Synthetic Studies Towards Dictyoxetane and the Dolabellanes

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for the degree of

MASTER OF SCIENCE
in CHEMISTRY

Karla Ruth MacKenzie
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Abstract

Dictyoxetane (**1**) has been isolated from *Dictyota dichotoma*, a brown alga found in the Indian Ocean. It has an unusual pentacyclic structure which has not yet been synthesised. It is a diterpene which is closely related to the dolabellanes, an important class of bioactive compounds.

A stereoselective synthesis of the linearly fused cyclohept[f]indene system is described. Selective epoxidation of cyclo-octadiene (**142**), followed by hydrolysis to the diol (**143**) and oxidative cleavage allowed preparation of the dialdehyde (**141**) on large scale. Treatment of this with potassium carbonate causes an intramolecular aldol reaction to form cycloheptadiene-carboxaldehyde (**140**). An *E*- selective Wittig reaction is performed with 4-carboxybutyl-triphenylphosphium bromide, to produce the acid (**139**). This is subsequently converted to the vinyl ketone (**138**) followed by an intramolecular Diels Alder reaction to produce the desired cyclohept[f]indene (**137a**).

Utilisation of a *Z*- selective Wittig reaction produced methyl ester (**145*z***). Conversion to cyclohept[f]indene occurred via an intramolecular Diels-Alder of the subsequent vinyl ketone (**138*z***). Conversion of acid (**139**) to the methyl ester (**145**) followed by an intermolecular Diels Alder gave the *endo*- product. Subsequent attempts to cyclise this to the cyclohept[f]indene via an intramolecular Claisen reaction to give the third isomer were unsuccessful.

Cyclohept[f]indene is the backbone for dictyoxetane and can be efficiently synthesised in eight steps from 1,5-cyclo-octadiene (**142**) in a diastereoselective synthesis. This route allows for further modification of functionality to the linearly fused ring system and paves the way for further synthetic studies towards the dolabellanes.

Acknowlegements

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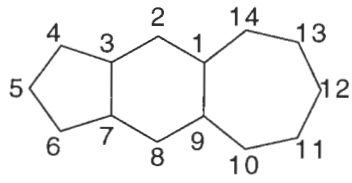
And finally to all my other friends and colleagues who supported me throughout the course of my Masters. Thanks a bunch just for being there. (I've made it!!)

List of Abbreviations

Ac	acetate
acac	2,4-pentanedione
AIBN	azodiisobutylnitrile
Am	amyl
APT	attached proton test
BHT	butylated hydroxytoluene
B.P.	boiling point
Bu	butyl
Bn	benzyl
Bz	benzoyl
COSY	correlated spectroscopy
CSA	camphorsulfonic acid
d	day(s); doublet (spectral)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarisation transfer
DIBAL	diisobutyl aluminium hydride
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
ECD	1,3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride
EDA	ethylenediamine
ee	enatiomeric excess
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
HETCOR	heteronuclear chemical shift correlation
hr(s)	hour(s)
HMPA	hexamethylphosphoramide
IMDA	intramolecular Diels-Alder
i	iso
Im	imidazole
IR	infrared
KHMDS	potassium hexamethyl disilazide

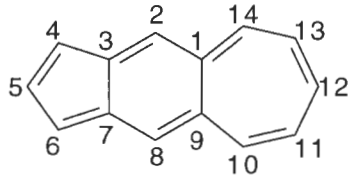
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyl disilazide
*m*CPBA	*meta*chloroperoxybenzoic acid
Me	methyl
MEM	2-methoxyethoxymethyl
MeOH	methanol
min(s)	minute(s)
MOM	methoxymethyl
M.P.	melting point
Ms	mesyl (methanesulfonyl)
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NIS	N-iodosuccinimide
NHMDS	sodium hexamethyl disilazide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
PPTS	pyridinium-*p*-toluenesulfonate
Pr	propyl
py	pyridine
RT	room temperature
t	tertiary; triplet (spectral)
TBAF	tetra butyl ammonium fluoride
TBS	tertiary butyldimethylsilyl
TBDPS	tertiary butyldiphenylsilyl
TLC	thin layer chromatography
THF	tetrahydrofuran
THP	tetrahydropyran
TMS	tetramethylsilane
Tol	tolyl
TPS	triisopropylsulfonyl
Ts	tosyl

Nomenclature



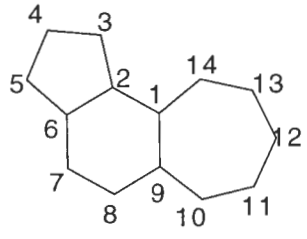
cyclohept[f]indane

The IUPAC name for the linearly fused [5,6,7] ring system shown is tricyclo[7.5.0.$0^{3,7}$]tetradecane. *Chemical Abstracts* refers to this structure as cyclohept[f]indane and the fully conjugated system is named cyclohept[f]indene.



cyclohept[f]indene

The angularly fused system, tricyclo[7.5.0.$0^{2,6}$]tetradecane is referred to as cyclohept[g]indane.

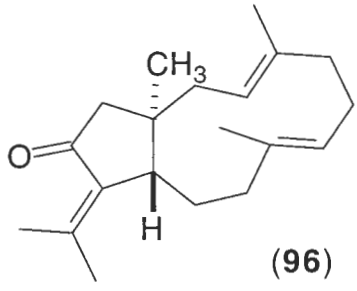


cyclohept[g]indene

Throughout this report cyclohept[f]indene refers to a linearly fused, unsaturated tricyclo[7.5.0.$0^{3,7}$]tetradecene skeleton (i.e. *not* fully conjugated). Further functionality is not differentiated by the use of this term. Cyclohept[g]indene is used in a similar manner.

Stereochemistry

Throughout this work the absolute stereochemistry of dictyoxetane and the dolabellanes are drawn according to Corey.[1] In his enatioselective synthesis of a naturally occurring dolabellatrienone, Corey observed a similar dextrorotation for compound (**96**) to that previously observed for the natural product.



(**96**)

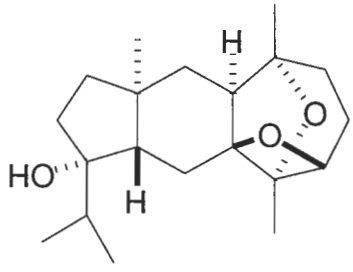
The natural product had previously been assigned the opposite absolute configuration (arbitrarily). Many of the publications relating to the isolation and synthesis of the dolabellanes are therefore believed to depict the wrong enantiomer.

1. Introduction

1.1 Dictyoxetane

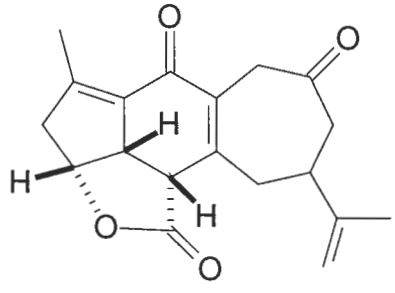
The pentacyclic diterpene dictyoxetane (**1**) is related to the dolabellanes, an important class of compounds displaying a wide range of therapeutic activity. Dictyoxetane was isolated from the cosmopolitan brown alga *Dictyota dichotoma*. This alga is widespread and has been extensively studied for therapeutic activity.

A number of other classes of diterpenes, including the dolabellanes, have been isolated from this alga.[2] Dictyoxetane was extracted from a sample of *Dictyota dichotoma* collected off the coast of India. Its structure was deduced by single crystal x-ray analysis.[3] The absolute stereochemistry of dictyoxetane is yet to be defined.



(1) dictyoxetane

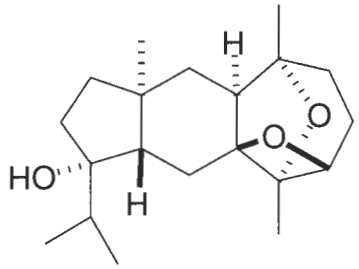
Although five, six and seven membered rings are common in natural products, the [5,6,7] linearly fused ring system is not. The only other example reported in the literature is yonarolide (**2**) which was isolated from a soft coral.[4] The structure of this norditerpenoid was determined by spectroscopic analysis, although its absolute stereochemistry has not been elucidated.



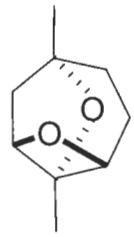
(2) yonarolide

1.1.1 Previous Synthetic Work

Previous synthetic work relating to dictyoxetane is limited to two published papers which describe the synthesis of the dioxatricyclononane moiety (**Figure 1**). The earlier work of Reinecke and Hoffman[5] published in 1995 employed an oxabicyclic ketone as the carbon skeleton and used an intramolecular S_N2 displacement of a tosylate to form the oxetane ring (**Scheme 1**).



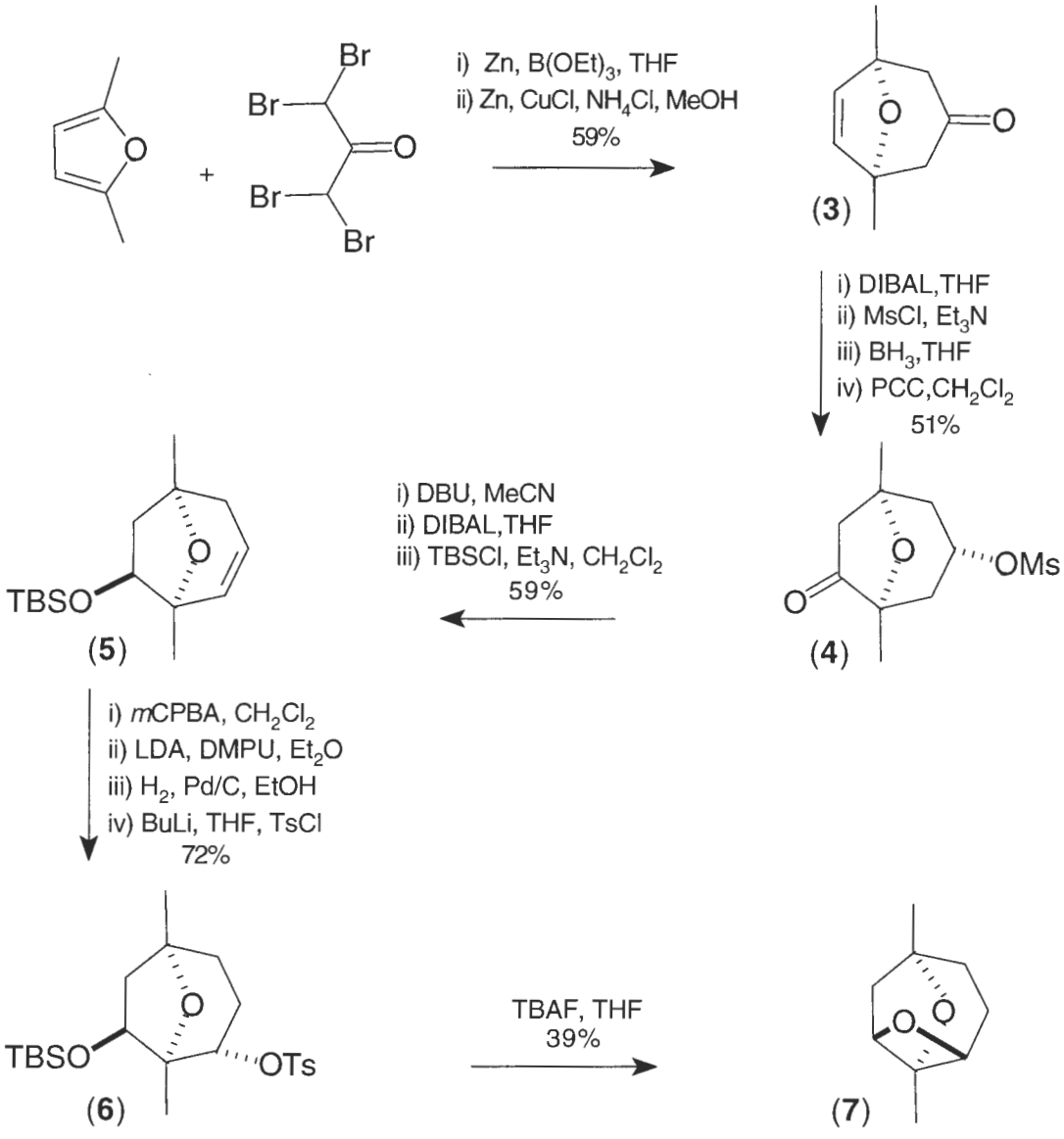
dictyoxetane



2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane

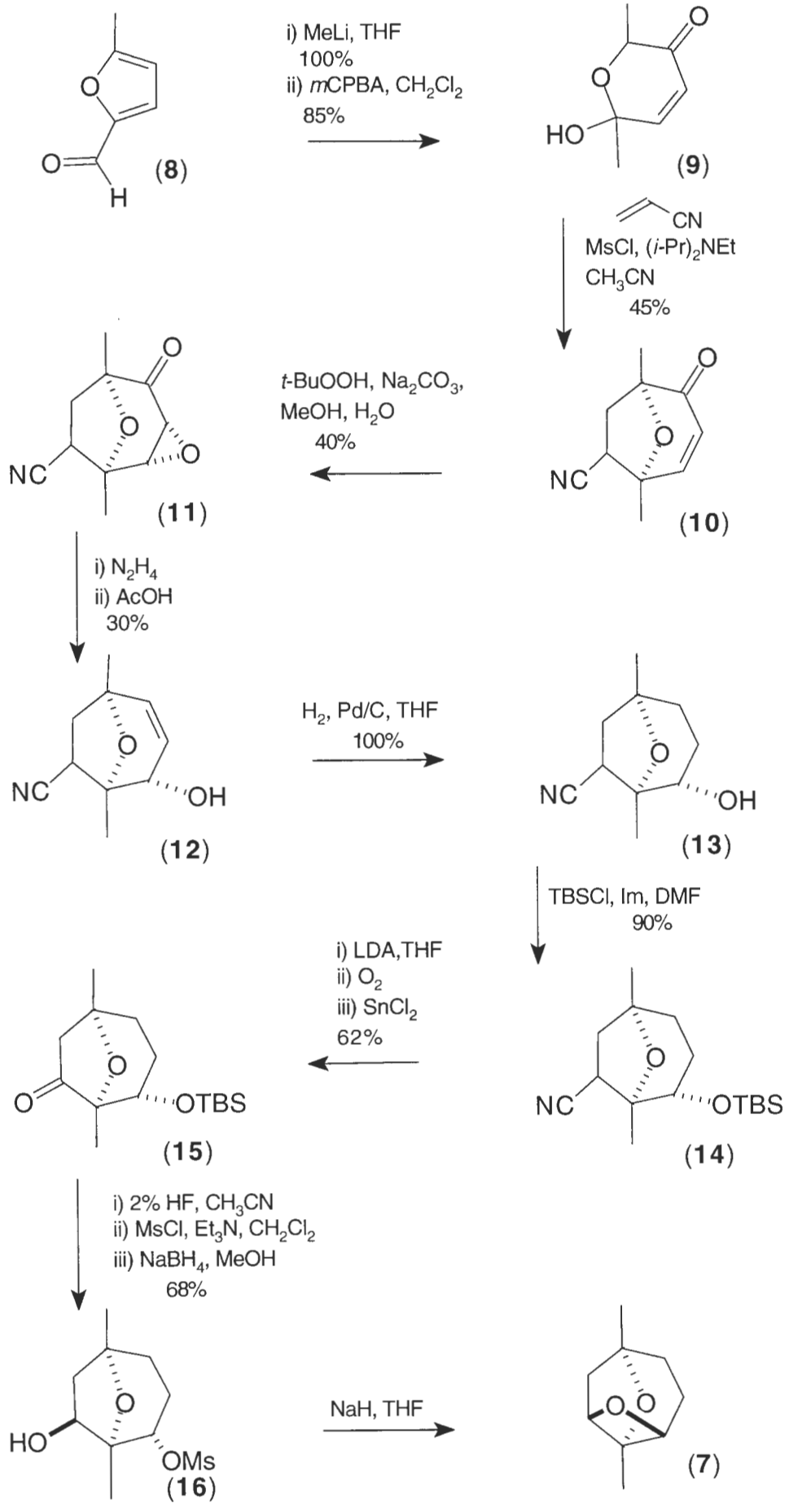
Figure 1

Bicyclic ketone (**3**) was synthesised from 2,5-dimethylfuran and 1,1,3,3-tetrabromo-2-propanone in the presence of copper and zinc powder under sonication. The resulting ketoolefin could be reduced stereoselectively to the alcohol with DIBAL. Mesylation followed by a hydroboration/oxidation gave the ketomesylate (**4**) and its regioisomer in 79% yield. Treatment with DBU gave a mixture of the two possible regioisomeric alkenes in an 8:1 ratio. Reduction with DIBAL produced the secondary alcohol which was protected (**5**) and subsequently epoxidised. The epoxide was subjected to base mediated ring opening (LDA, DMPU) to furnish the allylic alcohol. Hydrogenation followed by tosylation produced 7-*endo*-hydroxy-2-*exo*-tosylate (**6**) which was deprotected and cyclised in a single operation using TBAF to produce (**7**) as a volatile liquid in 39% yield (**Scheme 1**).



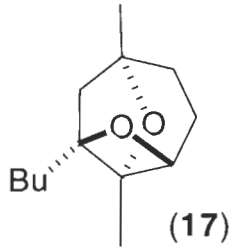
Scheme 1

The more recent work, carried out by the Heathcock group[6] employed a dipolar cycloaddition of a 3-oxidopyrylium salt with acrylonitrile to create the carbon skeleton and a similar intramolecular S_N2 displacement of a mesylate to form the oxetane ring (**Scheme 2**).

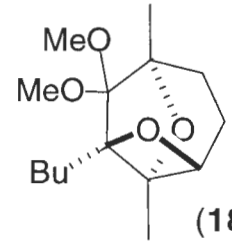

i) MeLi, THF
100%
ii) mCPBA, CH2Cl2
85%
(8)
(9)
CN
MsCl, (i-Pr)2NEt
CH3CN
45%
t-BuOOH, Na2CO3,
MeOH, H2O
40%
(10)
(11)
i) N2H4
ii) AcOH
30%
H2, Pd/C, THF
100%
(12)
(13)
TBSCl, Im, DMF
90%
i) LDA,THF
ii) O2
iii) SnCl2
62%
(14)
(15)
i) 2% HF, CH3CN
ii) MsCl, Et3N, CH2Cl2
iii) NaBH4, MeOH
68%
NaH, THF
(16)
(7)

Scheme 2

Treatment of commercially available 5-methylfurfural (**8**) with MeLi produced 2-furfurylcarbinol in quantitative yield. Oxidative rearrangement with *m*CPBA efficiently converted this to enone (**9**). Cycloadduct (**10**) was produced from (**9**) and acrylonitrile as a mixture of regioisomers (10:1, 45%). Nucleophilic epoxidation of enone (**10**) gave epoxy ketone (**11**) and subsequent Wharton transposition of (**11**) to (**12**) were both low yielding. Allylic alcohol (**12**) was hydrogenated to the saturated alcohol (**13**) which was silylated in high yield (**14**). Ketone (**15**) was obtained by oxidative decyanation of (**14**) with LDA and oxygen. Deprotection of the silyl group afforded the alcohol which was converted to the mesylate. Stereoselective sodium borohydride reduction of (**15**) gave the alcohol precursor (**16**). Treatment with NaH in refluxing THF produced the volatile tricyclic ether (**7**) which was determined only by proton NMR. Analogues of (**7**), compounds (**17**) and (**18**) were also prepared which had decreased volatility thus allowing full characterisation and stereochemical determination (**Figure 2**).



(**17**)



(**18**)

Figure 2

Although Heathcock's synthesis is more recent it is less efficient. It does exhibit similarities to Hoffman's process. Heathcock uses three steps and a [5+2] cycloaddition to produce a similar carbon skeleton to that of Hoffman's. In contrast Hoffman uses two steps and a [4+3] cycloaddition. They both use an intramolecular S_N2 displacement as the final step in the formation of the tricycle. Heathcock uses a mesylated alcohol and an alkoxide formed from the action of a strong base on an alcohol for the intramolecular displacement. Hoffman uses a tosylated alcohol with the alkoxide formed from the deprotection of a silylated alcohol. These racemic syntheses produced the dioxatricyclic component of dictyoxetane. The overall yield for Hoffman's twelve step scheme was 3%. The less efficient synthesis produced by Heathcock required fifteen steps and gave an overall yield of less than 2%. Heathcock was not able to obtain an accurate yield for the cyclisation step or fully characterise his original dioxatricycle due to volatility. Unfortunately these syntheses would appear to be unsuitable for application towards dictyoxetane, as they are not flexible enough to allow production of the tricycle annealated to another ring.

1.1.2 Biosynthesis of Dictyoxetane

Hoffman's synthesis of the dioxatricyclic core formed the basis of a biosynthetic proposal for dictyoxetane, in which a known metabolite, a dolabellane, is cyclised to produce the linearly fused [5,6,7] ring system.

The proposed biosynthetic pathway of dictyoxetane (**Figure 3**) is through the transannular cyclisation of a dolabellane (**19**), also isolated from *Dictyota dichotoma*.[5]

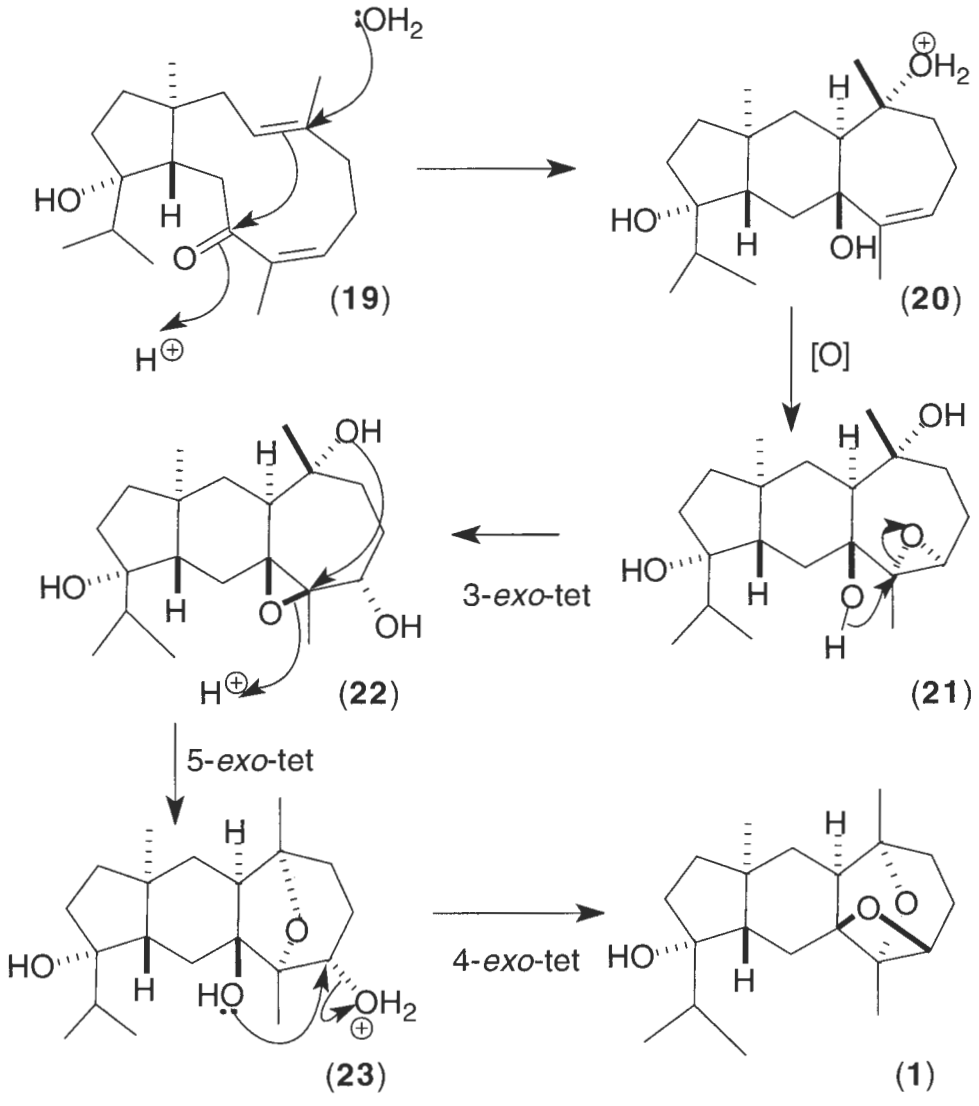
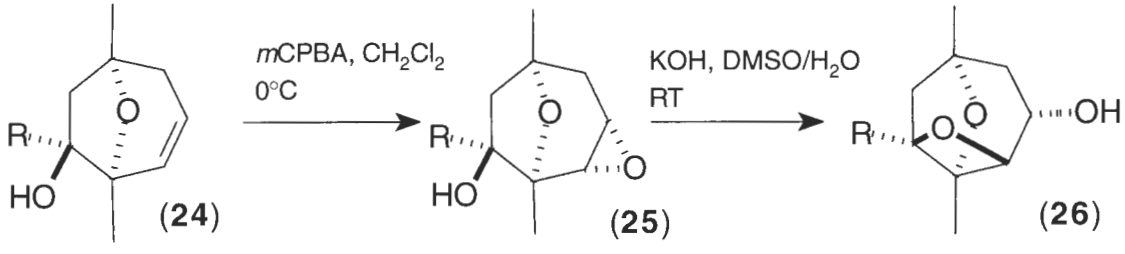


Figure 3

Thus it was proposed that the previously isolated metabolite (**19**) undergoes an acid catalysed transannular cyclisation to produce a tertiary carbocation which is trapped by addition of a water molecule from the bottom face (**20**). Epoxidation of alkene (**21**) produces (**22**) which subsequently undergoes a Payne rearrangement to produce the regioisomeric epoxide (**23**). Two successive transannular cyclisations form (**1**), completing the process.

It has been postulated that the dioxatricyclic moiety is too volatile to be biosynthesised prior to the formation of the linearly fused ring system. Hoffman and Reinecke produced evidence to support this proposal *in vitro.* Their synthesis of the oxatricyclic component of dictyoxetane and the formation of their other hydroxyoxetanes (**Scheme 3**) supports the rapid formation of the tricyclic oxetane core, under mild conditions, in high yields (80-82%).



R=H
R=Me

Scheme 3

Epoxidation of homoallylic alcohol (**24**) was carried out with *m*CPBA affording (**25**) in 75% yield (R=H) or 58% yield (R=Me). Tricyclic oxetane (**26**) was formed in high yield by the reaction of a relatively weak base with epoxyalcohol (**26**). As described above this facile cyclisation suggests that the formation of the hydroxyoxetane ring will occur readily in nature.