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

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Abstract.

3-Sulfolenes (2,5-dihydrothiophene-1,1-dioxides) are well known as diene equivalents which are readily unmasked by the cheleotropic 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-trimethyldodeca-1,3*E*,6*E*,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 3*Z*-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 cheleotropic 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 3*Z*-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 endoperoxy hydroperoxides (**1.11a**) and (**1.11b**) (85:15). Selective reduction of the hydroperoxides (**1.11a**) and (**1.11b**) gave the corresponding endoperoxy 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 3*E*-isomeric trienes (**1.7a**) and (**1.8a**), while the tertiary alcohol (**2.2**) and primary alcohol (**2.3a**) gave mixtures of the isomeric 3*E and* 3*Z*-trienes (**1.7a**)/ (**1.7b**) and (**1.8a**)/ (**1.8b**) dependant upon on 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 3*Z*-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.

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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-*t*-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(1*H*)-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

ε	molar extinction coefficient
FAB	fast atom bombardment
FVP	flash vacuum pyrolysis
GC	gas chromatography
GCMS	gas chromatography-mass spectrometry
GED	gas-phase electron diffraction
HETCOR	heteronuclear correlated spectroscopy
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum correlation
HPLC	high pressure liquid chromatography
hr(s)	hour(s)
Hz	Hertz
I.D.	internal diameter
*i*Pr	*iso*propyl
IR	infrared
J	coupling constant
K	degrees Kelvin
L	ligand
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
Lit.	literature
λ_{max}	absorption maxima (UV)
m	multiplet
M	molar
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MHz	megahertz
min(s)	minute(s)
mmHg	millimetres of mercury
mmol	millimole
mol	mole
m.p.	melting point
nm	nanometre
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance

Nu	nucleophile
ν_{max}	absorption maxima (IR)
o-	*ortho-*
p-	*para-*
*p*TSA	*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
*t*BHP	*tert*-butylhydroperoxide
THF	tetrahydrofuran
tlc	thin layer chromatography
TMEDA	N,N,N’,N’-tetramethylethylenediamine
Tol	tolyl
viz.	*videlicet* (namely)
UHP	urea hydrogen peroxide complex
UV	ultraviolet