

NOVEL HYPOIODITE FUNCTIONALIZATION OF LONGIFOLOL^{1,2}:
SYNTHESIS OF LONGIFOL-7(15)-EN-5 β -OL AND LONGIFOLAN-
3 α ,7 α -OXIDE-SESQUITERPENES FROM JUNIPERUS CONFERTA

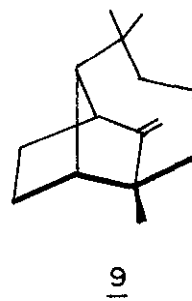
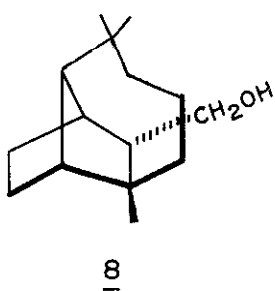
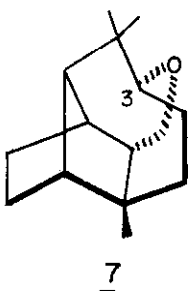
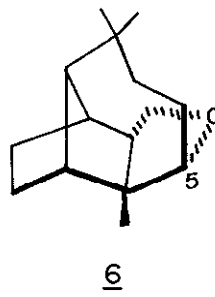
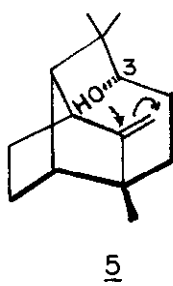
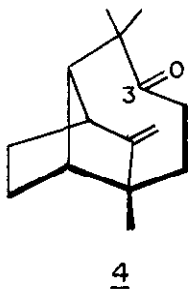
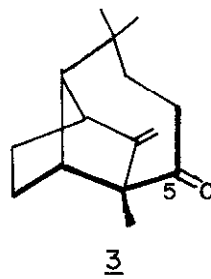
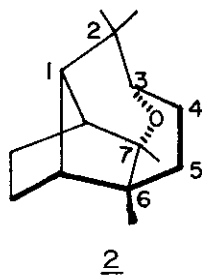
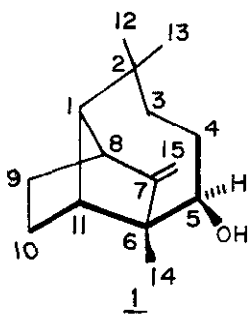
P. K. Jadhav and U.R. Nayak*
National Chemical Laboratory, Poona 8 (India)

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Two apparently simple longifolane-based mono oxygenated compounds - the carbinol 1 and the oxide 2 - were isolated by Japanese workers³ from the heartwood of Juniperus conferta as early as 1971. In spite of the extensive and exciting chemistry of longifolene uncovered during the recent past there has been, to date, no recorded synthesis of either of these two compounds from longifolene itself or otherwise. We now describe a unique synthetic venture in which a common longifolene derivative has been exploited to play a crucial dual role in one and the same reaction: to achieve site-specific oxygen functionalization at the desired inert carbon atoms and thus furnish two key synthons now amenable for the generation of the target compounds 1 and 2 respectively in an overall sequence of seven steps from longifolene 9.

In an integrated approach to the synthesis of the two Juniperus sesquiterpenoids 1 and 2, the objective was simply perceived as the generation of the two ketolongifolenes 3 and 4 as precursors for the final reduction to 1 and 2 respectively; in the case of 4, however, the resulting 3 α -hydroxy epimer is essentially the latent form of the oxide since this carbinol 5 collapses into the ether 2 on exposure to acid as a result of facile transannular cyclization (cf. 5).

The principle of functionalization of nonactivated centres was invoked in the generation of the desired ketolongifolenes and the viable oxides 6 and 7 assumed importance as points of departure in the design of 3 and 4 respectively. A nicely tailored substrate for the construction of the tetrahydrofuran 6 was seen in the framework molecular model of longifolol 8, a readily accessible⁴ longifolene derivative. More important, however, was the visualization that the oxy radical generated in the rigid system 8 was theoretically capable of a strategic double role: it could activate not only the C-5 atom by the usual 1,5-hydrogen transfer (cf. 6) but also functionalize the most crucial C-3 site (cf. 7) without any significant distortion of molecular geometry in either case. In the latter instance, the novel internal 1,7-



hydrogen transfer stems from the unique spatial disposition of 8 in which the large ring is blocked in a stable conformation such that C-3 and C-7 are in very close proximity. This particular frozen conformation, so well-entrenched in longifolene chemistry (on the basis of chemical⁵ and X-ray⁶ evidence), does not spatially permit oxide formation at C-4, the only other site left for consideration. Thus longifolol assumed overwhelming importance as a potential common substrate for the two key synthons 6 and 7 both derivable from one and the same reaction.

Our theoretical expectations were amply realized in practice. When longifolol was subjected to the hypiodite $[\text{Pb}(\text{OAc})_4\text{-I}_2]$ reaction⁷ in cyclohexane an excellent yield (80%) of the two targeted oxides 6^{8,9} (b.p. 90°/0.9 mm) and 7 (m.p. 38-39°) (separable¹⁰ by chromatography on silica gel) was obtained. Validity of the assigned structures 6 and 7 for the two ethers is borne out by the chemical transformation (*vide infra*) of the two compounds into 1 and 2 respectively wherein the large ring is oxygen functionalized at C-5 in the former and at C-3 in the latter, in conformity with the activation sites predicted for the two oxides.

In the next phase, an efficient four step transformation sequence was applied to both 6 and 7: Oxide \rightarrow lactone ($\text{CrO}_3\text{-AcOH}$) \rightarrow diol (LiAlH_4) \rightarrow keto-alcohol (NBS-aq. BuOH^t -pyridine) \rightarrow keto olefin (KHSO_4 for 6; acetate pyrolysis for 7). At this stage, in effect, synthesis of the 5-keto- and 3-keto-longifolenes 3 and 4 respectively had been achieved from longifolene itself in six steps. Finally, reduction of 3 with sodium-*n*-propanol completed the synthesis¹¹ of the 5 β -alcohol 1. In the case of 4, however, hydride (e.g. LiAlH_4) gave the desired 3 α -epimer 5 in only ca. 30% yield which under the acidic workup conditions was isolated as the expected ether 2 after chromatographic separation from the 3 β -carbinol which remained unaffected by acid.

Acknowledgement

We are thankful to Dr. T. Shibuya for providing us with the spectra (IR,PMR) of both the Juniperus sesquiterpenoids and also an authentic sample of the carbinol 1.

REFERENCES AND NOTES

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- 2 Newer Aspects of Longifolene-I.
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- 7 For recent reviews see: J. Kalvoda and K. Heusler, Synthesis 501 (1971); K. Heusler Heterocycles 3, 1035 (1975).
- 8 Only this oxide 6 (and not 7) was obtained in a poor yield (20-30%) by reaction of longifolol with $\text{Pb(OAc)}_4\text{-CaCO}_3$ in C_6H_6 : J. Lhomme and G. Ourisson, Chem. Comm. 436 (1967); Tetrahedron 24, 3177 (1968).
- 9 All compounds described in this communication were spectroscopically (IR, PMR and Mass) characterized and also gave satisfactory elemental analyses.
- 10 Six sharp singlets (of nearly similar intensities) in the methyl region of the PMR spectrum of the mixture was highly suggestive of two oxides; after separation, the two ethers displayed three singlets each: 6 (58, 63 and 72 Hz) and 7 (55, 60 and 65 Hz).
- 11 Compound identity was established in the standard manner: by direct comparison with an authentic sample (cf. carbinol 1); by physical data and superimposable spectra (IR, PMR) in the case of the oxide 2.