A methodology for the synthesis of cyclopentanoid natural products containing two vicinal quaternary carbon atoms

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Abstract
A six-step general methodology has been developed for the synthesis of cyclopentanones containing two vicinal quaternary carbon atoms starting from β, γ, γ-trisubstituted allyl alcohols. The three key reactions present in the sequence are: (i) the one-step Johnson’s ortho ester Claisen rearrangement of allyl alcohols; (ii) intramolecular cyclopropanation of γ, δ-unsaturated α′-diazoketones; and (iii) the regiospecific ring opening of the cyclopropyl ketones employing lithium in liquid ammonia reduction conditions. The synthetic utility of this methodology was exemplified by the total synthesis of the sesquiterpenoids, cyclolaurones, β-cuparenone, albene and thapsanes.

Key words: Claisen rearrangement, diazo ketone cyclopropanation, regiospecific cyclopropane ring cleavage.

1. Introduction
Sesquiterpenes, biogenetically derived from farnesyl pyrophosphate, are assembled in acyclic, mono-, bi-, tri- and even tetracyclic structures, containing small, medium and large rings with a wide range of functionalities1. The great diversity in their molecular architecture has made terpene synthesis a challenging and exciting area of research2. One common feature present in many multicyclic sesquiterpenes is the presence of quaternary carbon atoms. Even though a variety of methodologies have been developed for the formation of carbon-carbon bond, the presence of two or more quaternary carbon atoms in a contiguous manner often poses a formidable synthetic challenge. In continuation of our interest in the development of synthesis to sesquiterpenoids in our laboratory a general methodology has been exploited for the construction of a cyclopentane ring incorporating two vicinal quaternary carbon atoms, starting from β, γ, γ-trisubstituted allyl alcohols based on the Claisen rearrangement3, intramolecular diazo ketone cyclopropanation4 and a regiospecific cyclopropane ring

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cleavage sequence. The Johnson's ortho ester Claisen rearrangement of a β, γ, γ-trisubstituted allyl alcohol 1 generates the β, β-disubstituted γ,δ-unsaturated ester 2 creating the first quaternary carbon atom. Copper-catalysed decomposition of the diazo ketone 3, derived from the ester 2 via the corresponding acid and acid chloride, and the intramolecular insertion of the resultant ketocarbenoid into the olefin furnishes the cyclopropyl ketone 4, thus creating the second quaternary carbon atom vicinal to the first one. Regiospecific cleavage of the less-substituted cyclopropane bond generates the cyclopentanone 5 containing two vicinal quaternary carbon atoms. In this account, we describe the application of this strategy in the total synthesis of cyclopentanoid sesquiterpenes, (±)-cyclolauren, (±)-β-cuparenone, (±)-albene and (±)-thapsanes.

Scheme 1.

2. Synthesis of (±)-cyclolauren, (±)-epicyclolauren and (±)-β-cuparenones

Recently, Higa and Ichiba have reported the isolation of cyclolauren 6, the parent hydrocarbon of the tricyclic aromatic sesquiterpenes laurinterols, from the sea hare, Aplysia dactylomela along with cyclolaurenols and cupalaurenols. The bicyclic sesquiterpene, β-cuparenone (8) was first isolated from the ketonic fraction of Thuja orientalis (mayur pankhi), and later on its presence was detected in various essential oils. The methodology depicted in Scheme 1 readily identified the cyclopropyl ketone 9 as the common precursor for both the cyclolauren and β-cuparenones with the cinnamyl alcohol 10 as the requisite starting material. The synthetic sequence starting from p-methylacetophenone (11) is depicted in Scheme 2. Thus, Wittig-Horner-Emmons reaction (NaH, triethyl α-phosphonopropionate, THF, reflux) followed by reduction (LAH/EtOH) of the resultant cinnamate transformed the ketone 11 into the cinnamyl alcohol 10, the requisite starting material for the Claisen rearrangement. The first quaternary centre was created employing the ortho ester Claisen rearrangement.
Thermal activation of the cinnamyl alcohol 10 and triethyl ortho acetate in the presence of a catalytic amount of propionic acid in toluene (160°C, 36 h) followed by base-catalysed hydrolysis of the resultant ene-ester 12 furnished the ene-acid 13. Treatment of the acid chloride 14, obtained from the acid 13 and oxalyl chloride, with an excess of ethereal diazomethane generated the diazo ketone 15. Anhydrous copper sulfate-catalysed intramolecular cyclopropanation reaction of the diazo ketone
15 in refluxing cyclohexane furnished an inseparable (1:2) epimeric mixture of the cyclopropyl ketone 9, the common precursor for cyclolaurenes and β-cuparenone. Regiospecific cyclopropane ring cleavage of the epimeric mixture of cyclopropyl ketone 9 with lithium in liquid ammonia furnished the β-cuparenone (8). For the sake of separation of the epimers, the cyclopropyl ketone 9 was stereospecifically reduced by sodium borohydride to the endo alcohols 16 and 17. Oxidation of the alcohols 16 and 17 with PCC, buffered with NaOAc, furnished the cyclopropyl ketones 9a and 9b. Finally, Huang–Minlon-modified Wolff–Kishner reduction transformed the cyclopropyl ketones 9a and 9b into cyclolaurene (6) and epicyclolaurene (18), respectively7.

3. Regio- and stereospecific synthesis of (±)-albene

The trisnor sesquiterpene albene (19) was first isolated16 in 1962 from Petasites albus, and later on its presence was found ubiquitous in the plants of genera Petasites (white pestilence weed) and Adenostyles. The structure of albene as the exo isomer 19 was established13 conclusively in 1978 after an initial assignment18 as the endo isomer 20 (now commonly referred to as isoalbene). The unique exo 2,6-dimethyltricyclo[5.2.1.02,6]decane skeleton incorporating two vicinal quaternary carbon atoms makes albene an interesting synthetic target. Based on the general methodology described in Scheme 1, a regio- and stereospecific synthesis of albene was achieved8 via a prochiral precursor 21. The allyl alcohol 22 was chosen as the starting material in anticipation that the acetate side chain will be introduced from the less-hindered exo face of the norbornane system during the Claisen rearrangement which will result in the endo orientation for the tert-methyl group as required. The synthetic sequence is depicted in Scheme 3. The requisite starting material, allyl alcohol 22, was prepared from cyclopentadiene via the Diels–Alder reaction with tetrolic acid. Thus, thermal activation of a mixture of cyclopentadiene and tetrolic acid followed by esterification of the resultant adduct with ethereal diazomethane resulted in the norbornadiene 23. The adduct 23 was transformed regiospecifically into the allyl alcohol 22 by hydrogenation of the less-substituted olefin followed by reduction of the resultant dihydro derivative 24 with diisobutylaluminium hydride (DIBAH). As anticipated, the ortho ester Claisen rearrangement of the allyl alcohol 22 with triethyl ortho acetate in the presence of a catalytic amount of propionic acid (sealed tube, 180°C) furnished stereospecifically the ester 25, which on hydrolysis with aqueous sodium hydroxide furnished the ene-acid 26. Anhydrous copper sulfate-catalysed intramolecular cyclopropanation reaction of the diazo ketone 27, obtained from the ene-acid 26 via the corresponding acid chloride, furnished stereospecifically the cyclopropyl ketone 28.
via the insertion of the carbene from exo face of the norbornane system. Regiospecific cleavage of the cyclopropane ring using lithium in liquid ammonia reduction conditions transformed the cyclopropyl ketone 28 into the prochiral ketone 21. Alternatively, catalytic hydrogenation of the less-substituted cyclopropane bond in the cyclopropyl ketone 28 also furnished the prochiral ketone 21 in quantitative yield. Formation of the corresponding tosyl hydrazone (TsNHNH₂, EtOH) followed by a Sharpie reaction (n-BuLi, TMEDA-Et₂O) converted the prochiral ketone 21 into (+)-albene (19). 

![Chemical structure](attachment:chemical_structure.png)

**Scheme 3.** (a) (i) Δ; (ii) CH₃N₂, Et₂O, RT; (b) (i) H₂-Pd/C, EtOAc; (ii) DIBAH, toluene, -70°C; (c) (i) MeC(OEt)₂, EtCOOH, sealed tube, 180°C; (ii) MeOH, aq. NaOH, reflux; (d) (i) (COCl)₂, C₆H₆, RT; (ii) CH₃N₂, Et₂O, RT; (e) CuSO₄; c-C₆H₁₂, hv; (f) Li, liquid NH₃; (g) NH₂NH-Ts, EtOH, reflux; (h) n-BuLi, Et₂O-TMEDA, 0°C.

4. Synthesis of thapsanes

Recently, a series of thapsanes, both hemiacetalic and open form, have been isolated from the Mediterranean umbelliferous plant *Thapsia villosa var minor*. A characteristic of the structure of this new class of sesquiterpenes is the presence of
the unique cis, anti, cis-3b,4,4,7a-tetramethyldecahydroindenol[1,2-c]furan moiety, incorporating three contiguous quaternary carbon atoms. Generation of three contiguous quaternary carbon atoms in hydrindane framework in order to build the thapsane skeleton poses a considerable synthetic challenge. First attention was focussed\textsuperscript{9,10} on the construction of the crucial 3a,4,4,7a-tetramethylhydrindane system, e.g., 29 containing three contiguous quaternary carbon atoms.

\[
\begin{align*}
X = Y = H, & \quad Z = 0 \text{Ang} \\
X = Y = H, & \quad Z = 0 \text{Sen} \\
X = Y = H, & \quad Z = O \text{Coum} \\
X = Y = H, & \quad Z = 0 \text{Fer} \\
Y = Z = H, & \quad X = 0 \text{Ang} \\
X = Y = Z = H
\end{align*}
\]

\[
\begin{align*}
\text{Ang} = & \quad \overset{0}{\text{C}} - \overset{\text{Me}}{\text{C}} \equiv CHMe \\
\text{Sen} = & \quad \overset{0}{\text{C}} - \overset{\text{Me}}{\text{C}} \equiv CMe_2 \\
\text{Coum} = & \quad \overset{0}{\text{C}} - \overset{\text{Me}}{\text{C}} \equiv CHCH_2OH \\
\text{Fer} = & \quad \overset{0}{\text{C}} - \overset{\text{Me}}{\text{C}} \equiv CHCH_2OH
\end{align*}
\]

The methodology described in the previous sections readily identified cyclogeraniol \textsuperscript{30} as the starting material, containing one quaternary carbon atom. The synthetic sequence is depicted in Scheme 4. The ortho ester Claisen rearrangement of cyclogeraniol \textsuperscript{30} with triethyl ortho acetate and propionic acid followed by base-catalysed hydrolysis of the resultant ester \textsuperscript{31} furnished the ene-acid \textsuperscript{32}. Treatment of the acid chloride \textsuperscript{33}, obtained from the acid \textsuperscript{32} and oxalyl chloride, with an excess of ethereal diazomethane furnished the key diazo ketone \textsuperscript{34}. Anhydrous copper sulfate-catalysed intramolecular cyclopropanation reaction of the diazo ketone \textsuperscript{34}, stereospecifically generated the cyclopropyl ketone \textsuperscript{35}, a known degradation product\textsuperscript{21} of the sesquiterpene thujopsene. Finally, the regiospecific cleavage of the C\textsubscript{2}–C\textsubscript{3} cyclopropane bond by using lithium in liquid ammonia transformed the cyclopropyl ketone \textsuperscript{35} into hydrindanone \textsuperscript{29}, thus creating two vicinal quaternary carbon atoms in addition to the one present in cyclogeraniol (30) in a contiguous manner. However, for the construction of the thapsane skeleton, further elaboration of the hydrindanone \textsuperscript{29} posed serious regiochemical
problems as the two methylenes α to carbonyl group in 29 are not easily distinguishable. To overcome this, the sequence was slightly modified and diazoothane was used instead of diazomethane as depicted in Scheme 5. Thus, treatment of the acid chloride 33 with an excess of ethereal diazoothane generated the diazo ketone 36, which on intramolecular cyclopropanation reaction, furnished the cyclopropyl ketone 37. Regiospecific cleavage of the cyclopropane bond in the cyclopropyl ketone 37 using lithium in liquid ammonia furnished the pentamethylhydridanone 38 in a stereospecific manner. The fifteenth carbon required to complete the construction of the carbon skeleton present in thapsanes was introduced using a Wittig olefination reaction. Consequently, reaction of the hydridanone 38 with methylenetriphenylphosphorane resulted in the thaps-7(15)-ene (39), which on isomerisation with PTSA furnished the thaps-6-ene (40), the hypothetical biogenetic precursors of thapsanes. Oxidation of the thapsane 40 with tert-butyl hydroperoxide and a catalytic amount of chromium trioxide furnished the thapsenone 41, a degradation product of the natural thapsane.1

For the synthesis of a hemiacetalic thapsane, the methodology was slightly modified in order to have a functionalised fourteenth carbon as depicted in Scheme 6.11,12 Thus, one-pot Claisen rearrangement22 of cyclogeraniol (30) with 2-methoxypropene and a catalytic amount of propionic acid furnished the γ,δ-unsaturated enone 42. Generation of the kinetic enolate of the enone 42 with LiN(Me3Si)2 and quenching
Scheme 5. (a) MeCHN₂, Et₂O, RT; (b) CuSO₄; c-C₃H₇, hv(NV); (c) Li, liq. NH₃; (d) Ph₃P⁺CH₂⁺Br, K⁺-Or-Am, c-C₃H₇, k-AmOH; (e) PTSA, CH₂Cl₂, RT; (f) CrO₃, t-BuOOH, CH₂Cl₂, RT.

with ethyl chloroformate gave the β-ketoester 43. Transformation of the β-ketoester 43 into the key intermediate, α-diazo-β-ketoester 44 was conveniently achieved via the diazotransfer reaction with tosyl azide in the presence of triethyl amine. Decomposition of the diazo compound 44 with a catalytic amount of rhodium acetate in benzene stereospecifically furnished the cyclopropyl β-ketoester 45. Cleavage of the cyclopropane ring in 45 using lithium in liquid ammonia produced a 1:1 mixture of the β-ketoester 46 and the decalin derivative 47. Formation of the two products 46 and 47 can be rationalised as follows: transfer of an electron to the carbonyl group of either ketone or of ester, followed by the cleavage of the respective cyclopropyl bond which has maximum overlap with the π-orbital of the particular carbonyl system. The β-ketoester 46 was further elaborated and the final carbon was introduced.
by Wittig methylenation in refluxing benzene to furnish the ene-ester 48. The third ring in thapsanes was constructed via the epoxide 49. Reaction of the ene-ester 48 with magnesium monoperoxyphthalate resulted in the epimeric mixture of the epoxides 49. Treatment of the epoxide mixture 49 with a catalytic amount of BF$_3$.OEt$_2$ furnished the hemiacetal 50 instead of the expected ester aldehyde 51. Reduction of the hemiacetal 50 with triethylsilane in refluxing trifluoroacetic acid furnished the lactone 52, the oxidation product of the natural thapsane 53. Finally, the lactone 52 on reduction with DIBAH generated the thapsane 53.
In conclusion, a six-step synthetic sequence using Claisen rearrangement, intramolecular cyclopropanation of γ,δ-unsaturated α'-diazo ketones and reductive cyclopropane ring cleavage as the key steps was exploited for the construction of cyclopentanoids with two vicinal quaternary carbon atoms. The synthetic utility of this sequence has been exemplified by the synthesis of the sesquiterpenoids (±)-cyclolaurenes, (±)-cuparenone, (±)-albene and (±)-thapsanes. The recent discovery on the dramatic acceleration of the ortho ester Claisen rearrangement of allyl alcohols by employing microwave heating technique enhances the versatility of this methodology.

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References

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