by reacting (−)-**3c** with tritiated $NaBH_4$, is being used in binding studies of mouse brain homogenates.[3b] The new THC metabolites (−)-**2c**, (−)-**3c**, and (−)-**4c** are all very active compounds with (−)-**2c** being one of the most active THC derivatives tested.[3b]

## Experimental Section

All reagents were of commercial quality, reagent grade, and were used without further purification, except anhyd diethyl ether (ether), THF and $CH_3CN$, which were purchased (Aldrich) and used without purification. All reactions were carried out under $N_2$ atmosphere. Organic solutions were dried with $Na_2SO_4$. Melting points were determined on a Gallenkamp apparatus and are uncorrected. The IR spectra were obtained as films, KBr salts, or in $CCl_4$ solution. The NMR spectra were measured at 60, 300, or 400 MHz. The spectral data and TLC of optically active products were the same as reported for the corresponding racemic compounds. Optically active perillaldehyde was prepared by a slightly modified procedure of Tius et al.[22] In our hands, the intermediate Perillyl phenyl sulfoxide was a solid (mp 87–89 °C) and the crude could be recrystallized from hexane to give a white solid (mp 77–81 °C, ca. 90% pure) which was used in the subsequent step.

**(±)-4-(1-Hydroxy-1-methylethyl)cyclohex-2-enone (12).** A solution of the diene **8a** (25.33 g, 147 mmol) and methyl vinyl ketone (12.5 mL, 150 mmol) in 100 mL of anhyd benzene was refluxed for ca. 20 h. After the solution was cooled, the solvent was evaporated to yield 36.5 g of crude adduct **9**. It was dissolved in anhyd ether (160 mL), and a 3 M solution of $CH_3MgBr$ in ether (54 mL, 162 mmol) was added dropwise at 0 °C. After being stirred at rt for 1 h, the reaction was quenched with MeOH (20 mL) and then sat $NH_4Cl$ (50 mL). The mixture was extracted with ether, and the organic layers were washed with sat $NH_4Cl$, dried, and evaporated to give 36.0 g (95%) of crude **10**. A 1:1 mixture of cis and trans isomers was obtained which could be separated on silica gel ($R_f$ (cis)= 0.55, $R_f$ (trans) = 0.44): $^1H$ NMR (60 MHz, $CCl_4$, cis) 4.93 (d, 1 H, $J$ = 6 Hz), 3.87 (m, 1 H), 3.17 (s, 3 H), 2.93 (s, 1 H, $D_2O$ exchangeable), 1.07, 0.97 (2s, 6 H), 0.0 (s, 9 H); (trans) 4.67 (m, 1 H), 3.95 (m, 1 H), 3.80 (s, 1 H, $D_2O$ exchangable), 3.13 (s, 3 H), 0.97, 0.93 (2s, 6 H), 0.0 (s, 9 H). To crude **10** (36 g, 147 mmol) in reagent-grade ether[33] (450 mL) was added a solution of 2% $Cl_3CCOOH$ in $CCl_4$ (10 mL). The resulting solution was refluxed for 2 h, an additional portion of 2% $Cl_3CCOOH$ in $CCl_4$ (10 mL) was added, and refluxing continued for 3 h more. After the solution was cooled to rt, $Na_2CO_3 \cdot H_2O$ (15 g) was added and the mixture filtered. The solution was dried and evaporated. The residue was purified by chromatography on silica gel to give 15.9 g of **12** (71% from diene **8a**): IR ($CCl_4$) 3460, 1690, 1680, 1670 $cm^{-1}$; $^1H$ NMR (60 MHz, $CCl_4$) $\delta$ 7.18 (dt, 1 H, $J$ = 10, 2 Hz), 5.98 (dd, 1 H, $J$ = 10, 3 Hz), 3.13 (s, 1 H, $D_2O$ exchangable), 1.25 (s, 3 H), 1.15 (s, 3 H); HRMS $m/z$ ($M^+ - NH_4^+$) calcd for $C_9H_{18}NO_2$ 172.1338, found 172.1336.

**(±)-1-(1,3-Dithianyl)-4-(1-hydroxy-1-methylethyl)cyclohex-2-enol ((±)-13).** To 1,3 dithiane (3.30 g, 27 mmol) in anhyd THF (120 mL) at −30 °C was added a solution of 1.6 M nBuLi in hexanes (20 mL) dropwise. After the mixture was stirred at −30 °C (±10 °C) for 1.5 h, a solution of **12** (2.09 g, 13.5 mmol) in anhyd THF (20 mL) was added. The solution was warmed to rt and stirred for an additional 0.5 h. The solution was quenched with sat $NH_4Cl$ (100 mL) and extracted with ether. The ether extracts were washed with $H_2O$, dried, and evaporated. The residue was purified by chromatography with silica gel using 60% ethyl acetate/PE to give 2.49 g (66%) of (±)-**13** as a mixture of cis and trans isomers. The isomers could be separated by chro-

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(33) When anhydrous ether is used the tertiary hydroxyl eliminates.

matography. The major isomer (82%) was recrystallized from benzene, mp 117–118 °C: $^1$H NMR (60 MHz, $CDCl_3$) $\delta$ 6.02 (s, 2 H), 4.30 (s, 1 H), 2.93 (m, 4 H), 2.38 (s, 1 H, $D_2O$ exchangable), 1.67–2.33 (m, 5 H), 1.25 (s, 3 H), 1.22 (s, 3 H); HRMS *m/e* calcd for $C_{13}H_{22}S_2O_2$ 274.1061, found 274.1046. Anal. Calcd for $C_{13}H_{22}S_2O_2$: C, 56.88; H, 8.08; S, 23.38. Found: C, 56.76; H, 8.11; S, 23.39. Minor isomer (18%): $^1$H NMR (60 MHz, $CDCl_3$) $\delta$ 6.10 (d, 1 H, $J$ = 11 Hz), 5.93 (d, 1 H, $J$ = 11 Hz), 4.25 (s, 1 H), 2.93 (m, 4 H), 2.33–1.67 (m, 5 H), 1.25 (s, 3 H), 1.18 (s, 3 H).

**(±)-9-Normethyl-9-(1,3-dithianyl)-Δ$^9$-tetrahydrocannabinol ((±)-16a).** A solution of pTSA·$H_2O$ (80 mg, 0.42 mmol) and olivetol (**6a**) (847 mg, 4.70 mmol) in benzene (60 mL) was dried by azeotropic distillation (ca. 10 mL of benzene distilled). The reaction mixture was then cooled to 85 °C, and (±)-**13** (1.161 g, 4.16 mmol) was added as a warm solution in $CH_2Cl_2$ (5 mL) and benzene (10 mL). The mixture was then stirred at 85–90 °C (mild reflux) for 15 min. The mixture turned a dark blue. The solution was cooled in an ice bath and then added to a mixture of ether (50 mL) and 1 M NaOH (50 mL). The layers were separated, and the aqueous layer was extracted two times with ether. After the combined organic layers were washed once with 1 M NaOH, twice with $H_2O$, once with 1 M HCl, and once with brine, they were dried and the solvent was evaporated to give 1.4 g of an oil. This crude product was separated on silica gel (140 g, 20% EtOAc/PE) to give 260 mg (19% yield) of (±)-**16a**. When dissolved in $CH_2Cl_2$ and the solvent evaporated, (±)-**16a** was obtained as a light yellow foam: $R_f$ = 0.41 (20% EtOAc/hexanes);[34] mp 50–55 °C dec; $^1$H NMR (60 MHz, $CDCl_3$) $\delta$ 6.95 (br s, 1 H), 6.2 and 6.1 (2 br s, 2 H), 5.05 (br s, 1 H), 4.55 (s, 1 H), 3.0–2.7 (m, 4 H), 1.4 and 1.05 (2 s, 6 H). Anal. Calcd for $C_{24}H_{34}S_2O_2$: C, 68.85; H, 8.18; S, 15.32. Found: C, 68.76; H, 8.24; S, 15.40.

**(±)-11-Hydroxy-Δ$^9$-tetrahydrocannabinol ((±)-2a).** $BF_3$·$Et_2O$ (0.30 mL) was added to a mixture of HgO (277 mg) in 85% THF in $H_2O$ (4.8 mL). To the resulting suspension was added ±**13a** (241.4 mg, 0.5936 mmol) as a solution in THF (2 mL). The HgO gradually dissolved, and a red solution was formed. The reaction was stirred at rt for 1 h. The solvent was removed under a stream of $N_2$. The resulting residue was dissolved in ether and filtered through Celite under vacuum. The filtrate was washed with dil $NaHCO_3$, $H_2O$, 1 M HCl, and $H_2O$ and then dried and the solvent evaporated. The crude ±**3a** (160 mg, 80% yield) was obtained as a yellow/green film, $R_f$ = 0.41 (20% EtOAc/hexanes) and was used directly in the next reaction: IR ($CCl_4$) 3600–3200 (br), 2950, 2890, 1615, 1425, 1100 cm$^{-1}$; $^1$H NMR (60 MHz, $CDCl_3$) $\delta$ 9.40 (s, 1 H), 7.8 (br s, 1 H), 6.2 and 6.1 (2 br s, 2 H), 1.4 and 1.1 (2 s, 6 H). To $LiAlH_4$ (208 mg) in anhyd ether (15 mL) was added (±)-**3a** as a solution in ether (10 mL) dropwise. After the mixture was stirred at rt for 30 min, EtOAc followed by dil $NH_4Cl$ was added. The layers were separated, and the aqueous layer was extracted two times with ether. After the combined organic layers were washed once with dil $NH_4Cl$ and once with $H_2O$, they were dried and the solvent was evaporated to give 170 mg of an oil. This crude product was separated on silica gel (15 g, 50% EtOAc/hexanes) to give (±)-**2a** (91.8 mg, 53% yield). When dissolved in $CH_2Cl_2$ and the solvent evaporated, ±**2a** was obtained as a white solid: $R_f$ = 0.36 (50% EtOAc/hexanes); mp 101–103 °C; IR ($CCl_4$) 3700–3100 (br), 2950, 2890, 1650, 1425, 1090 (br) cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.67 (s, 1 H), 6.25 (s, 1 H), 6.11 (s, 1 H), 5.22 (br s, 1 H), 4.01 (br s, 2 H), 3.24 (br d, 1 H, $J$ = 10.8 Hz), 2.41 (d of d, 2 H, $J$ = 8.2, 6.0 Hz), 2.3–2.1 (m, 2 H), 2.0–1.9 (m, 1 H) 1.7–1.2 (series of m, 7 H), 1.40 (s, 3 H), 1.10 (s, 3 H), 0.86 (br t, 3 H, $J$ = 6.8 Hz); HRMS *m/e* calcd for $C_{21}H_{30}O_3$ 330.2195, found 330.2206.

**(±)-3-Norpentyl-3-(1′,1′-dimethylheptyl)-9-normethyl-9-(1,3-dithianyl)-Δ$^9$-tetrahydrocannabinol ((±)-16c).** A solution of pTSA·$H_2O$ (110 mg, 0.58 mmol) and **6c**[16] (1.526 g, 6.46 mmol) in benzene (100 mL) was dried by azeotropic distillation (ca. 15 mL distilled). The reaction mixture was then cooled to 45 °C, and ±**13** (1.612 g, 5.76 mmol) was added as a warm solution in $CH_2Cl_2$ (5 mL) and benzene (16 mL). The mixture was then stirred at 40–45 °C for 5 h. The mixture gradually turned a dark red. The solution was cooled in an ice bath and then added to a mixture of ether and 1 M NaOH (75 mL each). The layers were separated, and the aqueous layer was extracted two times with ether (75 mL). After the combined organic layers were washed once with 1 M NaOH, twice with $H_2O$, once with 1 M HCl, and once with brine, they were dried and the solvent was evaporated to give 3.0 g of an oil (two major spots by TLC). This crude product was separated on silica gel (150 g, first with 10% EtOAc/hexanes and then 40% EtOAc/hexanes) to give 1.18 g (43% yield) of (±)-**16c**.[35] When dissolved in $CH_2Cl_2$ and the solvent evaporated, (±)-**16c** was obtained as a light yellow foam: $R_f$ = 0.35 (20% EtOAc/hexanes); mp 64–68 °C dec; IR ($CCl_4$) 3450, 2950, 1625, 1575, 1425, 1325, 1275, 1080, 965 cm$^{-1}$; $^1$H NMR (60 MHz, $CDCl_3$) $\delta$ 6.95 (br s, 1 H), 6.3 and 6.2 (2 br s, 2 H), 5.05 (br s, 1 H, $D_2O$ exchangable), 4.50 (s, 1 H), 3.0–2.7 (m, 4 H), 1.35 and 1.15 (2 s, 6 H). Anal. Calcd for $C_{28}H_{42}S_2O_2$: C, 70.83; H, 8.92; S, 13.50. Found: C, 70.73; H, 8.94; S, 13.43.

**(±)-3-Norpentyl-3-(1′,1′-dimethylheptyl)-11-oxo-Δ$^9$-tetrahydrocannabinol ((±)-3c).** This compound was prepared as described above for ±**3a** and was obtained as a white solid (69%): mp 129–130 °C dec; IR ($CCl_4$) 3450, 2950, 1670, 1620, 1575, 1410, 1325, 1170, 1040, 960, 910 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.51 (s, 1 H), 7.95 (d, 1 H, $J$ = 1.8 Hz), 6.45 (d, 1 H, $J$ = 2 Hz), 6.33 (d, 1 H, $J$ = 2 Hz), 5.34 (br s, 1 H), 3.54 (m, 1 H), 2.6–2.3 (m, 2 H), 2.10–2.15 (m, 1 H), 1.85–1.0 (series of m, 12 H), 1.49 and 1.19 (2 s, 6 H), 1.24 (s, 6 H), 0.87 (t, 3 H, $J$ = 7 Hz). Anal. Calcd for $C_{25}H_{36}O_3$: C, 78.08; H, 9.41. Found: C, 77.90; H, 9.35.

**(±)-3-Norpentyl-3-(1′,1′-dimethylheptyl)-11-hydroxy-Δ$^9$-tetrahydrocannabinol ((±)-2c).** To a solution of (±)-**3c** (208 mg, 0.542 mmol) in absolute EtOH (7 mL) was added $NaBH_4$ (40 mg) in portions over 5 min. The reaction was stirred at rt for 1 h. The mixture was poured onto ether/$H_2O$. The aqueous layer was separated and extracted two times with ether. After the combined organic layers were washed twice with 1 M HCl and once with $H_2O$, they were dried and the solvent was evaporated to give 200 mg of an oil. This crude product was separated on silica gel (15 g, 60% ether/PE) to give 146 mg (70% yield) of (±)-**2c**. When dissolved in $CH_2Cl_2$ and the solvent evaporated (±)-**2c** was obtained as a white solid: mp 100–102 °C slight dec; IR ($CCl_4$) 3400 (br), 3000, 1425, 1340, 1050 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.70 (s, 1 H), 6.37 (d, 1 H, $J$ = 2 Hz), 6.24 (d, 1 H, $J$ = 2 Hz), 5.11 (br s, 1 H), 4.03 (br s, 2 H), 3.25 (br d, 1 H, $J$ = 11 Hz), 2.27 (m, 2 H), 1.98 (m, 1 H), 1.71 (m, 2 H), 1.5–1.00 (series of m, 11 H), 1.43 (s, 3 H), 1.11 (s, 3 H), 1.18 (s, 6 H), 0.83 (t, 3 H, $J$ = 6.9 Hz). Anal. Calcd for $C_{25}H_{38}O_3$: C, 77.68; H, 9.91. Found: C, 77.50; H, 9.99.

**(±)-9-Normethyl-9-(1,3-dithianyl)-Δ$^9$-tetrahydrocannabinol *tert*-Butyldimethylsilyl Ether.** A mixture of (±)-**16a** (870 mg, 2.14 mmol), TBDMSCl (1.0 g, 3 equiv) and imidazole (0.9 g, 6 equiv) in DMF (10 mL) was stirred at rt for 16 h. The solvent was removed under vacuum and the residue dissolved in ether/$H_2O$ (100 mL each). The aqueous layer was extracted with ether, and the combined organic layers were washed with 1 M HCl and $H_2O$. After drying ($Na_2SO_4$), the solvent was evaporated and the residue separated on silica gel (90 g, 5% EtOAc/PE) to give 683 mg (61%) of product: IR ($CCl_4$) 2900, 1610, 1560, 1450, 1425, 840 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.86 (br s, 1 H), 6.28 (s, 1 H), 6.20 (s, 1 H), 4.57 (s, 1 H), 3.15 (br d, 1 H, $J$ = 11 Hz), 2.85 (m, 4 H), 2.42 (m, 4 H), 2.2–1.5 (series of m, 6 H), 1.40 (s, 3 H), 1.06 (s, 3 H), 1.3 (m, 4 H), 1.02 (s, 9 H), 0.97 (m, 2 H), 0.89 (t, 3 H, $J$ = 7.0 Hz), 0.27 (s, 3 H), 0.17 (s, 3 H). Anal. Calcd for $C_{30}H_{48}O_2S_2Si$: C, 67.61; H, 9.08; S, 12.03. Found: C, 67.69; H, 9.13; S, 11.95.

**(±)-11-Oxo-Δ$^9$-tetrahydrocannabinol *tert*-Butyldimethylsilyl Ether ((±)-18a).** A mixture of the preceding product (198 mg, 0.38 mmol), $CH_3I$ (2 mL, 32 mmol), and $K_2CO_3$ (2.4 g) in DMF/$H_2O$ (92/8, 10 mL) was stirred at rt for 5 h. The mixture was poured onto ether/$H_2O$ (100 mL each) and further extracted with ether. The combined ether layers were washed with $H_2O$, dried, and evaporated. The residue (150 mg) was separated by preparative TLC (10% EtOAc/hexane) to obtain 102 mg (60% yield) of (±)-**18a**: IR ($CCl_4$) 2810, 2750, 1675, 1585, 1405, 1250, 1175, 1100, 1060, 835 cm$^{-1}$; $^1$H NMR (60 MHz, $CDCl_3$) $\delta$ 9.35 (s,

(34) Two other products were separated and tentatively identified, the abnormal THC product, **17**, $R_f$ = 0.30 (20% EtOAc/hexanes) and the ring opened diol product, **27**, $R_f$ = 0.10 (20% EtOAc/hexanes).

(35) None of the corresponding abnormal THC product was found.

1 H), 7.80 (br s, 1 H), 6.30 (d, 1 H, $J$ = 1 Hz), 6.35 (d, 1 H, $J$ = 1 Hz), 3.4 (br d, 1 H, $J$ = 10 Hz), 2.3–2.7 (m, 4 H), 2.0–0.8 (m, 12 H), 1.45 (s, 3 H), 1.15 (s, 3 H), 1.0 (s, 9 H), 0.3 (s, 3 H), 0.2 (s, 3 H). Anal. Calcd for $C_{27}H_{42}O_3Si$: C, 73.25; H, 9.56. Found C 73.26; H, 9.58.

**(±)-3-Norpentyl-3-(1′,1′-dimethylheptyl)-9-normethyl-9-(1,3-dithianyl)-$\Delta^9$-tetrahydrocannabinol *tert*-Butyldimethylsilyl Ether.** (±)-**16c** was silylated as described for **16a**: IR (neat) 2830, 1730, 1605, 1560 cm$^{-1}$; $^1$H NMR (60 MHz, $CDCl_3$) $\delta$ 6.9 (br s, 1 H), 6.35 (s, 2 H), 4.6 (s, 1 H), 3.4–3.0 (m, 5 H), 2.5–1.0 (m, 21 H), 1.4 (s, 3 H), 1.15 (s, 6 H), 1.0 (s, 9 H), 1.02 (s, 3 H), 0.25 (s, 3 H), 0.15 (s, 3 H). Anal. Calcd for $C_{39}H_{67}O_2S_2Si$: C, 69.33; H, 9.58; S, 10.89. Found: C, 69.26; H, 9.59; S, 10.80.

**(±)-3-Norpentyl-3-(1′,1′-dimethylheptyl)-11-oxo-$\Delta^9$-tetrahydrocannabinol *tert*-Butyldimethylsilyl Ether ((±)-18c).** The above dithiane was hydrolyzed as described for (±)-**16a**, 82% yield: mp 72.5–74.5 °C; IR ($CCl_4$) 2950, 2825, 1680, 1560, 1400, 1330, 1250, 1175, 1105, 1070, 835 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.46 (s, 1 H), 7.84 (br s, 1 H), 6.44 (d, 1 H, $J$ = 2 Hz), 6.40 (d, 1 H, $J$ = 2 Hz), 3.36 (dd, 1 H, $J$ = 11, 2 Hz), 2.52 (dd, 1 H, $J$ = 18, 6 Hz), 2.05 (m, 1 H), 2.35 (m, 1 H), 1.45 (s, 3 H), 1.22 (s, 3 H), 1.21 (s, 3 H), 1.14 (s, 3 H), 1.00 (s, 9 H), 1.8–1.0 (m, 12 H), 0.85 (t, 3 H, $J$ = 6.9 Hz), 0.30 (s, 3 H), 0.18 (s, 3 H). Anal. Calcd for $C_{30}H_{50}SiO_3$: C, 74.64; H, 10.10. Found: C, 74.64; H, 10.12.

**(*R*)-(+)-4-(2-Propenyl)-2-cyclohexen-1-one (22).** To (*R*)-(+)-perillaldehyde[22] (9.47 g, 63.09 mmol) and $Et_3N$ (18 mL) in $CH_2Cl_2$ (500 mL) at 0 °C was added TBSOTf (17 mL, 1.1 equiv) dropwise over 5 min. After being stirred at 0 °C for 30 min and then at rt for 15 min, the reaction mixture was worked up by pouring the mixture onto sat $NaHCO_3$. The layers were separated, and the aqueous layer was extracted once with $CH_2Cl_2$. The combined organic layers were dried, and the solvent was evaporated. The crude product **20** was used directly in the next reaction (assumed 100% yield): $^1$H NMR (60 MHz, $CDCl_3$) $\delta$ 6.1 (br s, 1 H), 5.9 (d of d, 1 H, $J$ = 10, 2 Hz), 5.05 (dd, 1 H, $J$ = 10, 3 Hz), 4.65 (br s, 2 H), 3.0–1.6 (m, 5 H), 1.65 (s, 3 H), 0.9 (s, 9 H), 0.1 (s, 6 H). To crude **20** (63.09 mmol) in ether (300 mL) with sat $NaHCO_3$ (300 mL) was added 85% MCPBA (14.3 g, 66 mmol) in portions over 5 min. The two phase mixture was stirred at rt for 0.5 h. The layers were separated and the aqueous layer extracted once with ether. The combined organic layers were dried and the solvent evaporated. The crude product **21** decomposed on silica gel and so was used directly in the next reaction (assumed 100% yield): $^1$H NMR (60 MHz, $CDCl_3$) $\delta$ 5.9 (dd, 1 H, $J$ = 10, 2 Hz), 5.1 (dd, 1 H, $J$ = 10, 2 Hz), 4.8 (s, 1 H), 4.75 (br s, 2 H), 3.0–1.0 (m, 5 H), 1.7 (s, 3 H), 0.95 (s, 9 H), 0.1 (s, 6 H). To a mixture of crude **21** (63 mmol), $CH_3CN$ (400 mL), and $NaIO_4$ (21.0 g, 98 mmol) were added concd HF (10 mL) and $H_2O$ (100 mL). Gradually, a white precipitate formed while stirring for 2 h at rt. The reaction was worked up by pouring onto $H_2O$ (800 mL) and extracting three times with ether (400 mL). The organic layers were dried and the solvent was evaporated to give a crude yellow oil which was chromatography on silica gel (750 g, 20% EtOAc/PE) to give 4.92 g (58% yield from **19**) of **22**: $R_f$ = 0.30 (20% EtOAc/hexanes); $[\alpha]^{26}_D$ = +192.2° ($c$ = 0.0162, $CH_3OH$);[36] IR (neat) 3300 (w), 2900, 1675, 1425, 1375, 1240, 1200, 955, 890, 850, 730 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.88 (dd, 1 H, $J$ = 10.2, 2.3 Hz), 6.06 (dd, 1 H, $J$ = 10, 2 Hz), 4.92 (d, 1 H, $J$ = 1 Hz), 4.80 (br s, 1 H), 3.06 (m, 1 H), 2.6–1.9 (m, 4 H), 1.82 (s, 3 H); HRMS $m/z$ ($M^+ - NH_4^+$) calcd for $C_9H_{16}NO$ 154.1231, found 154.1239.

**(4*R*)-1-(1,3-Dithianyl)-4-(2-propenylepoxy)-2-cyclohexen-1-ol (25).** To a solution of **22** (4.54 g, 33.3 mmol) in $CH_2Cl_2$ (350 mL) was added 85% MCPBA (7.4 g, 1.1 equiv) in portions. The solution was stirred for 10 h after which 10% aqueous $Na_2SO_3$ (1 mL) was added and the mixture was poured onto sat $NaHCO_3$ (300 mL). The layers were separated and the aqueous layer was extracted two times with $CH_2Cl_2$. After the combined organic layers were washed with sat $NaHCO_3$ and brine, they were dried and the solvent was evaporated to give 4.6 g of a light yellow oil. The crude product was separated on silica gel (100 g, 50% EtOAc/PE) to give 4.2 g (85% yield) of **24** as a mixture of two isomers (colorless oil): $R_f$ = 0.30 (50% EtOAc/hexanes); IR ($CCl_4$) 3300 (w), 2900, 1750 (m), 1617 (s), 1450, 1380, 915, 875 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) ca. 1:1 mixture of two isomers, $\delta$ 7.00 and 6.82 (2 m), 6.10 (m, 1 H), 2.7–1.8 (m, 7 H), 1.37 and 1.30 (2 d, 3 H, $J$ = 6.3 Hz). To 1,3-dithiane (3.46 g, 28.78 mmol, 1.05 equiv) in THF (150 mL) at −30 °C was added dropwise 1.6 M $n$-BuLi in hexanes (18.0 mL). The solution was stirred for 1.5 h at −35 to −25 °C. The reaction was quickly brought to rt, and a solution of **24** (4.17 g, 28.40 mmol) in THF (25 mL) was added quickly over 1 min. The mixture was stirred for 30 min at rt (longer reaction times led to lower yields). The reaction was worked up by pouring onto a dil $NH_4Cl$/ether mixture. The layers were separated and the aqueous layer was extracted two times with ether. After the combined organic layers were washed two times with $H_2O$ and once with brine, they were dried and the solvent was evaporated to give 7.0 g of a light yellow oil. The crude product was separated on silica gel (200 g, 50% EtOAc/PE) to give 4.2 g (60% yield) of **25** as a mixture of isomers (colorless oil):[37] $R_f$ = 0.39 (50% EtOAc/hexanes); $^1$H NMR (400 MHz, $CDCl_3$), 4 isomers in ratio of 0.4:0.4:0.1:0.1, $\delta$ 5.94 (s, 0.40 H), 6.1–5.8 (m, 1.2 H), 5.32 (s, 0.4 H), 4.29 (s, 0.4 H), 4.28 (s, 0.4 H), 4.24 (s, 0.2 H), 3.0–1.6 (m, 14 H), 1.35 (s, 1.2 H), 1.32 (s, 0.3 H), 1.31 (s, 1.2 H), 1.27 (s, 0.3 H). Anal. Calcd for $C_{13}H_{19}O_2S_2$: C, 57.31; H, 7.40; S, 23.54. Found: C, 57.32; H, 7.42; S, 23.45.

**(4*R*)-1-(1,3-Dithianyl)-4-(2-(2-hydroxypropanyl))-2-cyclohexen-1-ol ((4*R*)-13).** To $LiAlH_4$ (590 mg) in anhyd ether (100 mL) at 0 °C was added dropwise **25** (4.21 g, 15.5 mmol) as a solution in anhyd ether (50 mL). The mixture was stirred at rt for 1 h. The reaction was quenched by the addition of EtOAc and then dil $NH_4Cl$. The layers were separated, and the aqueous layer was extracted two times with ether. The combined organic layers were dried, and the solvent was evaporated to give 4.2 g of a colorless oil. The crude product was separated on silica gel (100 g, 60% EtOAc/PE) to give 3.30 g (78% yield) of (4*R*)-**13** as a mixture of cis and trans isomers (colorless oil): $R_f$ = 0.28 (60% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$, essentially same as ±**13** except ca. 0.7:0.3 ratio of isomers) $\delta$ 5.94 (m, 2 H), 4.29 (s, 0.7 H), 4.24 (s, 0.3 H), 2.91 (m, 4 H), 2.5–1.4 (5 m, 7 H), 1.25 (s, 2.1 H), 1.21 (s, 2.1 H), 1.24 (s, 0.9 H), 1.18 (s, 0.9 H).

**(−)-11-Hydroxy-$\Delta^9$-tetrahydrocannabinol ((−)-2a).** Prepared from (4*R*)-**13** as described for (±)-**2a** from (±)-**13**: mp 140.5–141.5 °C (lit.[38] mp 136.5–138 °C, $[\alpha]^{26}_D$ = −161.9° ($c$ = 0.0459, EtOH) [lit.[7d] $[\alpha]^{26}_D$ = −125° ($c$ = 0.26, EtOH)].

**(−)-3-Norpentyl-3-(1′,1′-dimethylheptyl)-11-oxo-$\Delta^9$-tetrahydrocannabinol ((−)-3c).** Prepared from (4*R*)-**13** as described for (±)-**3c** from (±)-**13**: mp 129–130 °C dec; $[\alpha]^{26}_D$ = −206° ($c$ = 0.0121, EtOH).

**(−)-3-Norpentyl-3-(1′,1′-dimethylheptyl)-11-hydroxy-$\Delta^9$-tetrahydrocannabinol ((−)-2c).** Prepared from (4*R*)-**13** as described for (±)-**3c**: mp 117.5–118.5 °C (slight dec.). $[\alpha]_D^{26}$ = −149.5° ($c$ = 0.0110, EtOH).

**(+)-3-Norpentyl-3-(1′,1′-dimethylheptyl)-11-oxo-$\Delta^9$-tetrahydrocannabinol ((+)-3c).** Prepared from (4*S*)-**13** as described for (±)-**3c** from (±)-**13**: mp 126–128° dec; $[\alpha]^{25}_D$ = +201° ($c$ = 0.0110, EtOH).

**(+)-3-Norpentyl-3-(1′,1′-dimethylheptyl)-11-hydroxy-$\Delta^9$-tetrahydrocannabinol ((+)-2c).** Prepared from (4*S*)-**13** as described for (±)-**3c**: mp 116–118 °C slight dec; $[\alpha]^{25}_D$ = +157° ($c$ = 0.0115, EtOH). Anal. Calcd for $C_{25}H_{38}O_3$: C, 77.68; H, 9.91. Found: C, 77.51; H, 9.87.

**(+)-3-Norpentyl-3-(1′,1′-dimethylheptyl)-11-nor-9-carboxy-$\Delta^9$-tetrahydrocannabinol ((+)-4c).** Prepared from (4*S*)-**13** via (+)-**18a** as previously described.[18] The material had spectral properties identical to those reported: mp 153–156 °C dec; $[\alpha]^{25}_D$ = +159° ($c$ = 0.0085, EtOH).

**(−)-1-Acetoxy-4-(2-acetoxy-2-methylethyl)cyclohex-1-ene ((4*S*)-38).** To (1*R*)-(+)-nopinone (**30a**) (4.07 g, 20 mmol) and $Zn(OAc)_2$ 6 g, 33 mmol) was added $Ac_2O$ (70 mL) and the mixture cooled to 0 °C. To the stirred mixture was added $BF_3$·$OEt_2$ (1.7 mL, 14 mmol) dropwise. The mixture was warmed to ca. 10 °C (±5 °C) and maintained at that temperature for 10 h. The

(36) The enantiomer of **22** has been prepared $[\alpha]^{26}_D$ = −153.8° (10.3 mg/mL, $CH_3OH$): Stevens, R. V.; Albizati, K. F. *J. Org. Chem.* **1985**, *50*, 632.

(37) A slower moving spot ($R_f$ = 0.17, 50% EtOAc/hexanes) was also isolated and was tentatively identified as the double addition product of 1,3-dithiane to both the ketone and epoxide (ca. 5% yield).

(38) Wall, M. E.; Brine, D. R.; Brine, G. A.; Pitt, C. G.; Freudenthal, H.; Christensen, D. *J. Am. Chem. Soc.* **1970**, *92*, 3466.

orange-colored solution was poured onto ice (ca. 200 g) and stirred for ca. 0.75 h. The mixture was extracted two times with ether, and the combined ethereal extracts were stirred (two times) with sat $NaHCO_3$. The organic layer was separated, washed once with $H_2O$ and brine, dried, and evaporated. Purification by flash chromatography (300 g silica gel, EtOAc/hexanes (1:4)) gave 3.92 g of (−)-**38**. Further purification (EtOAc/hexanes (1:9)) of impure fractions gave a further 1.6 g of product, combined yield 79%: $[\alpha]^{29.5}_D$ = −48.3° (*c* = 0.0325, EtOH); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.36 (m, 1 H), 2.34 (m, 1 H), 2.12 (s, 3 H), 2.14–1.85 (m, 6 H), 1.98 (s, 3 H), 1.47 and 1.45 (2s, 6 H). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.96; H, 8.39. Found: C, 65.07; H, 8.42.

**(−)-4-(2-Acetoxy-2-methylethyl)cyclohex-2-enone ((4*S*)-33).** To $Pd(OAc)_2$ (725 mg, 3.2 mmol), 1,2-bis(diphenylphosphino)-ethane (1.28 g, 3.2 mmol), and allyl ethyl carbonate (19.5 g, 150 mmol) was added (−)-**38** (14.47 g, 60 mmol) in anhyd $CH_3CN$ (570 mL) and the mixture stirred until homogeneous (10–20 min). Tri-*n*-butyltin methoxide (3.6 mL, 13 mmol) was then added and the mixture refluxed for 7 h. To the cooled mixture was added brine (600 mL) and the turbid mixture filtered through Celite and washed with ether. The organic layer was separated and the aqueous layer extracted with ether. The combined organic layers were washed with sat $NaHCO_3$ and brine and dried. Purification was effected by flash chromatography with silica gel (200 g) plus alumina (200 g, basic, Brockman I, placed on top of the silica gel) and eluted with EtOAC/hexanes (1:4). The fractions showing the main spot were combined and again chromatographed with silica gel (300 g) and alumina (300 g) as before. Following this procedure gave 8.06 g (68%, 91% based on recovered **38** (3.68 g)) of (4*S*)-**33**: $[\alpha]^{27}_D$ = −49° (*c* = 0.06015, EtOH); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.93 (dd, *J* = 10, 2 Hz, 1 H), 6.07 (dd, *J* = 10, 2 Hz, 1 H), 3.17 (m, 1 H), 2.44 (m, 2 H), 2.07 (m, 1 H), 1.78 (m, 1 H), 2.01 (s, 3 H), 1.50 (s, 3 H), 1.44 (s, 3 H). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.36; H, 8.29.

**1-(1,3-Dithianyl)-4-(2-hydroxy-2-methylethyl)cyclohex-2-enol ((4*S*)-13).** To 1,3-dithiane (15.5 g, 127 mmol) in anhyd THF(450 mL) at −30 °C was added, dropwise, a solution of 1.6 M nBuLi in hexanes (80 mL, 128 mmol). After the solution was stirred at −30 °C (±10 °C) for 1.5 h, a solution of **33** (8.06 g, 41 mmol) in anhyd THF (150 mL) was added. The solution was warmed to rt and stirred for an additional 0.5 h. The solution was quenched with sat $NH_4Cl$ (200 mL) and the organic layer separated. The aqueous layer was extracted with ether, and the combined organic solutions were washed with brine and dried. Evaporation under reduced pressure gave the crude product, which was dissolved in anhyd ether (300 mL), and $LiAlH_4$ (2 g) was added in several portions over 0.5 h. The mixture was allowed to warm to rt and stirred at that temperature for 3 h. The solution was then cooled to 0 °C and quenched with EtOAc (110 mL). After the solution was stirred for 0.25 h, sat $NH_4Cl$ was added and the mixture filtered through Celite. The Celite layer was washed with ether and the organic layer separated. The aqueous layer was extracted once with ether, and the combined organic solutions were washed with $H_2O$ and brine and dried. After evaporation, the crude product was chromatographed (silica gel, 120 g; EtOAc/PE (1:9) follwed by EtOAc/PE (3:2)) to yield 9.22 g (82%) of (4*S*)-**13**.

**3,3-Dideuterionopinone (34).**[28] To **30a** (2.5 g) was added $D_2O$ (4 mL) and anhyd $K_2CO_3$ (5 g) and the mixture heated at 65–70 °C for 4 days. The mixture was cooled, diluted with ether and extracted twice with ether. The combined ether extracts were washed with brine and dried. This procedure was repeated 4 more times with $D_2O$ (6 mL) and $K_2CO_3$ (5 g). The deuterium content as estimated by $^{13}$C NMR[39] was $d_2$ ca. 90%; $d_1$ ca. 10%.

**3-(Phenylselenenyl)nopinone (30b,c).** To a solution of LDA prepared from diisopropylamine (2.6 mL) and 1.6 M nBuLi (11.5 mL, 18.4 mL) in THF (50 mL) at −78 °C was added dropwise a solution of (+)-**30a** (2.32 g, 16.77 mmol) in THF (15 mL). After the solution stirred for 30 min at −78 °C, a solution of phenylselenenyl bromide (4.4 g, 18.8 mmol) in THF (15 mL) was added rapidly and, after 5 min, the solution was poured on $NH_4Cl$ solution, extracted twice with ether, washed with $H_2O$, dil $NaHCO_3$, and brine, and dried. Evaporation gave (4.5 g, 91%) of **30b,c** (0.7:0.3; trans/cis): $^1$H NMR (400 MHz, $CDCl_3$) δ 7.63 (m, 4 H), 7.30 (m, 6 H), 4.38 (dd, *J* = 11, 8 Hz, 0.3 H), 3.83 (dd, *J* = 10, 2 Hz, 0.7 H), 2.70 (m, 2 H), 2.56 (m, 3 H), 2.95 (m, 4 H), 1.84 (d, *J* = 11 Hz, 0.7 H), 1.5 (d, *J* = 10 Hz, 0.3 H), 1.32 and 1.29 (2 s, 6 H), 0.82 and 0.81 (2 s, 6 H). Anal. Calcd for $C_{15}H_{18}Se$: C, 61.21; H, 6.17. Found: C, 61.43; H, 6.30.

**2-Acetoxy-3-(phenylselenenyl)-5-(2-acetoxy-2-methylethyl)cyclohex-1-ene (31a,b).** Prepared as described above for **33** in 69% yield after chromatography (EtOAc/hexanes (1:4)); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.60 (m, 2 H), 7.29 (m, 3 H), 5.48 (m, 1 H), 4.10 (m, 1 H), 2.48–1.92 (m, 11 H), 2.05 (s, 3 H), 1.95 (s, 3 H), 1.42 (s, 3 H), 1.45 (s, 3 H). Anal. Calcd for $C_{19}H_{24}O_4Se$: C, 57.79; H, 6.28. Found: C, 58.74; H, 6.65.

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**Abbreviations:** dilute (dil), petroleum ether (PE), room temperature (rt), saturated (sat).

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