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Synthesis of α-Farnesene Autoxidation Products and Cross-conjugated Polyenes.

Presented in partial fulfilment of the requirements for the degree of

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Synthesis of

α-Farnesene Autoxidation Products

and Cross-conjugated Polyenes

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3-Sulfolenes (2,5-dihydrothiophene-1,1-dioxides) are well known as diene equivalents which are readily unmasked by the chelotropic elimination of sulfur dioxide under thermal conditions. This chemistry has been used in the synthesis of conjugated triene autoxidation products of α-farnesene and previously unknown cross-conjugated polyene hydrocarbons.

α-Farnesene (3,7,11-trimethylundeca-1,3E,6E,10-tetraene) is a sesquiterpene found in the surface coating of apples. The in vivo autoxidation of α-farnesene is believed to cause superficial scald, a serious post harvest disorder of the fruit. The principal α-farnesene autoxidation product, “Anet’s Trienol” (1.8a), was prepared in five steps from geraniol. The isomeric 3Z-trienol (1.8b) was also observed as a minor component (ca. 5%). Key steps involved the use of TMEDA to effect the regioselective alkylation of 3-methyl-3-sulfolene and the chelotropic elimination of sulfur dioxide from the resultant 2,3-disubstituted-3-sulfolene. The acid catalysed hydroperoxidation of “Anet’s Trienol” was achieved with anhydrous hydrogen peroxide in THF and gave the conjugated trienyl hydroperoxide (1.7a) as a single regioisomer in good yield (47%) together with traces of the stereoisomeric 3Z-trienyl hydroperoxide (1.7b) (ca. 4%). The trienyl hydroperoxides (1.7a) and (1.7b) (96:4) were cyclised efficiently under an oxygen atmosphere in the presence of “samarium peroxide” to afforded a diastereoisomeric mixture (ca. 1:1.2) of endoperoxyl hydroperoxides (1.11a) and (1.11b) (85:15). Selective reduction of the hydroperoxides (1.11a) and (1.11b) gave the corresponding endoperoxyl alcohols (1.12a) and (1.12b) (85:15) again as a mixture of diastereoisomers (ca. 1:1.2).

Alternative syntheses of these α-farnesene autoxidation products were investigated. Three regioisomeric allylic alcohols (2.1), (2.2) and (2.3a) were prepared from geranial and, when exposed to water or anhydrous hydrogen peroxide in the presence of an acid catalyst, underwent highly regioselective oxygen transposition reactions to give “Anet’s Trienol” (1.8) and the corresponding trienyl hydroperoxide (1.7) respectively as mixtures of stereoisomers. The secondary allylic alcohol (2.1) gave only the 3E-isomeric trienes (1.7a) and (1.8a), while the tertiary alcohol (2.2) and primary alcohol (2.3a) gave mixtures of the isomeric 3E and 3Z-trienes (1.7a)/(1.7b) and (1.8a)/(1.8b) dependant upon the regiochemistry of the allylic alcohol starting material. E/Z
isomeric ratios of transposition products indicated that intermediate carbocations did not interconvert under the reaction conditions. An analogous radical mechanism has been presented to explain the formation of minor 3Z-trienyl species formed under conditions consistent with the generation of farnesene peroxy radicals.

The Stille cross-coupling of simple iodinated and stannylated sulfolene derivatives was investigated as a route to bis-sulfolenes. 3-Iodo-3-sulfolene (3.37), prepared in 4 steps from 3-sulfolene, was coupled with 3-tributylstannyl-3-sulfolene (3.33) to give the bis-3-sulfolene (3.26) in excellent yield (95%). This constitutes the first synthesis of a bis-sulfolene. Molecules of this type represent masked cross-conjugated polyenes ([n]-dendralenes). In an effort to access the higher, unknown [n]-dendralenes, the Stille cross-coupling of 3-iodo-3-sulfolene (3.37) with a variety of mono- and bis-stannanes was investigated and bis-sulfolene precursors to [4]-, [5]-, [6]- and [8]-dendralene were prepared. The utility of 3-iodo-3-sulfolene (3.37) as a coupling partner in the Stille reaction was briefly investigated and a range of other, novel cross-conjugated polyene precursors were prepared. The carbonylative Stille cross-coupling of 3-iodo-3-sulfolene (3.37) was also achieved. 3,4-Diiodo-3-sulfolene (4.15) was prepared in four steps from 2-butyne-1,4-diol and coupling with 3-tributylstannyl-3-sulfolene (3.33) yielded the first example of a tris-3-sulfolene (4.13) in 43% yield.

Capillary pyrolysis (CP) was developed as a practical alternative to flash vacuum pyrolysis and proved a valuable technique for the cheleotropic elimination of sulfur dioxide from the cross-conjugated polyene precursors prepared by the Stille coupling of iodo-3-sulfolenes. Using CP, [3]-, [4]-, [5]-, [6]- and [8]-dendralene were prepared (52-89%) and their spectral characterisation was achieved. This constitutes the first general strategy for the synthesis of this poorly represented class of fundamental hydrocarbons. The synthesis of other novel cross-conjugated polyenes was achieved using CP and further demonstrated the value of this technique.

The diene-transmissive Diels-Alder reaction of the [n]-dendralenes with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) was investigated briefly and evidence for the occurrence of the theoretical maximum number of diene-transmissive Diels-Alder reactions, viz. [n-1] was obtained.
To
Andrea, my wife
and
Frank, my granddad.
Acknowledgements.

I would very much like to thank **Mick Sherburn** for his constant help and encouragement throughout the course of my Ph.D. I greatly appreciated his technical advice in the lab and enjoyed his company over a beer or two. I would have perhaps finished a little sooner had I spent more time doing chemistry rather than talking about it with Mick!

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Abbreviations.

AIBN 2,2'-azo-bis-isobutyronitrile
b.p. boiling point
aq. aqueous
br. broad
Bu butyl
BuLi n-butyl lithium
°C degrees Celsius
ca. circa (approximately)
cat. catalytic
cf. confer (compare)
cm⁻¹ wave number
con- conrotatory
COSY correlated spectroscopy
CP capillary pyrolysis
d doublet
dba dibenzylidene acetone
DBPO di-\text{-}t\text{-}butylperoxylate
DBU 1,8-diazabicyclo-[5,4,0]-undec-7-ene
DEPT distortionless enhancement by polarisation transfer
DIBALH diisobutylaluminium hydride
dis- disrotatory
DMF dimethylformamide
DMPU 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO dimethyl sulfoxide
DPA diphenylamine
DTDA diene-transmissive Diels-Alder
δ chemical shift
E electrophile
EI electron ionisation
eq. equation
equiv. molar equivalent(s)
Et ethyl
eV electron volts
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<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>ε</td>
<td>molar extinction coefficient</td>
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<tr>
<td>FAB</td>
<td>fast atom bombardment</td>
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<tr>
<td>FVP</td>
<td>flash vacuum pyrolysis</td>
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<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>GCMS</td>
<td>gas chromatography-mass spectrometry</td>
</tr>
<tr>
<td>GED</td>
<td>gas-phase electron diffraction</td>
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<tr>
<td>HETCOR</td>
<td>heteronuclear correlated spectroscopy</td>
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<td>HMPA</td>
<td>hexamethylphosphoramide</td>
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<td>HPLC</td>
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<tr>
<td>I.D.</td>
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<td>iPr</td>
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<tr>
<td>IR</td>
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<td>J</td>
<td>coupling constant</td>
</tr>
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<tr>
<td>L</td>
<td>ligand</td>
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<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
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<td>LiHMDS</td>
<td>lithium hexamethyldisilazide</td>
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<td>λ_max</td>
<td>absorption maxima (UV)</td>
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<td>mCPBA</td>
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<td>NMP</td>
<td>1-methyl-2-pyrrolidinone</td>
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<td>NMR</td>
<td>nuclear magnetic resonance</td>
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Nu nucleophile

ν_{max} absorption maxima (IR)

o- ortho-

p- para-

pTSA para-toluensulfonic acid

Ph phenyl

PhH benzene

ppm parts per million

PTAD 4-phenyl-1,2,4-triazoline-3,5-dione

pyr. pyridine

q quartet

quant. quantitative

quint quintet

rel. int. relative intensity

rfx. reflux

rt room temperature

s singlet

sat. saturated

sext sextet

sh. shoulder

sol. solution

t triplet

tBHP tert-butylhydroperoxide

THF tetrahydrofuran

tlc thin layer chromatography

TMEDA N,N,N',N'-tetramethylethlenediamine

Tol tolyl

viz. videlicet (namely)

UHP urea hydrogen peroxide complex

UV ultraviolet