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NEW SYNTHESIS OF DL-SATIVENE, DL-COPACAMPHENE, DL-*CIS*-SATIVENEDIOL AND DL-HELMINTHOSPORAL

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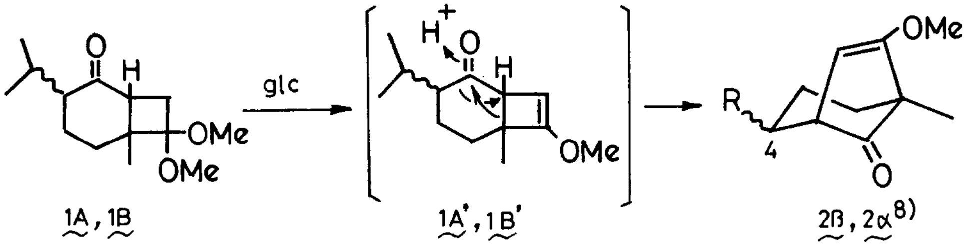
Photocycloadducts from dl-piperitone and 1,1-dimethoxyethylene afforded bicyclo[3.2.1]oct-6-en-8-one derivatives under glc conditions in excellent yields. The synthesis of the title sesquiterpenes was accomplished using the bridged bicyclic compounds as intermediates.

We report here a new synthesis of sativene (I),[1] copacamphene (II),[1d-e,2] *cis*-sativenediol (III)[3] and helminthosporal (IV)[4] from photocycloadducts 1A[5,6] and 1B,[5,6] which are readily obtainable from dl-piperitone and 1,1-dimethoxyethylene. On being passed through a column (Thermol-3 on Shimalite,[7] 200°, He), each of the adducts eliminated MeOH and rearranged to give the same (55:45) mixture of isomeric enol ethers 2β[8] [bp 100-103°/3 mmHg, ν(neat) 1765, 1625 cm^{-1}, δ[9] 4.78 (d, 3.5 Hz, 1H), 3.63 (s, 3H), 2.97 (d, 3.5 Hz, 1H), 0.94 (s, 3H), 0.90 (d, 5 Hz, 3H), 0.84 (d, 5 Hz, 3H)] and 2α[8] [ν(neat) 1765, 1620 cm^{-1}, δ 4.77 (d, 3.5 Hz, 1H), 3.63 (s, 3H), 2.88 (t, 3.5 Hz, 1H), 0.98 (d, 5 Hz, 3H), 0.92 (s, 3H), 0.90 (d, 5 Hz, 3H)] in a 94% yield.[10] The products were separated by preparative glc (DGSP, 180°, 95%). Stereochemistry of the isopropyl group in 2β and 2α was determined on the basis of the multiplicity of the signal due to the bridgehead proton of these compounds.



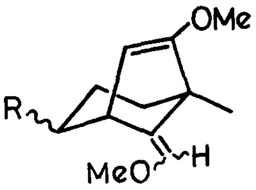
A remarkable difference in reactivity in the Wittig reaction was observed between 2β and 2α. Treatment of the mixture of 2β and 2α with ph$_3$P$^+$CH$_2$OCH$_3$ Cl$^-$ (*t*-AmONa,[11] benzene, rt, 5 min) afforded an E, Z mixture of 3β [bp 105-120°/3 mmHg] and unchanged α isomer 2α. Selective hydrolysis of the endocyclic enol ether group of the products was effected by passing the mixture through a silica gel column (benzene). By this procedure, the resulting ketones 4β [δ 5.94 (s, 1H), 3.45 (s, 3H), 1.17 (s, 3H)], 5β [δ 5.60 (s, 1H), 3.50 (s, 3H), 0.94 (s, 3H)] (79:21, 66% based on 2β) and a diketone derived from 2α were separated. Further hydrolysis (dil HCl, An) of the remaining exocyclic enol ether group of 4β and 5β afforded an epimeric mixture of aldehyde

6β [δ 9.71 (d, 2 Hz)] and **7β** [δ 9.82 (s)] (1:1, yield 92%), which was equilibrated to a mixture enriched in **6β** (85%) with NaOEt (EtOH, rt, 1 min). Selective Wittig reaction at the aldehyde group of **6β**-**7β** with 1.2 equiv of $\mathrm{ph_3P^+CH_2OCH_3\ Cl^-}$ (*t*-AmONa, benzene, rt, 5 min) gave a mixture of E and Z enol ethers **8β** [bp 128-130°/1 mmHg], which afforded a homogeneous aldehyde **9β**12) [bp 145-148°/1.5 mmHg, δ 9.72 (t, 1.5 Hz), 98%] after hydrolysis (HCl, acetone). The aldehyde **9β** was reduced with $\mathrm{NaBH_4}$ to an alcohol **10β** [bp 125°/0.5 mmHg, 96%]. Intramolecular alkylation (*t*-BuOK/BuOH) of mesylate **11β**, derived from 10β, to tricyclic ketone **12β**14) [δ 2.83 (bs, W_h=6 Hz, 1H), 2.17 (s, 1H), 1.87 (m, 1H), 0.92 (s, 3H), 85% yield] and subsequent methylation of **12β** with MeLi produced a single carbinol **13β**13) [δ 1.09 (s, 3H), 0.88 (d, 5 Hz, 6H), 0.81 (s, 3H)]. Treatment of **13β** with MsCl in pyridine (rt, 12 hr) furnished dl-sativene (I)14) [δ 4.72 (s, 1H), 4.40 (s, 1H), 2.60 (bs, 1H), 1.82 (bs, 1H), 1.05 (s, 3H), 0.92 (d, 5 Hz, 3H), 0.88 (d, 5 Hz, 3H), m/e 204 (M^+)] in 94% yield.

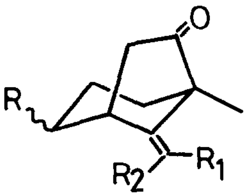
Similarly copacamphene was synthesized from **2α**. Treatment of **2α**15) with $\mathrm{ph_3P^+CH_2OCH_3\ Cl^-}$/*t*-AmONa (DME, reflux, 30 min) gave E, Z isomeric enol ethers **3α** [bp 110°/3 mmHg, yield 68%]. Successive transformations of **3α**, through the sequence **3α**→**4α**→**5α**→**6α** (**7α** was not formed)→**8α**→**9α**→**10α**→**11α**→**12α**→**13α** (an isomer **13α'** at C-7 was formed. **13α**:**13α'** = 4:1)→II under conditions essentially identical to those employed in the case of sativene, afforded dl-copacamphene (II)14) [δ 4.74 (s, 1H), 4.47 (s, 1H), 2.45 (bs, 1H), 1.00 (s, 3H), 0.90 (d, 5 Hz, 6H), m/e 204 (M^+)] in a comparable yield in each step, except for the last dehydration (76%).

cis-Sativenediol and helminthosporal were obtained as follows. The isomeric mixture of keto aldehydes **6β** and **7β** (85:15) was treated with $\mathrm{MeP^+ph_3\ Br^-}$ (*t*-AmONa, benzene, rt) to give **14** [bp 105°/3 mmHg] in 89% yield as a single product.12) Bromination of **14** (1 equiv. $\mathrm{Br_2}$, $\mathrm{CHCl_3}$, rt) afforded a mixture of dibromides **15**16) and **16** (4:1 by nmr and glc, yield 100%) [δ 1.10 and 1.05 (each s, 4:1, 3H)]. Intramolecular alkylation of the mixture of **15** and **16** proceeded smoothly (*t*-BuOK/BuOH, rt, 5 min) to afford a bromide **17** [δ 1.35 (s, 3H), m/e 284, 286 (1:1)] and an olefin **18** [δ 6.47 (m, 1H), 6.00 (m, 1H), 0.93 (s, 3H)] (93%, 45:12 by glc). The bromide **17** was converted to the olefin **18** after prolonged reflux with *t*-BuOK (30 min).16) Treatment of a solution of **18** with MeLi under reflux (DME, 12 hr) gave an alcohol **19**17) [δ 6.71 (t, 2 Hz, 2H), 2.39 (b, 1H), 1.05 (s, 3H), 0.79 (s, 3H)] in 90% yield. Oxidation of **19** ($\mathrm{OsO_4}$, benzene-pyridine, then $\mathrm{H_2S}$) afforded a triol **20** [mp 80-82°, δ ($\mathrm{CDCl_3}$) 3.93 (s, 2H), 3.2 (OH, 3H), 2.43 (b, 1H), 1.10 (s, 3H), 0.98 (s, 3H)]. The triol **20** was then acetylated and the product [δ 4.98 and 4.90 (AB, 7 Hz, each 1H)] was treated with MsCl in pyridine to give *cis*-sativenediol diacetate **21**14) [mp 87.5-88°, δ 5.05 (bs, 1H), 4.72 (bs, 1H), 4.92 and 4.77 (AB, 6 Hz, each 1H), 2.68 (bs, 1H), 2.44 (bs, 1H), 2.00 (s, 3H), 1.15 (s, 3H)]. Reductive cleavage of the acetate with $\mathrm{LiAlH_4}$ afforded dl-*cis*-sativenediol (III)14) [mp 50.5-51°, δ 4.92 (bs, 1H), 4.60 (bs, 1H), 4.08 and 3.67 (AB, 6 Hz, each 1H), 2.68 (bs, 1H), 2.44 (bs, 1H), 1.05 (s, 3H)].

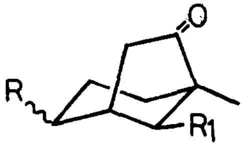
Oxidation of **20** [$\mathrm{NaIO_4}$, methanol-water (4:1)] gave an aldehyde **22** [δ 9.83 (s, 1H), 9.64 (d, 3.5 Hz, 1H), 3.4 (OH, 1H), 2.96 (s, 1H), 2.55 (m, 1H), 2.17 (s, 1H), 1.14 (s, 3H), 1.10 (s, 3H), 0.92 and 0.86 (each d, 6 Hz, 3H), 88% yield], which on treatment with 1M-NaOMe in Ar atmosphere (1 min, rt) afforded, after purification by chromatography ($\mathrm{SiO_2}$), dl-helminthosporal (IV)14) [oil, δ 9.93 (s, 1H), 9.42 (d, 3.5 Hz, 1H), 3.33 (bs, 1H), 2.06 (s, 3H), 1.16 (s, 3H), λ_{max}^{EtOH} 266



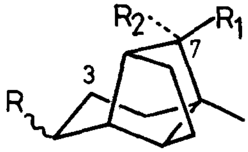
3β, 3α



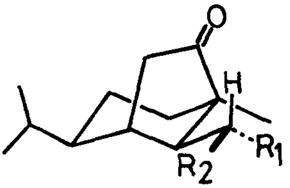
4β, 4α R_1 = OMe, R_2 = H
5β, 5α R_1 = H, R_2 = OMe



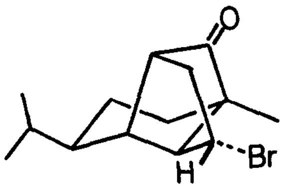
6β, 6α R_1 = CHO
7β, 7α C-8 epimers of 6β and 6α
8β, 8α R_1 = CH=CHOMe
9β, 9α R_1 = CH_2CHO
10β, 10α R_1 = CH_2CH_2OH
11β, 11α R_1 = CH_2CH_2OMs



12β, 12α R_1, R_2 = O
13β, 13α R_1 = Me, R_2 = OH
I R = β-isopr, R_1, R_2 = CH_2
II R = α-isopr, R_1, R_2 = CH_2



14 R_1, R_2 = CH_2
15 R_1 = CH_2Br, R_2 = Br
16 R_1 = Br, R_2 = CH_2Br



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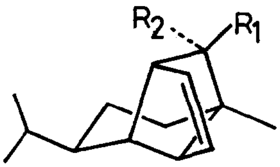
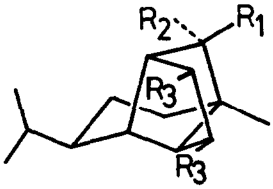
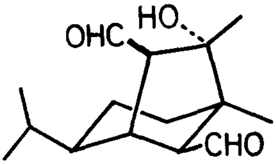


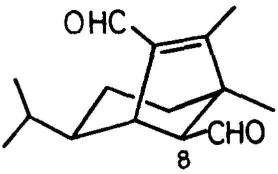
18 R_1, R_2 = O
19 R_1 = Me, R_2 = OH



20 R_1 = Me, R_2 = R_3 = OH
21 R_1, R_2 = CH_2 R_3 = OAc
III R_1, R_2 = CH_2 R_3 = OH



22



IV

nm (ε 10500) and 8-epi-helminthosporal [oil, δ 9.94 (s, 1H), 9.75 (s, 1H), 3.55 (d, 5 Hz, 1H), 2.42 (dd, 5 and 2 Hz, 1H), 2.03 (s, 3H), 1.25 (s, 3H)], in 60 and 6% yields, respectively.

References and Notes

1) Isolation: a) P. de Mayo and R. E. Williams, J. Amer. Chem. Soc., 87, 3275 (1965).
Synthesis: b) J. E. McMurry, J. Amer. Chem. Soc., 90, 6821 (1968); c) G. L. Hodgson, D. F.

MacSweeney and T. Money, *J. Chem. Soc. Perkin I*, 2113 (1973); d) C. R. Eck, G. L. Hodgson, D. F. MacSweeney, R. W. Mills and T. Money, *J. Chem. Soc. Perkin I*, 1938 (1974); e) E. Piers, M. B. Geraghty, R. D. Smillie and M. Soucy, *Can. J. Chem.*, **53**, 2849 (1975).

2) Synthesis: a) J. E. McMurry, *Tetrahedron Lett.*, 3731 (1970); b) ref 1c, d.

3) Isolation: a) M. Nukina, H. Hattori and S. Marumo, *J. Amer. Chem. Soc.*, **97**, 2542 (1975); b) F. Dorn, P. Bernasconi and D. Arigoni, *Chimia*, **29**, 24 (1975). Synthesis: c) E. Piers and H. Isenring, *Synthetic Comm.*, **6**, 221 (1976); *idem*, *Can. J. Chem*. **55**, 1039 (1977).

4) Isolation and structure: a) P. de Mayo, E. Spencer and R. E. White, *Can. J. Chem.*, **39**, 1608 (1961); b) *idem*, *ibid*, **41**, 2996 (1963). Synthesis: c) E. J. Corey and S. Nozoe, *J. Amer. Chem. Soc.*, **87**, 5728 (1965).

5) Stereochemistry of the isopropyl group of **1A** and **1B** is not clear at present.

6) Satisfactory elemental analytical and spectral data were obtained for all new compounds in this paper.

7) Acidic character of Shimalite (equivalent to chromosorb P) has been demonstrated. T. Matsuura, H. Komae, T. Araya and S. Hayashi, *Kogyo Kagaku Zasshi* (*Journal of the Chemical Society of Japan, Industrial Section*), **64**, 795 (1961).

8) Throughout this paper, suffixes α and β mean the presence of 4α- and 4β-isopropyl groups respectively.

9) Unless otherwise stated nmr spectra were measured in CCl_4 solution.

10) An acid-washed alumina catalyzed skeletal transformation (28% yield) similar to **1A'**, **1B'** → **2β**, **2α** was reported: R. L. Cargill and J. W. Crawford, *J. Org. Chem.*, **35**, 356 (1960).

11) J. M. Conia and J. C. Limasset, *Bull. Soc. Chim. France*, 1936 (1967).

12) The α-aldehyde **7β** was converted to the desirable β-aldehyde **6β** in the course of the Wittig reaction by the base.

13) The configuration of the OH group was deduced by nmr. In the presence of $Eu(fod)_3$, large shift of signals due to the C-3 axial proton (W=42 Hz) was observed. See also footnote 17.

14) Spectral data were identical with those reported.$^{1-4)}$

15) The compound **2α** can be obtained conveniently by distilling the reaction product of the mixture (**2α** and **2β**) and $(EtO)_2PO\ CH_2CO_2Et/NaH$ (DME, rt, 30 min). Only **2β** underwent the reaction under these conditions and the product boiled at higher temperature (bp 135-140°/3 mmHg) than **1α**.

16) Since *exo*-*syn*-elimination is preferred to *endo*-*syn*-elimination in the norbornane system [K. Fukui and H. Fujimoto, *Tetrahedron Lett.*, 4303 (1965)], the *endo*-bromine structure was assigned to **17**. The low field chemical shift of the C-1 methyl group of **17** (δ 1.35) supported this formulation. The debromo compound **12β** of **17** exhibits the corresponding peak at δ 0.92. Since the ratio of **17** to **18** is close to **15** to **16**, **15** (or **16**) is most probably the precursor of **17** (or **18**). Therefore the stereostructures of bromocompounds are expressed as shown in the formulas.

17) S values [A. F. Cockerill and D. M. Rackham, *Tetrahedron Lett.*, 5149 (1970)] are as follows: C-3 ax H (W=42 Hz) S = 26.5, C-6 H S = 7.4, C-7 methyl S = 6.1, C-1 methyl S = 2.8, C-9 and C-10 H S = 2.0.

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