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TOTAL SYNTHESIS OF α- AND β-PANASINSENE

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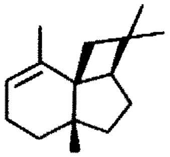
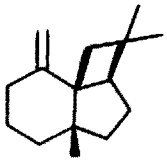
Abstract. α- and β-Panasinsene have been synthesized by a route which employs intramolecular cuprous triflate catalyzed photocyclization of an olefin with an allylic alcohol.

For centuries, extracts of the root of *Panax ginseng* have been used as tonics, and wondrous properties have been ascribed to these preparations.[1] Chemical investigations of natural products from *Panax ginseng* have been undertaken by a number of groups,[2] and in 1975 Hirose and Yoshihara reported[3] their results on the isolation and characterization of ginseng sesquiterpenes. In addition to the known compounds β-caryophyllene, α-neoclovene, and β-neoclovene, two new sesquiterpene hydrocarbons were discovered. These compounds, α- and β-panasinsene, were unequivocally shown to have the structures indicated:



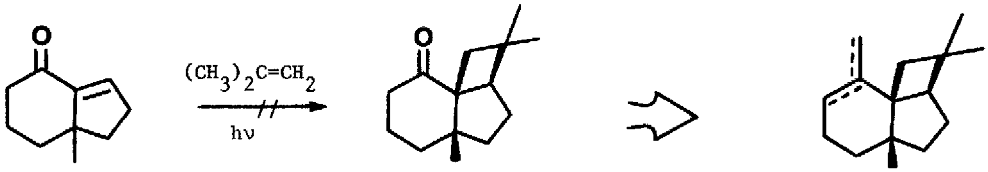
α-panasinsene (*1*)



β-panasinsene (*2*)

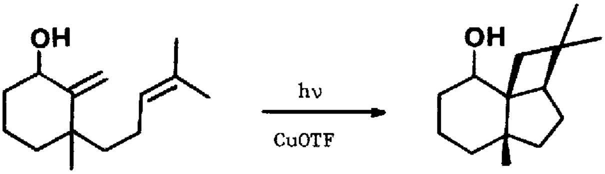
The fused 4-5-6 tricyclic skeleton of the panasinsenes is unique among sesquiterpenes and aroused our interest in devising a total synthesis of these compounds.

In our hands, total synthesis of the panasinsenes turned out to be a considerably more difficult task than we had originally thought, and more than a few synthetic plans came to naught. One might imagine, for example, that the well-known photocycloaddition[4] of isobutylene to known[5] enone *3* would provide ketone *4*. Further transformation of *4* should be straightforward. In practice, however, this obvious (and relatively uninteresting) synthesis was not successful. Photoreaction of enone *3* with isobutylene under a variety of conditions gave none of the expected product.



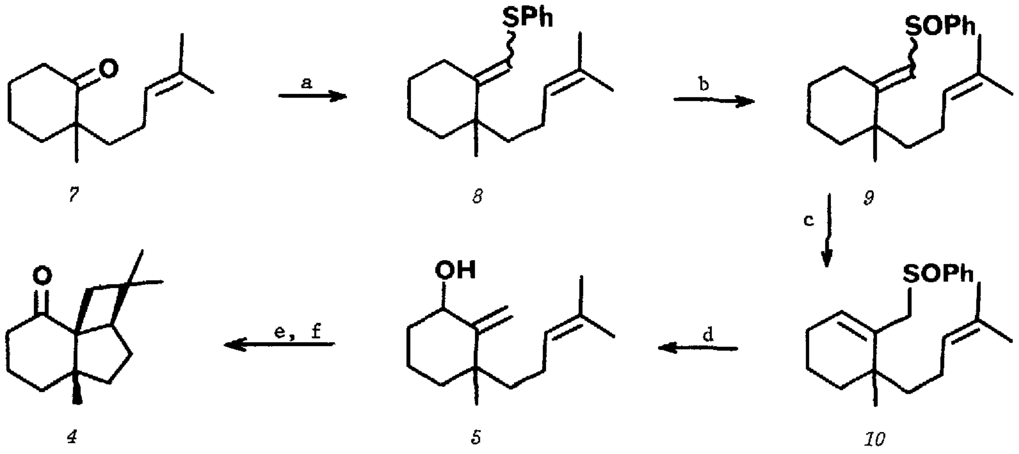
3 *4* *1, 2*

Our ultimately successful route to the panasinsenes took advantage of a newly published method of cyclobutane synthesis. Salomon has shown[6] that cuprous triflate catalyzes the photocycloaddition of an olefin to an allylic alcohol. Although no intramolecular examples of the reaction were provided in the initial communication,[6a] we decided to examine the copper triflate catalyzed photolysis of *5* as a key step for panasinsene synthesis. Inspection of models indicates that cycloaddition would be expected to occur with the desired stereochemistry.



5 *6*

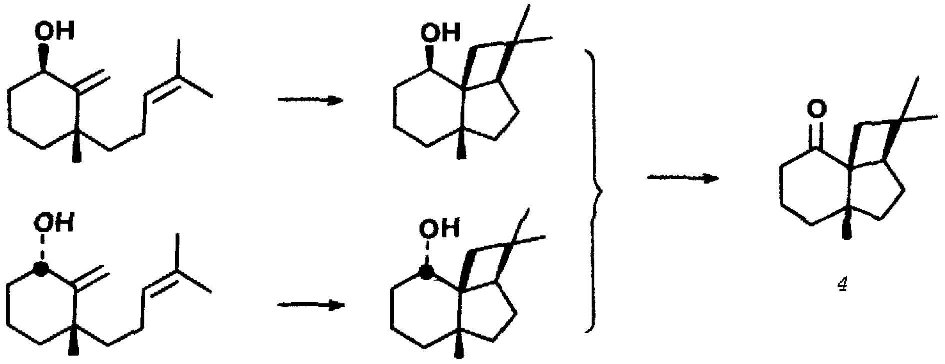
Alkylation[7] of the sodium enolate of 2-methylcyclohexanone with 1-bromo-4-methyl-3-pentene provided the starting material *7*. Reaction of *7* with the lithio salt of dimethyl phenylthiomethylphosphonate[8] gave a 9:1 mixture of vinyl sulfides *8*. This mixture was oxidized to sulfoxide *9* with sodium periodate,[9] and the resulting sulfoxide was deconjugated[10] by treatment with dimsyl potassium[11] in DMSO. Allylic sulfoxide *10* was obtained as a 3:2 mixture of diastereomers, but no attempt was made to separate them since both sulfoxide diastereomers were useful for our purposes. Thus *10* was treated with trimethylphosphite according to Evans' procedure,[12] and diene alcohol *5* was obtained as a mixture of diastereomers in 47% overall yield from *7*. Photolysis of an ether solution of *5* in the presence of cuprous triflate proceeded smoothly and gave a mixture of saturated alcohols (55%) which, on oxidation with pyridinium chlorochromate,[13] gave a single ketone, *4*. Ketone *4* was identical with an authentic sample prepared from caryophyllene,[14] thus confirming that the intramolecular photocyclization had occurred as desired with the correct all *cis* stereochemistry. These transformations are summarized below.



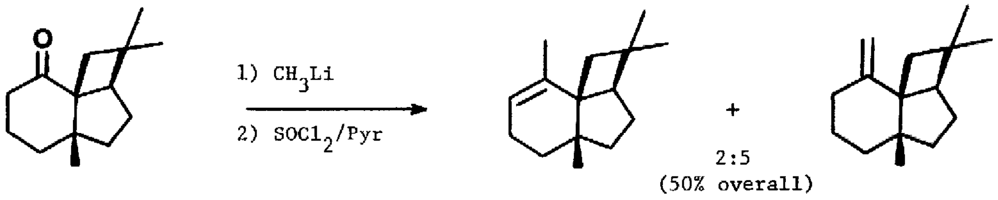
a) $PhSCH_2PO(OCH_3)_2$, sec-BuLi, 77%; b) $NaIO_4$, *p*-dioxane-H_2O, 82%; c) $K^+\ {}^-CH_2SOCH_3$, DMSO, r.t., 82%; d) $(CH_3O)_3P$, CH_3OH, 90%; e) hν (254 nm), CuOTf, 55%; f) PCC, NaOAc, CH_2Cl_2, 97%.

Although not necessary for synthetic purposes since both epimers of *5* yield the same ketone *4* after oxidation, we nevertheless decided to separate the diastereomers and study the photocyclization of each individually. Little is known about the mechanism of the reaction[6] and the nature of the role played by the catalyst is unclear. We were therefore hopeful that study of the two epimeric alcohols *5* might provide information about the geometry of the transition state for photocyclization.

The 3:2 mixture of alcohols *5* was separated by HPLC into a major and a minor component, but careful nmr analysis did not allow us to confidently assign stereostructures. Cuprous triflate catalyzed photocyclization of the major alcohol required 24 hr. and gave a single tricyclic product in 45% yield. Photocyclization of the minor alcohol also occurred stereospecifically, but more smoothly (4.5 hr) and in higher yield (65%). Both alcohols therefore undergo stereospecific photocyclization at roughly comparable rates, and we conclude that the stereochemistry of the allylic hydroxyl does not play a large role in the cyclization. This suggests that a hydroxyl coordinated copper ion is not intimately involved in the transition state.



The remainder of the synthesis was completed in a straightforward manner. Although *4* was inert to methylenetriphenylphosphorane in DMSO, reaction with methyllithium followed by dehydration with thionyl chloride in pyridine gave a 5:2 mixture of β- and α-panasinsene. The syntheti materials were separated by preparative gas chromatography and were identical with the natural products by spectroscopic comparison (i.r. and nmr).[15]



4 *1* *2*

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