A crude phasing model was achieved by a multisolution weighted tangent formula approach. There was some difficulty in deducing a reasonable molecular fragment using these early $E$ syntheses. The scattering is dominated by the long hydrocarbon chain. The two largest normalized structure factors are the 402 (5.00) which defines the orientation of the long alkyl chain and the $80\bar{1}2$ (4.04) which defines the spacing along the chain. All attempts at deducing phases led to $E$ syntheses with infinite alkyl chains and little else. With the aid of model building we were able to select a correct fragment of this chain, and this eventually led to the correct structure. The important consideration turned out to be putting a "kink" in the structure which clustered all of the hydroxyl and carboxyl groups about a crystallographic twofold axis. Full-matrix least-squares refinements have currently converged to a standard crystallographic $R$ value of 0.074 for the observed data. Additional crystallographic material is available as supplementary material.

(17) All crystallographic calculations were done on a Prime 400 computer operated by the Materials Science Center and the Department of Chemistry, Cornell University. The principal programs used were as follows: REDUCE and UNIQUE, data reduction programs, M. E. Leonowicz, Cornell University, 1978; BLS, block-diagonal least-squares refinement, K. Hirotsu, Cornell University, 1978; ORFLS (modified), full-matrix least-squares, W. R. Busing, K. O. Martin, and H. S. Levy, Oak Ridge National Laboratory, Report ORNL-TM-305; ORTEP, crystallographic illustration program, C. Johnson, Oak Ridge National Laboratory, Report ORNL-3794; BOND, structural parameters and errors, K. Hirotsu, Cornell University, 1978; MULTAN-76, direct methods and fast fourier transform, G. Germain, P. Main, and M. Woolfson, University of York.

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**Registry No.** 1, 71582-80-4; 1 acetate, 71582-81-5; 2 (R′ = H), 71582-82-6; 2 (R′ = $CH_3$), 71582-83-7; 3, 71582-84-8; 5, 71582-85-9; 6, 71582-86-0; 7, 71582-87-1; 8, 71582-88-2; 9, 71582-89-3; 10, 71582-90-6; $Ac_2O$, 108-24-7.

**Supplementary Material Available:** Tables of atomic coordinates, thermal parameters, bond distances, bond angles (4 pages). Ordering information is given on any current masthead page.

# Acylation–Cycloalkylation. A New Annelation Route to Eudesmanes

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Condensation of vinylacetyl chloride (3) with 9-chloro-1-*p*-menthene (1) followed by distillation and chromatography gave 4*H*-7-(2′-chloro-1′-methylethyl)-4a,5,6,7,8,8a-hexahydro-4a-methyl-1-naphthalenone (4) (38% yield) and 2*H*-7-(2′-chloro-1′-methylethyl)-3,4,5,6,7,8-hexahydro-4-methyl-1-naphthalenone (9) (33% yield). Catalytic hydrogenation of 4, followed by ketalization, elimination of hydrogen chloride with potassium *tert*-butoxide in $Me_2SO$, and hydrolysis afforded 7-isopropenyl-4a-methyloctahydro-1-naphthalenone (16). Condensation of 16 with methylenetriphenylphosphorane afforded (+)-$\beta$-selinene (17) while reaction with methylmagnesium iodide yielded neointermedeol (18). The structure of ketone 9 was shown by conversion to occidol (22).

Acylation–cycloalkylation[1] provides an annelation route which, unlike the traditional Robinson synthesis,[2] yields a reactive carbonyl function adjacent to a newly created bridgehead position. Herein we illustrate the use of this annelation in the synthesis of the eudesmanes, $\beta$-selinene, and neointermedeol. The eudesmane sesquiterpenes are widely distributed in nature,[3] and their synthesis[4] and role in biosynthesis[5] have received considerable attention in recent years.

Our synthetic approach begins with chloride 1,[6] prepared from (+)-limonene (2) by hydroboration[7] followed by treatment of the resulting alcohol with triphenylphosphine and carbon tetrachloride.[8] Condensation of vinylacetyl chloride (3) with chloride 1 by using stannic chloride or aluminum chloride in methylene chloride under a variety of conditions gave negligible amounts of the desired conjugated ketone 4. By contrast, the reaction of 3 with 1-methylcyclohexene, 2,3-dimethyl-2-butene, and 2-methyl-2-butene under comparable conditions afforded ketones 5, 6, and 7 and 8, respectively, in moderate yield.

When the annelation was conducted in nitromethane with aluminum chloride, there was isolated by distillation and chromatography a 38% yield of ketone 4 and a 33%

(1) J. Wolinsky, R. Lau, J. J. Hamsher, and C. M. Cimarusti, *Synth. Commun.*, 2, 327 (1972); J. T. Valko and J. Wolinsky, *J. Org. Chem.*, 44, 1502 (1979).

(2) H. O. House, "Modern Synthetic Reactions", 2nd ed., W. A. Benjamin, Menlo Park, CA, 1972, pp 606, 621.

(3) Recent reports on the isolation of eudesmanes from natural sources include: J. Gavin, G. Nicollier, and R. Tabacchi, *Helv. Chim. Acta*, 61, 352 (1978); B. M. Lawrence and J. W. Hogg, *Phytochemistry*, 12, 2995 (1973), S. G. Agarwal, V. N. Vashist, and C. K. Atal, *ibid.*, 13, 2024 (1974); M. Miyakado, T. Kato, N. Ohno, and T. J. Mabry, *ibid.*, 15, 846 (1976); T. C. Jain and R. J. Striha, *ibid.*, 15, 847 (1976); F. Bohlmann and P. K. Mahanta, *ibid.*, 17, 1189 (1978).

(4) J. A. Marshall, M. T. Pike, and R. D. Carroll, *J. Org. Chem.*, 31, 2933 (1966); D. C. Humber, A. R. Pinder, and R. A. Williams, *ibid.*, 32, 2335 (1967); C. H. Heathcock and T. R. Kelley, *Tetrahedron*, 24, 1801 (1968); J. W. Huffman and M. L. Mole, *J. Org. Chem.*, 37, 13 (1972); R. G. Carlson and E. G. Zey, *ibid.*, 37, 2468 (1972); R. B. Miller and R. D. Nash, *ibid.*, 38, 4424 (1973); G. H. Posner, G. L. Loomis, and H. S. Sawaya, *Tetrahedron Lett.*, 1373 (1975); O. P. Vig, M. L. Sharma, R. Anand, and S. D. Sharma, *J. Indian Chem. Soc.*, 53, 81 (1976); J. L. Cooper and K. E. Harding, *Tetrahedron Lett.*, 3321 (1977); S. R. Wilson and D. T. Mao, *J. Am. Chem. Soc.*, 100, 6289 (1978).

(5) S. S. Martin, J. H. Langenheim, and E. Zavarin, *Phytochemistry*, 15, 113 (1976); W. Parker, J. S. Roberts, and R. Ramage, *Q. Rev., Chem. Soc.*, 21, 331 (1967).

(6) Attempts to perform the annelation reaction on *p*-menthenes functionalized (OAc, $OCH_3$, Cl, $OSiMe_3$) at the 8-position failed due to cleavage of these tertiary derivatives by the Lewis acid.

(7) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, 83, 1241 (1961).

(8) I. M. Downie, J. B. Holmes, and J. B. Lee, *Chem. Ind. (London)*, 900 (1966); J. Hooz and S. S. H. Gilani, *Can. J. Chem.*, 46, 86 (1968); R. G. Weiss and E. I. Snyder, *J. Org. Chem.*, 36, 403 (1971).

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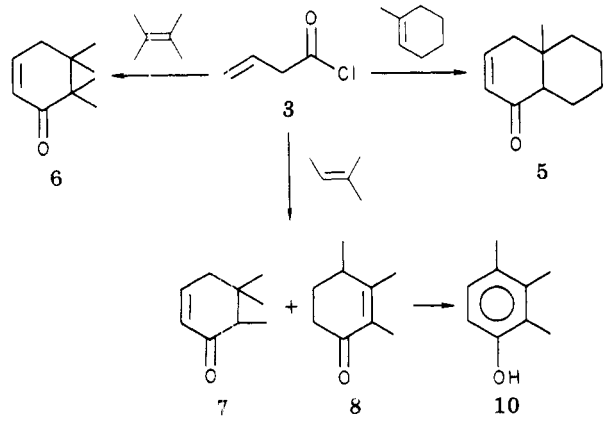
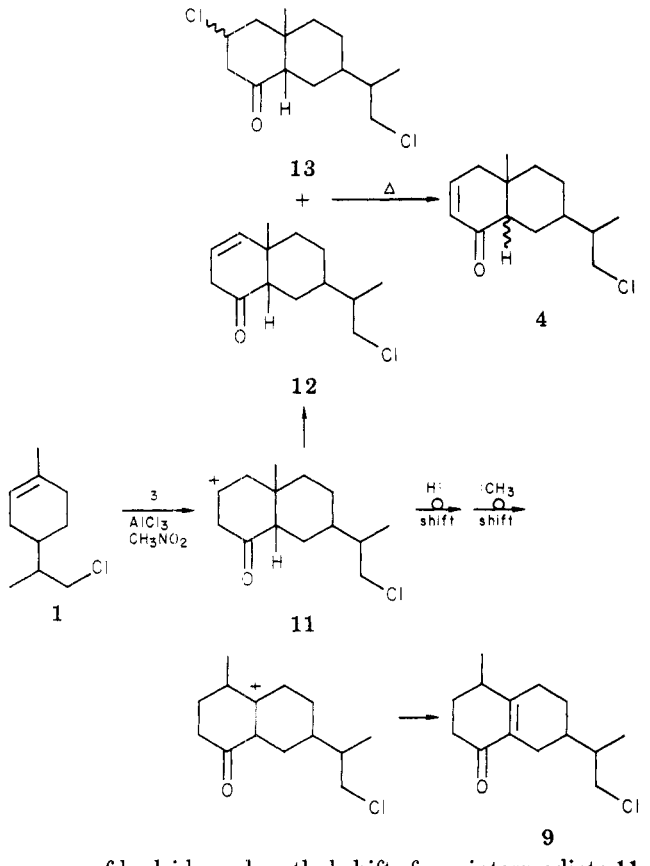


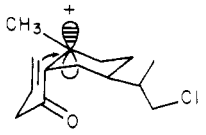
yield of ketone **9**. Ketone **9** most likely forms by a sequence of hydride and methyl shifts from intermediate **11**. 2,3,4-Trimethyl-2-cyclohexenone (**8**), which becomes the major product from the reaction of **3** with 2-methyl-2-butene when the reaction is carried out in nitromethane, must form by a similar sequence of events. The structure of ketone **8** was demonstrated by spectral comparison[9a] and by aromatization to 2,3,4-trimethylphenol (**10**).[10]



NMR spectral examination of the crude condensation product of vinylacetyl chloride (**3**) with chloride **1** indicated the absence of the desired ketone **4** and the presence, instead, of cis $\beta,\gamma$-unsaturated ketone **12** (5.7 ppm) containing a small amount of $\beta$-chloro ketone **13** (4.2 ppm). Distillation of the crude reaction product brought about dehydrochlorination of $\beta$-chloro ketone **13**, conjugation of $\beta,\gamma$-unsaturated ketone **12**, as well as partial epimerization of the bridgehead methyne, giving conjugated ketone **4** as a mixture of the cis and trans ring-fused isomers.

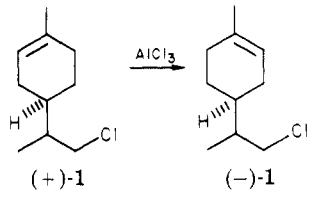
Comparison of the bridgehead methyl resonances of **12** (1.16 ppm) and **4** (1.10 and 0.84 ppm) with those of the C-19 methyl of 5$\alpha$- and 5$\beta$-4-oxo steroids[11] suggests a cis ring fusion for **12** and a cis and trans mixture for **4**. Equilibration of **4** with sodium methoxide resulted in the predominant formation of the more stable trans isomer showing the upfield signal at 0.84 ppm. The cis relationship of the bridgehead methyl to the chloroisopropyl group was established by the subsequent conversion of **4** to $\beta$-selinene.

The stereochemistry of the annelation reaction is viewed as a consequence of initial axial approach of the acylium ion derived from **3** to the carbon–carbon double bond of **1** in its most stable conformation (chloroisopropyl group pseudoequatorial) resulting in cation **14**. Subsequent



cycloalkylation from the same face of the molecule (trans addition is impossible without a conformational change) results in a cis ring fusion and fixes the newly formed bridgehead methyl with a cis relationship to the chloroisopropyl group.

Catalytic hydrogenation of $\alpha,\beta$-unsaturated ketone **4** proceeded quantitatively to give ketone **15** containing a small amount of the cis fused isomer. Ketalization of **15** with ethylene glycol and dehydrochlorination with *tert*-butoxide in $Me_2SO$ followed by hydrolysis afforded an 85% yield of ketone **16** containing ca. 10% of the cis-fused isomer. The Wittig reaction of ketone **16** with methylenetriphenylphosphorane in $Me_2SO$[12] gave (+)-$\beta$-selinene (**17**) in 77% yield. GLC-purified $\beta$-selinene showed an optical rotation of +21.5°,[13] suggesting some racemization of **1** had occurred in the original annelation reaction.[14]



Addition of methylmagnesium iodide to ketone **16**[15] (freed of the cis isomer by column chromatography) afforded neointermedeol (**18**) in 90% yield. The NMR and IR spectra of **18** were identical with those of an authentic sample.[16,17]

(9) (a) K. A. Ananthanarayan and T. S. Sorensen, *Can. J. Chem.*, **50**, 3550 (1972); (b) J. M. Coxon, R. P. Garland, and M. P. Hartshorn, *Aust. J. Chem.*, **23**, 2531 (1970).

(10) (a) K. v. Auwers and F. Wieners, *Chem. Ber.*, **58**, 2815 (1925); (b) D. D. Shrewsbury, *Spectrochim. Acta*, **16**, 1294 (1960); (c) T. Banwell, C. S. Morse, P. C. Myhre, and A. Vollmar, *J. Am. Chem. Soc.*, **99**, 3042 (1977).

(11) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, 1964, p 19.

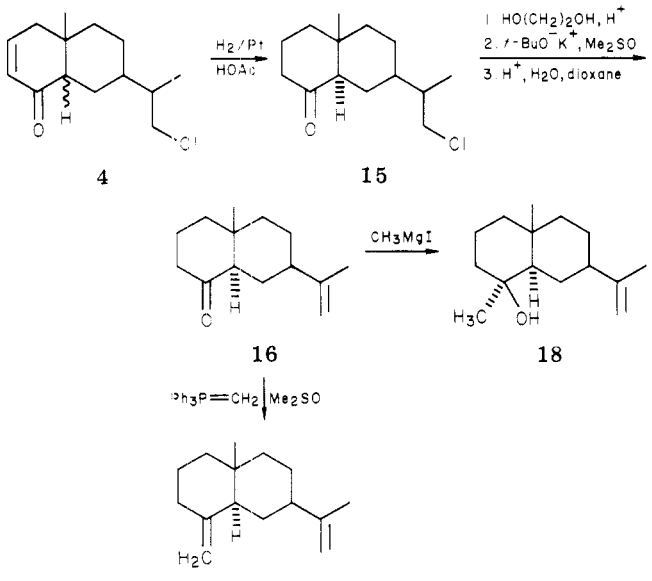
(12) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963). Although the Wittig reaction was performed on the epimeric mixture, the selinene produced was exclusively trans fused. For an example of such selectivity in the Wittig reaction of a related decalone see Marshall, et al.[4]

(13) Natural $\beta$-selinene shows $[\alpha]_D$ +43°: C. Ganter and B. Keller-Wojtkiewicz, *Helv. Chim. Acta*, **54**, 183 (1971).

(14) The extent of olefin **1** isomerization appears to vary from 20–40%, affording products which are 40–80% racemic. The use of the aluminum chloride complex of the unsaturated acid which was found to minimize olefin isomerization in earlier work[1] failed here since the acid chloride **3** underwent isomerization and led to products derived from crotonyl chloride.

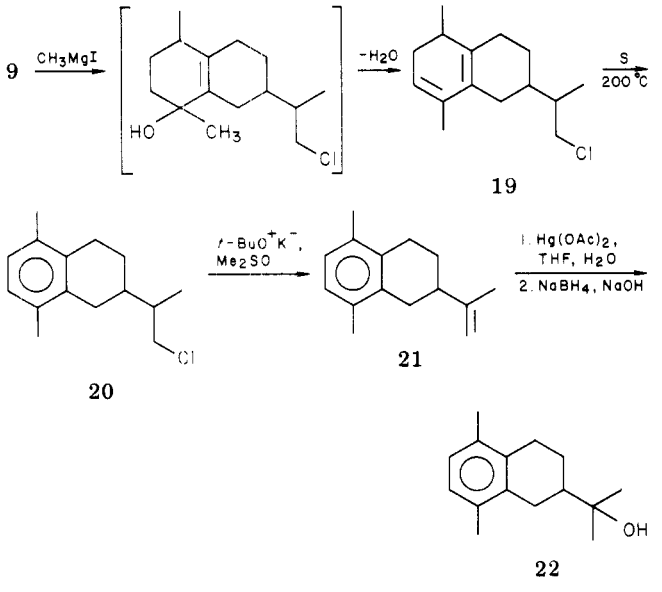
(15) V. B. Zalkow, A. M. Shaligram, and L. H. Zalkow, *Chem. Ind. (London)*, 194 (1964).

(16) Spectra of authentic neointermedeol were graciously provided by Professor L. H. Zalkow.




4 15 16 18 17

We turn finally to ketone **9** whose structure was established by conversion to (+)-occidol (**22**). Addition of methylmagnesium iodide to ketone **9** was accompanied by dehydration in the workup, giving diene **19** in 72% yield.




19 20 21 22

Heating **19** with sulfur brought about the aromatization of the diene to the tetrahydronaphthalene **20** in 76% yield. Absorption at 12.4 $\mu$ in the IR spectrum of **20** is assigned to two adjacent hydrogens on a benzene ring, confirming the suspected para relationship of the ring methyl groups. Dehydrochlorination of **20** with *tert*-butoxide in $Me_2SO$ gave **21** in 86% yield. Oxymercuration–demercuration[18] of **21** proceeded in 66% yield to afford (+)-occidol (**22**).[19]

## Experimental Section

**General Procedure for the Lewis Acid Catalyzed Reaction of Vinylacetyl Chloride (3) with Olefins.** To 23 mmol of the Lewis acid catalyst in 100 mL of $CH_2Cl_2$ in a three-necked flask fitted with an addition funnel and a sintered-glass nitrogen bubbling tube was added dropwise over 1.5 h a solution of 21.5 mmol of vinylacetyl chloride and 43 mmol of the olefin in 75 mL of $CH_2Cl_2$. The mixture was stirred an additional 2 h before 100 mL of saturated NaCl solution was added. The layers were separated, and the organic phase was washed with 5% HCl, saturated $NaHCO_3$, and $H_2O$. The solution was dried ($MgSO_4$) and concentrated, and the products were isolated by distillation.

**5,5,6,6-Tetramethyl-2-cyclohexenone (6).** The reaction of 5.9 mL (50 mmol) of 2,3-dimethyl-2-butene with 2.25 g (21.5 mmol) of vinylacetyl chloride (**3**) and 3.1 g (23 mmol) of $AlCl_3$ yielded on distillation 1.17 g of a semicrystalline mass, bp 43–73 °C (0.35 mm). Preparative GLC on 20% DC-200 afforded ketone **6** (36% yield by GLC): IR ($CHCl_3$) 3.40, 5.96, 6.80, 7.21, 7.78, 8.54, 9.00 $\mu$; NMR ($CDCl_3$) 0.96 (s, 6, $C(CH_3)_2$), 1.03 (s, 6, $C(CH_3)_2$), 2.19–2.31 (m, 2, $CH_2$), 5.85–6.04 (m, 1, OCCH=), 6.60–6.84 ppm (m, 1, OCC=CH).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 79.10; H, 10.67.

**5,5,6-Trimethyl-2-cyclohexenone (7) and 2,3,4-Trimethyl-2-cyclohexenone (8).** The reaction of 5.3 mL (50 mmol) of 2-methyl-2-butene with 2.25 g (21.5 mmol) of vinylacetyl chloride and 3.1 g (23 mmol) of $AlCl_3$ yielded two fractions on distillation: 1.79 g, bp 49–85 °C (0.05 mm), and 0.33 g, bp 85–125 °C (0.05 mm). Preparative GLC on 20% DC-200 yielded two components: ketone **7**[9b] (32% yield by GLC); IR (neat) 3.40, 5.93, 6.81, 7.18, 7.28, 8.11, 12.17, 13.6 $\mu$; NMR ($CDCl_3$) 0.91 and 1.07 (2 s, 6, $C(CH_3)_2$), 1.06 (d, 3, $J$ = 7 Hz, $CH_3$), 5.83–6.11 (m, 1, OCCH=), 6.61–7.00 ppm (m, 1, OCC=CH); ketone **8**[9a] (11% yield by GLC) showed UV $\lambda_{max}$ (MeOH) 246 nm (log $\epsilon$ 3.98); IR (neat) 3.40, 6.04, 7.29, 11.05 $\mu$; NMR ($CDCl_3$) 1.20 (d, 3, $J$ = 7 Hz, $CH_3$), 1.77 (s, 3, OCC=$CCH_3$), 1.93 (s, 3, OCC($CH_3$)=), 1.99–2.66 ppm (m, 5, CH).

**4*H*-4a,5,6,7,8,8a-Hexahydro-4a-methyl-1-naphthalenone (5).** The reaction of 5.23 g (50 mmol) of vinylacetyl chloride, 9.60 g (0.10 mmol) of 1-methylcyclohexene, and 13.04 g (50 mmol) of anhydrous $SnCl_4$ yielded two fractions on distillation: 1.85 g, bp 65–95 °C (0.1 mm), and 2.02 g, bp 96–140 °C (1.0 mm). Column chromatography (silica gel, 10% ether/pentane) yielded ketone **5** (27% yield by GLC): IR (neat) 3.40, 5.93, 6.90, 7.20, 8.00, 8.24, 12.7, 12.8, 13.3 $\mu$; NMR ($CDCl_3$) 0.92 (s, $CH_3$, trans isomer), 1.00 (s, $CH_3$, cis isomer), 6.0 (d, 1, $J$ = 12 Hz, OCCH=), 6.7–7.0 ppm (m, 1, OCC=CH).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.42. Found: C, 80.16; H, 9.98.

**Reaction of Vinylacetyl Chloride (3) with 2-Methyl-2-butene in Nitromethane.** The reaction of 2.25 g (21.5 mmol) of vinylacetyl chloride with 3.5 g (5.0 mmol) of 2-methyl-2-butene and 3.1 g (23 mmol) of $AlCl_3$ was carried out in nitromethane. Half an hour was allowed for the addition, and 5 additional min of stirring was allowed prior to workup. Distillation afforded 1.27 g of product, bp 30–35 °C (0.1 mm). GLC analysis on a 20% DC-200 column revealed the distillate to be a 1:3 mixture of ketone **7** (11% yield by GLC) and ketone **8** (30% yield by GLC).

**2,3,4-Trimethylphenol (10).** A solution of 0.312 g (2.26 mmol) of ketone **8** in 15 mL of xylene was refluxed over 0.2 g of 10% Pd/C for 18 h. After filtration the solution was extracted twice with 10 mL of 3 N NaOH. The extract was washed with ether, acidifed with concentrated HCl, and extracted with four 10-mL portions of ether. The combined ether extracts were dried ($MgSO_4$), and the solvent was evaporated to give 0.183 g (60% yield) of 2,3,4-trimethylphenol (**10**)[10] which after recrystallization from hexane showed the following: mp 78.1–79.2 °C (lit.[10a] mp 81 °C); IR ($CS_2$) 2.98, 3.42, 7.65, 7.83, 8.16, 8.45, 8.61, 9.24, 9.47, 12.32, 12.54, 13.53 $\mu$; NMR ($CDCl_3$) 2.1–2.2 (3 s, 9, $ArCH_3$), 4.8–5.0 (br s, 1, OH), 6.46 (d, 1, $J$ = 8 Hz, ArH), 6.80 ppm (d, 1, $J$ = 8 Hz, ArH).

**9-Chloro-1-*p*-menthene (1).** A solution of 33.1 g (0.215 mol) of 1-*p*-menthen-9-ol,[7] 56.3 g (0.215 mol) of triphenylphosphine, and 20.7 mL (0.215 mol) of $CCl_4$ in 75 mL of $CH_2Cl_2$ was stirred at room temperature for 64 h. After removal of the solvent 200 mL of pentane was added, and the mixture was filtered. Rotary evaporation and distillation of the filtrate yielded 26.0 g (70% yield) of 9-chloro-1-*p*-menthene (**1**),[20] $[\alpha]_D$ +86.4° (*c* 12.49, hexane);

(17) Carefully purified synthetic neointermedeol exhibited an optical rotation of −1.2°. A value of +7.5° was reported for the natural alcohol. We presently have no explanation for this discrepancy.

(18) H. C. Brown and P. Geoghegan, Jr., *J. Am. Chem. Soc.*, **89**, 1522 (1967).

(19) (a) Y. Hirose and T. Nakatsuka, *Bull. Agric. Chem. Soc. Jpn.*, **23**, 143 (1959); (b) *ibid.*, **23**, 253 (1959); (c) T. Ho, *Can. J. Chem.*, **50**, 1098 (1972).

(20) 1-*p*-Menthen-9-ol[21] and 9-chloro-1-*p*-menthene (**1**) are mixtures of diastereoisomers.

bp 35–37 °C (0.1 mm); IR (neat) 3.45, 6.97, 7.29, 12.55, 13.7 μ; NMR ($CDCl_3$) 0.97 (d, 3, $J$ = 6 Hz, $CH_3$), 1.62 (s, 3, $=CCH_3$), 3.52 (d, 2, $J$ = 8 Hz, $CH_2Cl$), 5.2–5.45 (m, 1, =CH).

**4*H*-7-(2′-Chloro-1′-methylethyl)-4a,5,6,7,8,8a-hexahydro-4a-methyl-1-naphthalenone (4) and 2*H*-7-(2′-Chloro-1′-methylethyl)-3,4,5,6,7,8-hexahydro-4-methyl-1-naphthalenone (9).** To 16.2 g (0.12 mol) of $AlCl_3$ in 200 mL of $CH_3NO_2$ in a three-necked flask fitted with an addition funnel and a sintered-glass nitrogen bubbling tube were added dropwise over 0.5 h 10.5 g (61 mmol) of 9-chloro-1-*p*-menthene (1) and 9.54 g (91 mmol) of vinylacetyl chloride in 40 mL of $CH_3NO_2$. After the mixture was stirred for an additional 5 min, workup in the usual manner and distillation yielded 11.1 g of yellow oil, bp 122–147 °C (0.3 mm). Column chromatography (silica gel, gradient elution using ether/pentane) afforded 5.50 g (38% yield) of ketone **4**: $[\alpha]_D$ +6.74° (*c* 1.513, hexane); IR (neat) 3.40, 5.92, 6.92, 7.20 μ; NMR ($CDCl_3$) 0.84 (s, $CH_3$, trans isomer), 1.01 (d, 3, $J$ = 6 Hz, $CH_3$), 1.10 (s, $CH_3$, cis isomer), 3.52 (d, 2, $J$ = 6 Hz, $CH_2Cl$), 5.96 (d, 1, $J$ = 10 Hz, OCCH=), 6.68–6.91 ppm (m, 1, OCC=CH); mass spectrum, $m/e$ (rel intensity) 242 (3), 240 (8), 225 (32), 109 (44), 107 (21), 97 (20), 95 (47), 86 (62), 84 (100), 79 (23), 68 (54), 67 (24), 55 (27), 49 (26), 47 (32), 41 (40), 39 (24). Later fractions contained 4.87 g (33% yield) of ketone **9**: UV $\lambda_{max}$ (EtOH) 247 nm (log ε 4.3); IR (neat) 3.40, 6.00, 6.10, 6.87, 7.22, 7.91, 8.32, 13.7 μ; NMR ($CDCl_3$) 1.06 (d, 3, $J$ = 6 Hz, $CH_3$), 1.16 (d, 3, $J$ = 7 Hz, $CH_3$), 3.61 ppm (d, 2, $J$ = 5 Hz, $CH_2Cl$); mass spectrum, $m/e$ (rel intensity) 142 (5), 140 (13), 163 (77), 107 (25), 105 (23), 103 (23), 95 (28), 93 (22), 91 (48), 79 (45), 77 (43), 68 (50), 67 (27), 65 (20), 55 (45), 53 (37), 51 (27), 43 (43), 41 (100), 39 (55).

Anal. Calcd for $C_{14}H_{21}ClO$: C, 69.84; H, 8.79; Cl, 14.72. Found for ketone **4**: C, 69.67; H, 9.02; Cl, 14.80. Found for ketone **9**: C, 69.65; H, 8.81; Cl, 14.80.

**7-(2′-Chloro-1′-methylethyl)-4a-methyloctahydro-1-naphthalenone (15).** A solution of 2.50 g (10.4 mmol) of ketone **4** in 30 mL of glacial acetic acid was stirred over 0.1 g of Pt (from $PtO_2$) until 260 mL of $H_2$ had been absorbed. After filtration, 50 mL of $H_2O$ was added, and the mixture was extracted with four 25-mL portions of pentane. The combined extracts were washed successively with $H_2O$, saturated $NaHCO_3$, and $H_2O$. After the extracts were dried ($MgSO_4$), rotary evaporation yielded 2.49 g (99% yield) of ketone **15**. An analytical sample was obtained by preparative TLC (silica gel, ether/pentane): IR (neat) 3.40, 5.80, 6.80, 6.90, 7.20, 13.6 μ; NMR ($CDCl_3$) 0.72 (s, 3, $CH_3$), 0.98 (d, 3, $J$ = 7 Hz, $CH_3$), 3.50 ppm (d, 2, $J$ = 6 Hz, $CH_2Cl$); mass spectrum, $m/e$ (rel intensity) 244 (2), 242 (6), 199 (24), 111 (100), 109 (22), 98 (30), 95 (26), 93 (21), 81 (34), 79 (26), 77 (21), 68 (25), 67 (49), 55 (65), 53 (33), 43 (21), 41 (96), 39 (41).

Anal. Calcd for $C_{14}H_{23}OCl$: C, 69.26; H, 9.55; Cl, 14.60. Found: C, 69.33; H, 9.82; Cl, 14.88.

**7-Isopropenyl-4a-methyloctahydro-1-naphthalenone (16).** A solution of 2.29 g (9.4 mmol) of ketone **15**, 0.1 g of *p*-toluenesulfonic acid, and 5 mL of ethylene glycol in 15 mL of benzene was refluxed for 18 h under a Soxhlet extractor containing 5 Å molecular sieves. The mixture was washed with $H_2O$ and saturated $NaHCO_3$ and dried ($MgSO_4$).

The solvent was removed, and the residue was stirred at 80 °C for 20 h with 3 g (27 mmol) of potassium *tert*-butoxide in 30 mL of $Me_2SO$. The mixture was poured into 30 mL of 5% HCl and was extracted with four 10-mL portions of pentane. The solvent was removed, and the residue was stirred with 5 mL of 5% HCl and 10 mL of dioxane for 2 h. Water (20 mL) was added, and the mixture was extracted with four 10-mL portions of pentane. The combined extracts were washed with water, dried ($MgSO_4$), and distilled to yield 1.66 g (85% yield) of ketone **16**, bp 81–87 °C (0.2 mm). An analytical sample of **16** was prepared by preparative TLC (silica gel, ether/pentane): $[\alpha]$ +3.74° (*c* 1.418, hexane); IR (neat) 3.40, 5.82, 6.08, 6.90, 11.3 μ; NMR ($CDCl_3$) 0.76 (s, 3, $CH_3$), 1.70 (s, 3, $=CCH_3$), 4.70 ppm (br s, 2, $=CH_2$); mass spectrum, $m/e$ (rel intensity) 216 (27), 191 (17), 134 (18), 111 (26), 106 (22), 93 (27), 91 (24), 81 (25), 79 (34), 77 (26), 68 (29), 67 (50), 55 (63), 53 (49), 43 (24), 42 (30), 41 (100), 40 (21), 39 (71). A small amount of the cis fused isomer was isolated from the product by column chromatography (silica gel, ether/pentane): IR (neat) 3.40, 5.80, 6.09, 6.90, 11.3 μ; NMR ($CDCl_3$) 1.12 (s, 3, $CH_3$), 1.73 (s, 3, $=CCH_3$), 4.70 ppm (s, 2, $=CH_2$).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.63; H, 11.02.

**(+)-β-Selinene (17).** A 6.0-mL aliquot of a 1.2 M solution of methylsulfinyl carbanion in $Me_2SO$[12] was placed via syringe into a 50-mL flask maintained under positive $N_2$ pressure. A solution of 3.5 g (9.8 mmol) of methyltriphenylphosphonium bromide in 10 mL of $Me_2SO$ was added via syringe and after 5 min was followed by 1.42 g (6.9 mmol) of ketone **16** in 5 mL of $Me_2SO$. The solution was stirred at 80 °C for 65 h, cooled, and poured into an equal volume of $H_2O$. The mixture was extracted with four 10-mL portions of pentane, and the combined pentane extracts were washed twice with 10 mL of 50% $Me_2SO/H_2O$ and three times with 10 mL of $H_2O$. After the product was dried ($MgSO_4$) and rotary evaporated, the product was adsorbed onto a short silica gel column and eluted with 400 mL of pentane. The pentane was removed to yield 1.07 g (77%) of (+)-β-selinene (**17**).[13] An analytical sample was prepared by preparative GLC on a 5% SE-30 column: $[\alpha]_D^{25}$ +21.5° (*c* 6.52, hexane); IR (neat) 3.25, 3.42, 6.10, 6.97, 7.27, 11.4 μ; NMR ($CCl_4$) 0.71 (s, 3, $CH_3$), 1.70 (s, 3, $=CCH_3$), 4.41 (s, 1, vinyl H) and 4.68 (s, 3, vinyl H).

**Neointermedeol (18).** A solution of 0.412 g (2 mmol) of ketone **16** (previously freed of the cis-fused isomer by column chromatography) in 15 mL of ether was added via syringe over 1–2 min to an ice-cooled solution of methylmagnesium iodide (prepared from 0.592 g of methyl iodide and 0.1 g of Mg) in 15 mL of ether. After being stirred for 0.5 h, the reaction mixture was poured onto 20 mL of saturated $NH_4Cl$ solution. The aqueous phase was extracted with ether, and the combined ether extracts were washed with 5% HCl and $H_2O$. The solution was dried ($MgSO_4$), and the ether was removed to yield 0.403 g (90% yield) of neointermedeol (**18**): IR (neat) 2.85, 3.40, 6.05, 6.87, 7.27, 8.40, 8.80, 9.45, 10.5, 10.8, 11.0, 11.3 μ; NMR ($CCl_4$) 1.00 (s, 3, $CH_3$), 1.09 (s, 3, $CH_3$), 1.69 (s, 3, $=CCH_3$), 4.5–4.7 ppm (m, 2, $=CH_2$). Column chromatography (silica gel, ether/pentane) afforded an oil which was homogeneous according to TLC (silica gel; ether/pentane, ethyl acetate/pentane, chloroform/pentane) and displayed $[\alpha]_D^{25}$ −1.2° (*c* 4.90, $CH_3OH$).

**2-(2′-Chloro-1′-methylethyl)-5,8-dimethyl-1,2,3,4,5,6-hexahydronaphthalene (19).** A solution of 1.97 g (8.2 mmol) of ketone **9** in 20 mL of ether was added to 14 mL of a 2.3 M ether solution of $CH_3MgI$. After being stirred for 0.5 h, the reaction mixture was poured onto 25 mL of saturated $NH_4Cl$. The aqueous layer was extracted with 10 mL of ether, and the combined ether extracts were washed with 5% HCl and $H_2O$. The solution was dried ($MgSO_4$) and evaporated, and the residue was adsorbed onto a short silica gel column and eluted with pentane to yield 1.40 g (72% yield) of diene **19**: IR (neat) 3.44, 6.90, 7.26, 11.5, 12.6, 13.6 μ; NMR ($CDCl_3$) 0.9–1.11 (two partially resolved doublets, 6, $CH_3$), 1.70 (s, 3, $=CCH_3$), 3.5–3.7 (m, 2, $CH_2Cl$), 5.3–5.5 ppm (m, 1, =CH).

**2-(2′-Chloro-1′-methylethyl)-5,8-dimethyl-1,2,3,4-tetrahydronaphthalene (20).** A mixture of 1.19 g (4.9 mmol) of diene **19** and 0.151 g (4.7 mmol) of sulfur was heated under $N_2$ at 200 °C for 1.5 h in a reflux apparatus. After being cooled, the mixture was taken up in 25 mL of pentane and washed with 3 N NaOH and twice with $H_2O$. The solution was dried ($MgSO_4$) and distilled to yield 0.898 g (76% yield) of **20**: bp 114–117 °C (0.2 mm); IR (neat) 3.40, 6.85, 7.39, 12.4 μ; NMR ($CDCl_3$) 1.05 (d, 3, $J$ = 6 Hz, $CH_3$), 2.13 (s, 6, $ArCH_3$), 3.54 (d, 2, $J$ = 6 Hz, $CH_2Cl$), 6.85 ppm (s, 2, ArH); exact mass, $m/e$ 236.133 (calcd for $C_{15}H_{21}Cl$, $m/e$ 236.133).

**2-Isopropenyl-5,8-dimethyl-1,2,3,4-tetrahydronaphthalene (21).** A solution of 0.90 g (3.8 mmol) of **20** and 0.85 g (7.6 mmol) of potassium *tert*-butoxide in 15 mL of $Me_2SO$ was stirred at 60 °C for 12 h. An equal volume of $H_2O$ was added, and the solution was extracted with four 10-mL portions of pentane. The combined pentane extracts were washed with 5% HCl and $H_2O$, dried ($MgSO_4$), and evaporated to afford 0.657 g (86% yield) of **21**. An analytical sample was prepared by preparative TLC and microdistillation: IR (neat) 3.40, 6.09, 6.85, 6.95, 7.30, 11.3, 12.4 μ; NMR ($CDCl_3$) 1.78 (s, 3, $=CCH_3$), 2.13 (s, 6, $ArCH_3$), 4.76 (s, 2, $=CH_2$), 6.85 ppm (s, 2, ArH).

Anal. Calcd for $C_{15}H_{20}$: C, 89.94; H, 10.06. Found: C, 89.83; H, 9.97.

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**(+)-Occidol (22).** A solution of 0.452 g (2.26 mmol) of **21** in 3 mL of THF was added to a solution of 0.715 g (2.25 mmol) of mercuric acetate in 2.5 mL of $H_2O$ and 2.5 mL of THF. After the mixture was stirred for 1.5 h, 2.5 mL of 3 N NaOH followed by 2.5 mL of 0.5 N $NaBH_4$ in 3 N NaOH was added. The mixture was extracted twice with 10 mL of ether, and the combined ether extracts were washed with 3 N NaOH, 5% HCl, and $H_2O$. After the extracts were dried ($MgSO_4$) and evaporated, the product was adsorbed onto a short silica gel column and eluted with pentane (300 mL) followed by acetone (200 mL). On evaporation the acetone fraction yielded 0.327 g (66% yield) of occidol (**22**)[19] as a semicrystalline mass. A portion of the product was purified by preparative TLC (silica gel, 40% ether/pentane) and showed $[\alpha]_D^{25}$ +34° (*c* 1.46, $CHCl_3$) (lit.[19a] $[\alpha]_D$ +164°). Recrystallization of the remainder from hexane afforded occidol displaying mp 99–100 °C, indicating the racemate had selectively crystallized (lit.[19b] mp 101–102 °C); IR ($CCl_4$) 2.76, 3.39, 6.78, 6.85, 6.94, 6.99, 7.25, 7.33, 8.66, 8.94, 9.71, 10.5, 10.9, 11.1 $\mu$; NMR ($CDCl_3$) 1.28 (s, 6, $CH_3$) 2.21 (s, 6, $ArCH_3$), 6.90 ppm (s, 2, ArH).

**Registry No.** 1 isomer 1, 71616-11-0; 1 isomer 2, 71616-12-1; **3**, 1470-91-3; **4**, 71616-13-2; *cis*-**5**, 71616-14-3; *trans*-**5**, 71616-15-4; **6**, 71616-16-5; **7**, 31188-03-1; **8**, 22070-24-2; **9**, 71616-17-6; **10**, 526-85-2; **15**, 71616-18-7; *cis*-**16**, 71616-19-8; *trans*-**16**, 5003-59-8; **17**, 17066-67-0; **18**, 5945-72-2; **19**, 71616-20-1; **20**, 71616-21-2; **21**, 71616-22-3; **22**, 5986-36-7; 2,3-dimethyl-2-butene, 563-79-1; 2-methyl-2-butene, 513-35-9; 1-methylcyclohexene, 591-49-1; 1-*p*-menthen-9-ol, isomer 1, 13835-30-8; 1-*p*-menthen-9-ol, isomer 2, 13835-75-1.

# Synthesis of the Sulfonyl Analogue of Hypoxanthine, Imidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-Dioxide[1]

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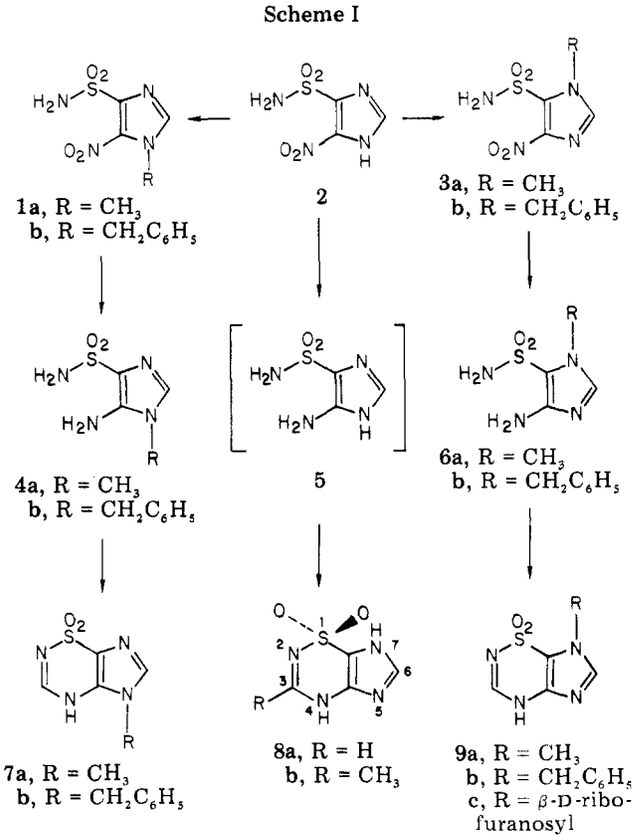
The unsubstituted imidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-dioxide was prepared in good yield by reduction of 4(5)-nitroimidazole-5(4)-sulfonamide and immediate ring closure of the unstable aminoimidazole intermediate. Ribosylation of the product by the modified Hilbert–Johnson method afforded a single nucleoside analogue, which is shown to be the 7-(β-D-ribofuranosyl) derivative by comparison of its properties to those of the 5- and 7-methyl derivatives.

A number of compounds that closely resemble the presumed transition state for certain reactions have proved to be potent, specific inhibitors of enzymes that effect those reactions.[2-5] Several examples of such "transition state analogue" inhibitors have been reported for enzymes that catalyze aminations or deaminations. The sulfone and sulfoximine derivatives of L-methionine inhibit glutamine synthetase,[6] while several alcohol derivatives, including 1,6-dihydro-6-(hydroxymethyl)nebularine,[3,7] coformycin,[8] and tetrahydrouridine,[9] are excellent inhibitors of adenosine or cytidine deaminases. The transition state analogues for these reactions all have an overall geometry close to that of the natural substrate but contain a tetrahedrally substituted atom at the position associated with reaction in the normal substrate. The imidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-dioxide system, **8a** (Scheme I), is an isosteric analogue of hypoxanthine in which the 6-carbonyl has been replaced by a sulfonyl moiety. The tetrahedral arrangement of atoms in the sulfonamide of **8a** suggested that appropriate nucleoside derivatives of it might prove to be stable transition-state analogues for enzymatic transformations at the 6-position of purines.[10] For example, the 5-ribosyl derivative, **7** (R = β-D-ribofuranosyl), might be a transition-state analogue inhibitor for adenosine deaminase while the 5-(5′-phosphoribosyl) derivative might act as such an inhibitor of adenylosuccinate synthetase. Despite the obvious structural similarity of the imidazo-[4,5-*e*]thiadiazine ring system to the purine system and the

Scheme I

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