Synthesis and Biological Activity of Monoterpenoid Analogues of *cis*-Sativenediol and Helminthosporal

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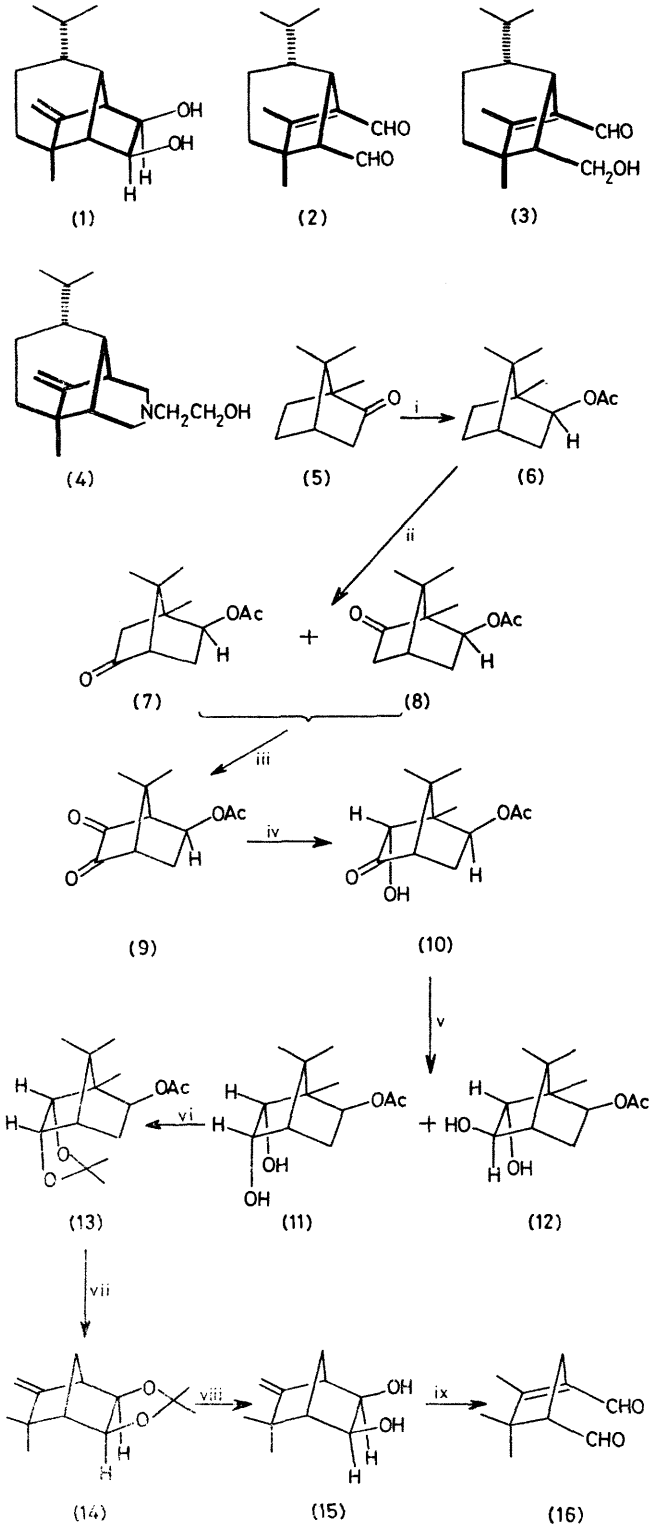
Summary Synthetic routes from (+)- or (−)-camphor to enantiomers of 5-*exo*-6-*exo*- and 5-*endo*-6-*exo*-dihydroxycamphene and 1,4-diformyl-2,3,3-trimethylcyclopentene have been developed and a preliminary assessment of their phytohormone activity has been made.

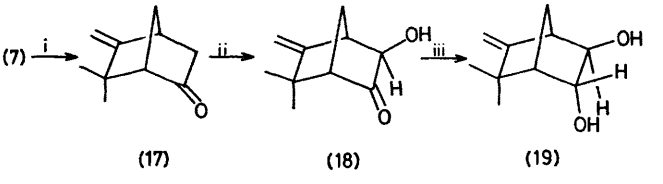
IT has been reported by several research groups that the fungal sesquiterpenoids, (−)-*cis*-sativenediol (**1**),[1] helminthosporal (**2**),[1,2] helminthosporol (**3**),[1-3] and victoxinine (**4**)[4] display plant growth-promoting or plant growth-inhibiting properties. Although the structure–activity relationships of phytohormones[5] are obscure it seems reasonable to assume that the biological activity of compounds (**1**)—(**4**) is associated with enzymic interaction with the accessible functional groups attached to their rigid bicyclic or tricyclic carbon framework. We have considered the possibility that the total carbocyclic framework of compounds (**1**)—(**4**) may not be essential for biological activity of their monoterpenoid analogues which are indicated by the thickened lines of structures (**1**)—(**4**).



(i), (1) $LiAlH_4$, (2) Ac_2O–C_5H_5N; ii, CrO_3–Ac_2O–HOAc; iii, SeO_2; iv, Zn–HOAc; v, $NaBH_4$; vi, Me_2CO–H^+; vii, (1) Na_2CO_3–MeOH–H_2O, (2) $MeSO_2Cl$–C_5H_5N, heat; viii, 6N HCl–MeOH–20 °C; ix, HIO_4–Et_2O,

To test the validity of this speculation we have devised a synthetic route from (−)-camphor (**5**) to (−)-5-*exo*-6-*exo*-dihydroxycamphene (**15**) and the dialdehyde (**16**), the monoterpenoid analogues of (−)-*cis*-sativenediol (**1**)[6] and helminthosporal (**2**) respectively. The synthetic route involves initial conversion of (−)-camphor (**5**) into (+)-isobornyl acetate (**6**) followed by remote oxidation (CrO_3–HOAc–Ac_2O) to a mixture (4:1) of 5-oxoisobornyl acetate (**7**) and its 6-oxo isomer (**8**).[7,8] Oxidation of the mixture of (**7**) and (**8**) with SeO_2 gave 5,6-dioxoisobornyl acetate (**9**)[7] which underwent regiospecific and stereoselective reduction (Zn–HOAc) to provide 6-*endo*-hydroxy-5-oxoisobornyl acetate (**10**).[9] Reduction of (**10**) with $NaBH_4$ gave a mixture (1:1) of 5-*endo*-6-*endo*-dihydroxyisobornyl acetate (**11**) and the *trans*-isomer (**12**) which were separated by selective formation of the *OO*-isopropylidene derivative (**13**) followed by column chromatography (silica gel, grade III). Hydrolysis (Na_2CO_3–MeOH–H_2O) and Wagner–Meerwein rearrangement ($MeSO_2Cl$–C_5H_5N) of the derived alcohol provided the *OO*-isopropylidene derivative (**14**) which on mild hydrolysis (6N HCl, MeOH, 4 days, room temperature) gave (−)-5-*exo*-6-*exo*-dihydroxycamphene (**15**)† as a colourless crystalline solid, m.p. 90—92 °C, $[\alpha]_D$ − 53·6 (*c* 0·55, $CHCl_3$). Subsequent periodic acid oxidation of the diol (**15**) in anhydrous ether provided (+)-1,4-diformyl-2,3,3-trimethylcyclopentene (**16**)† in 67% yield, $[\alpha]_D$ + 3·07 (*c* 1·37, $CHCl_3$).

Since we were also interested in assessing the phytohormone activity of 5-*endo*-6-*exo*-dihydroxycamphene (**19**) a synthesis of this compound was developed. Separation of pure 5-oxoisobornyl acetate (**7**) from the 6-oxo isomer by column chromatography (Florisil) followed by hydrolysis and Wagner–Meerwein rearrangement ($MeSO_2ClC_5H_5N$) provided 5-oxocamphene (**17**).[10] Stereoselective hydroxylation of (**17**) was accomplished in 71% yield using the Vedejs procedure [MoO_5–hexamethylphosphoric triamide (HMPA)–C_5H_5N][11] and the resulting 6-*exo*-hydroxy-5-oxocamphene (**18**) was stereoselectively reduced with $NaBH_4$ to provide, after sublimation, (−)-5-*endo*-6-*exo*-dihydroxycamphene (**19**)[12]† as a colourless crystalline solid, m.p. 97—99 °C (sealed tube), $[\alpha]_D$ −51·67 (*c* 0·42, $CHCl_3$).



i, (1) Na_2CO_3–MeOH–H_2O, (2) $MeSO_2Cl$–C_5H_5N, heat; ii, MoO_5–HMPA–C_5H_5N; iii, $NaBH_4$.

The *cis*-diol (**15**), *trans*-diol (**19**), and the dialdehyde (**16**) and their enantiomers [derived from (+)-camphor] were evaluated for phytohormone or phytotoxin activity using gibberellic acid as a standard. Bioassays were conducted by measuring the growth-promoting or growth-inhibiting effect of the compounds on two varieties (*Indica, cv. Century Patna* and *Japonica, cv. Tanginbozu*) of rice seedlings (*Oryza sativa*) and the results shown in Tables 1

† Satisfactory spectroscopic and analytical data have been obtained for this compound.

and 2 indicate that the *cis*-diol (**15**), *trans*-diol (**19**), and the dialdehyde (**16**) and their enantiomers are devoid of growth-promoting or growth-inhibiting effects at the concentration tested.‡

TABLE 1. Effect of synthetic monoterpenoids on rice seedlings (*Oryza sativa*) (estimated by the agar medium method).[a]

Compound	Length of second leaf sheath (relative to control)[a] *Indica cv. Century Patna*	*Japonica cv. Tanginbozu* (dwarf)
(−)-*cis*-Diol (**15**)	—	94
(+)-*cis*-Diol	—	101
(−)-*cis*-Sativenediol (**1**) [b]	—	234
(+)-*cis*-Sativenediol	—	100
Gibberellic acid	200	432
Control expt.	100	100
(+)-Dialdehyde (**16**)	—	94
(−)-Dialdehyde	—	96
(−)-*trans*-Diol (**19**)	80	101
(+)-*trans*-Diol	89	104

[a] Germinated rice seedlings (3 days old) supported on 0·75% agar–water (2·5 ml) were mixed with the test solution (2·5 ml; 3×10^{-4} M). The length of the second leaf sheath was measured after 6—7 days of growth. Test solutions of other concentrations (6×10^{-4} and 12×10^{-4} M) gave similar results. [b] In this case the test solution was 2×10^{-5} M.

At this stage we conclude that the reported biological activity of (**1**)—(**4**) is associated with the total carbocyclic structure or with a structural sub-unit not represented by the monoterpenoid compounds described above.

TABLE 2. Effect of synthetic monoterpenoids on rice seedlings (*Oryza sativa*) (estimated by the microdrop method).[a,b]

Compound	Length of second leaf sheath (relative to control)[b] *Indica cv. Century Patna*	*Japonica cv. Tanginbozu* (dwarf)
(−)-*cis*-Diol (**15**)	97	95
(+)-*cis*-Diol	100	102
(−)-*cis*-Sativenediol (**1**)	106	105
(+)-*cis*-Sativenediol	103	105
Gibberellic acid	142	252
Control expt.	100	100
(+)-Dialdehyde (**16**)	—	—
(−)-Dialdehyde	106	98
(−)-*trans*-Diol (**19**)	98	104
(+)-*trans*-Diol	99	106

[a] See Y. Murakami, *Japan Agric. Res. Quart.*, 1970, **5**, 5. We thank Dr. I. E. P. Taylor and Mr. R. Radley, Department of Botany, University of British Columbia, for informing us of this method and providing us with advice about the experimental details. [b] The rice seedlings were supported on wet filter paper or agar. Activities were determined by measuring the average length of the second leaf sheath 5 days after addition of the compound ($0{\cdot}4 \times 10^{-9}$ M) to the coleoptile of 4 days old test plants.

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‡ *Added to proof*: These results have recently been confirmed by Professor S. Marumo, Nagoya University, Japan.

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