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Proof of a Radical Transannular Hydrogen Migration in the Longifolene Series.

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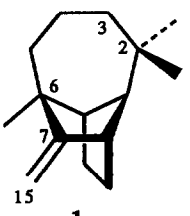
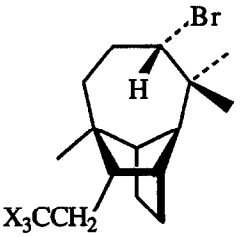
Abstract. Radical decarboxylation of isolongifolic acid **3a** *affords in good yield the thio-ether* **4** *through a reaction involving a clean 1,5-transannular hydrogen shift. The thio-ether* **4** *was further converted in almost quantitative yield into the olefin* **7** *through sequential oxidation-elimination.*

Longifolene **1** is a sesquiterpene discovered by Simonsen in *Pinus longifolia*, and encountered in many other *Pinus* species[1]. Its structure was established by X-ray crystallography[2] and extensive degradative studies[3]. Longifolene allies the rigidity of the camphene skeleton and a supplementary severe steric hindrance due to the presence of the cycloheptane ring bridging C-1 and C-5. Compounds of this type can undergo numerous Wagner-Merwein rearrangements and cationic hydride migrations[4]. Furthermore, when treated with tetrabromomethane (or bromotrichloromethane) in the presence of peroxides, longifolene **1** did not afford the normal product of addition of $^{\bullet}CX_3$ and $X^{\bullet}$ moieties (X= Br, Cl) across the 7(15) double bond, but yielded unexpected trihalogeno-bromo derivatives (10% and 30% yields respectively) to which structure **2** were assigned on the basis of nmr data and the study of the products of solvolysis[5]. A mechanistic interpretation was proposed in which the 1,5- shift of an H-atom was the key step. Although a few examples of such transannular hydrogen migrations were later reported[6], the possible operation of an ionic pathway (viz. normal addition across the double bond followed by heterolysis of the C-Br bond and hydride migration from C-3 to C-7, possibly catalysed by traces of HBr) could also be put forward.

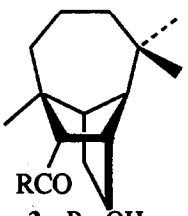
The last decade has witnessed an impressive development of synthetically useful and practical methods to generate carbon radicals under smooth and well-controlled conditions[7]. In parallel, a growing body of data concerning the kinetics of these processes now allows sharp "tuning" of radical reactions, thus rendering them selective and high-yielding. With these tools in hand, we decided to test the above hypothesis. A substrate of choice is isolongifolic acid[1,8] **3a** , since decarboxylation using the Barton thiohydroxamate reaction[10] would lead to the desired C-7 radical.



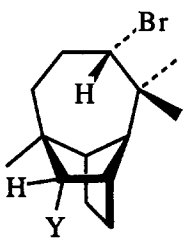
1



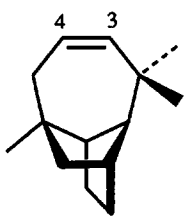
2a, X= Br
2b, X= Cl



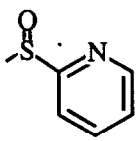
3a, R= OH
3b, R= Cl
3c, R= O-N



4, X= pyridine-2'-thiyl, Y=H
5, X= H, Y= pyridine-2'-thiyl



7

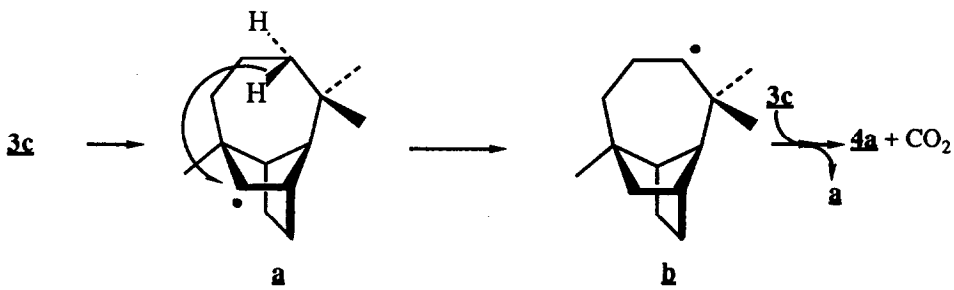
6, X= 

, Y= H

Acid **3a**, easily obtained from longifolene **1** by chromic oxidation[1], was converted to the corresponding acid chloride **3b** and added slowly (2-3 hrs) to a suspension of the sodium salt of N-hydroxy 2-thiopyridone in refluxing benzene under ordinary laboratory lighting. Under these conditions, the reaction gave essentially a single product in very high yield (96% from isolongifolic acid). This new product, isolated as an oil ($[\alpha]_D$ +8°, chloroform), had a molecular formula $C_{19}H_{27}NS$ as shown by mass spectrometry and elemental analysis; ^1H and ^{13}C 200 MHz n.m.r. analysis indicated the loss of one carbon from **3c** and the presence of an S-pyridyl residue. Multiplicities of the carbon atoms and proton coupling constants (see note 11), were in agreement with, but did not prove structure **4** as the

signal for the proton on C-3 appeared only as a large doublet (J = 11.2 Hz, the coupling constant with the other hydrogen is smaller than the resolution of the spectrometer, even at 400 MHz). Definitive confirmation was obtained by oxidising sulphide **4** with mCPBA in dichloromethane to the corresponding sulphoxide **6** (yield 96%; only one of the two possible diastereoisomers is formed in this oxidation). In the sulphoxide, the proton on C-3 appears as expected as a doublet of doublets (pyridine-d_5, 200 MHz, δ 3.52 ppm, J= 9.2 Hz, J'= 2.3 Hz). Upon thermolysis in pyridine, **6** cleanly afforded olefin **7** (quantitative yield by n.m.r.; pyridine-d_5, 200 MHz, H-3, δ= 5.25 ppm, J= 10 Hz; H-4, δ= 5.15 ppm, J= 10 Hz, J'= 7.5 Hz, J"= 2.5 Hz).

It has been amply demonstrated that thermal or photochemical decomposition of thiohydroxamic anhydrides derived from N-hydroxy pyridinethione is a radical chain reaction[10]. The only plausible mechanism for the above transformation is therefore the one depicted below. Moreover, when the decomposition of the ester **3c** was carried out at low temperature (0°C, irradiation with a tungsten lamp), a minor compound **5** (9%, H-7 δ 4.59 ppm, J=4.1 Hz, J'=1.8 Hz) was also observed, corresponding to the "normal" decarboxylative rearrangement product. This compound was present in very small amount (1-3%) in the first thermal experiment.



The radical mechanism proposed[5] thus receives a strong experimental support. The origin of the amazingly clean rearrangement described above is probably the result of several factors: a) severe steric hindrance at position 7 slows the trapping of the intermediate radical **a** by the ester **3c**; b) Hβ on C-3 is in fact very close to C-7 so the migration of Hβ from C-3 onto C-7 radical requires only a very slight motion of this hydrogen atom[12]; finally c) 2-norbornyl radicals are known to deviate from planarity[13] and are expected to be somewhat more reactive than a simple alkyl radical. These considerations probably explain the selective remote functionalisation of the C-3 unactivated methylene group, and account for the ease with which the initial tertiary radical is converted to a secondary radical in the reaction of longifolene

with bromo trihalomethanes. The clean conversion of the longifolene 1 into the tricyclic olefin 7 opens a facile access to a new class of compounds, the biological (in particular organoleptic) properties of which probably deserve further attention.

References and Notes.

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11. N.m.r. data :
    compound 4, ^{1}H (200 MHz, $CDCl_3$), δ ppm: 8.40 (1H, d, J= 4.9 Hz), 7.41 (1H, dt, J=1.9, J'= 8 Hz, J"= 8 Hz), 7.10 (1H, d, J= 8 Hz), 6.90 (1H, d, J= 5 Hz), 4.30 (1H, d, J =11.2 Hz), 1.20 (3H, s), 1.13 (3H, s), 0.98 (3H, s). ^{13}C δ ppm CH and CH_3: 149.5, 135.6, 122.7, 116.8, 66.2, 51.6, 44.2, 39.0, 30.2, 29.7; CH_2 and quaternary C: 160.4, 47.7, 43.6, 39.8 (C-2 or C-6), 37.4 (C-6 or C-2), 32.1, 29.8, 25.9. For comparison, chemical shifts of C-2 and C-6 in methyl isolongifolate and in compound 5 are δ 33.3, 43.0 and d 33.4, 41.6 ppm respectively.
    Compound 6, ^{1}H (200 MHz, pyridine-d_5), δ ppm: 3.52 (1H, dd, J= 9.2 Hz, J'= 2.3 Hz), 1.50 (3H, s), 1.45 (3H, s), 0.78 (3H, s).
    Compound 7, ^{1}H (200 MHz, pyridine-d_5), δ ppm: 5.25 (1H, d, J= 10 Hz), 5.15 (1H, ddd, J= 10 Hz, J'=7.5 Hz, J"= 2.5 Hz), 1.01 (6H, s), 0.95 (3H, s).
    We thank Dr. D. Helminger (Givaudan, Dubendorff) for kindly sending us unpublished ^{13}C n.m.r. data concerning numerous compounds of the longifolene series.
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