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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′-diazo ketones; 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, cyclolaurenes, 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 functionalities[1]. The great diversity in their molecular architecture has made terpene synthesis a challenging and exciting area of research[2]. 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 rearrangement,[3] intramolecular diazo ketone cyclopropanation[4] and a regiospecific cyclopropane ring

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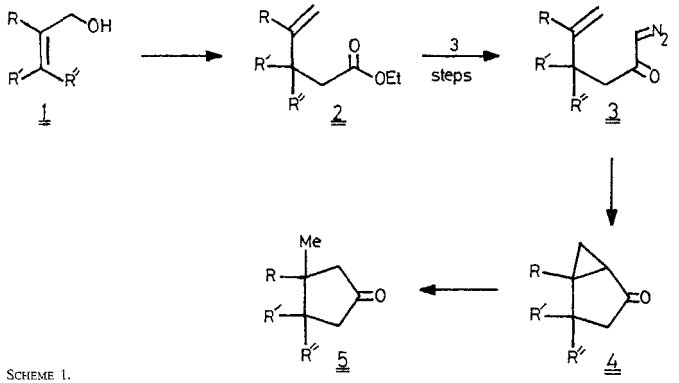
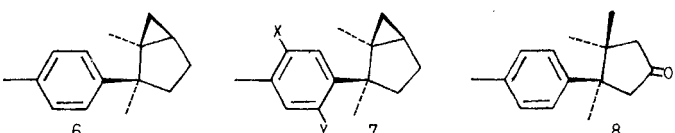
cleavage[5] sequence. The Johnson's *ortho* ester Claisen rearrangement[6] of a β, γ, γ-trisubstituted allyl alcohol **1** generates the β, β-disubstituted γ,δ-unsaturated ester **2** creating the first quaternary carbon atom. Copper-catalysed decomposition of the diazo ketone **3**, derived from the 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[7–12] in the total synthesis of cyclopentanoid sesquiterpenes, (±)-cyclolaurenes, (±)-β-cuparenone, (±)-albene and (±)-thapsanes.



SCHEME 1.

2. Synthesis of (±)-cyclolaurene, (±)-epicyclolaurene and (±)-β-cuparenones

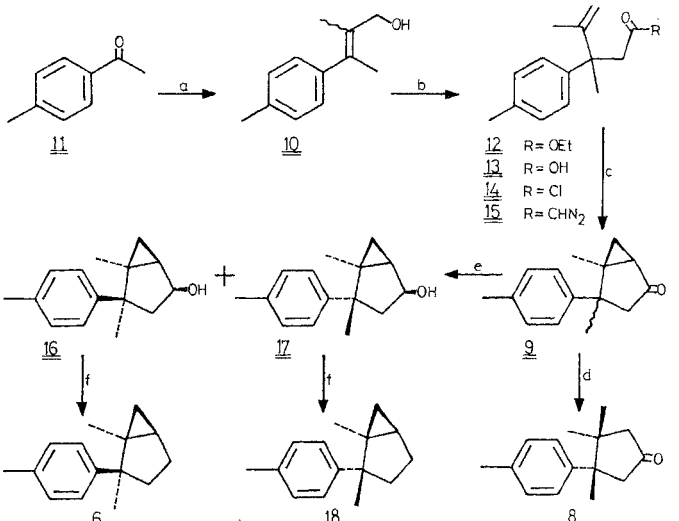
Recently, Higa and Ichiba[13] have reported the isolation of cyclolaurene **6**, the parent hydrocarbon of the tricyclic aromatic sesquiterpenes laurinterols **7**[14], from the sea hare, *Aplysia dactylomela* along with cyclolaurenols and cupalaurenols. The bicyclic sesquiterpene, β-cuparenone (**8**) was first isolated[15] 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 cyclolaurene and β-cuparenones with the cinnamyl alcohol **10** as the requisite starting material[7]. 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/Et_2O) 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.



6 7 8

X=Br or H; Y=OH
X=OH or OAc; Y=Br

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



11 10 12 R=OEt
13 R=OH
14 R=Cl
15 R=CHN2

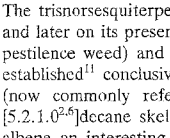
16 17 9 6 18 8

SCHEME 2. (a) (i) $(OEt)_2P(O)CHMeCOOEt$, NaH, THF, reflux; (ii) LAH, Et_2O, −78°C; (b) $MeC(OEt)_3$, EtCOOH, toluene, sealed tube, 160°C; (c) (i) MeOH, 10% aq. NaOH, reflux; (ii) $(COCl)_2$, C_6H_6, RT; (iii) CH_2N_2, Et_2O, RT; (iv) $CuSO_4$, *c*-C_6H_{12}, *hν*; (d) Li, liquid NH_3; (e) $NaBH_4$, MeOH, RT; (f) (i) PCC, NaOAc, CH_2Cl_2, RT; (ii) NH_2NH_2, digol, reflux,; Na in digol, reflux

15 in refluxing cyclohexane furnished an inseparable (1:2) epimeric mixture of the cyclopropyl ketone **9**, the common precursor for cyclolaurenes and β-cuparenones. 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**), respectively[7].

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

The trisnorsesquiterpene albene (**19**) was first isolated[16] 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 established[11] conclusively in 1978 after an initial assignment[18] as the *endo* isomer **20** (now commonly referred to as isoalbene). The unique *exo* 2,6-dimethyltricyclo [5.2.1.$0^{2,6}$]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 achieved[8] *via* a prochiral precursor **21**. The allyl alcohol **22** was chosen as the starting material in



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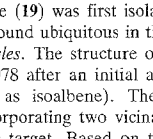

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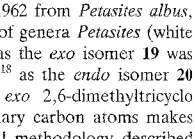

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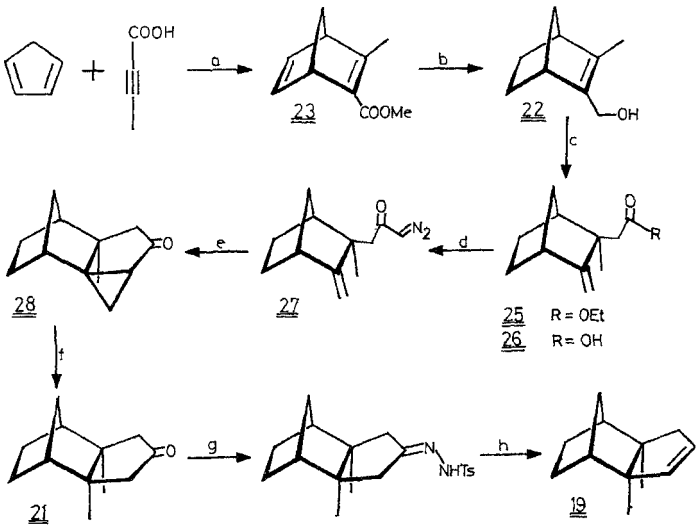
anticipation that the acetate side chain will be introduced from the less-hindered *exo* face of the norbornane system during the Claisen rearrangement which will result in the *endo* orientation for the *tert*-methyl group as required. The synthetic sequence is depicted in Scheme 3. The requisite starting 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 ($TsNHNH_2$,EtOH) followed by a Sharpiro reaction (*n*-BuLi, TMEDA–Et_2O) converted the prochiral ketone **21** into (±)-albene (**19**)[8].

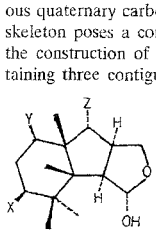


SCHEME 3. (a) (i) Δ; (ii) CH_2N_2, Et_2O, RT; (b) (i) H_2–Pd/C, EtOAc; (ii) DIBAH, toluene, −70°C; (c) (i) $MeC(OEt)_3$, EtCOOH, sealed tube, 180°C; (ii) MeOH, aq. NaOH, reflux; (d) (i) $(COCl)_2$, C_6H_6, RT; (ii) CH_2N_2, Et_2O, RT; (e) $CuSO_4$; c-C_6H_{12}, *hν*; (f) Li, liquid NH_3; (g) NH_2NH–Ts, EtOH, reflux; (h) *n*-BuLi, Et_2O–TMEDA, 0°C.

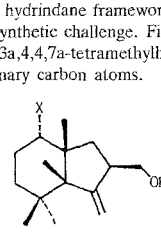
4. Synthesis of thapsanes

Recently, a series of thapsanes, both hemiacetalic and open form, have been isolated[19] from the Mediterranean umbelliferous plant *Thapsia villosa* var *minor*. A characteristic of the structure of this new class of sesquiterpenes is the presence of

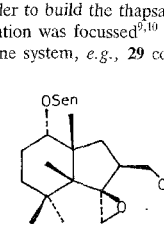
the unique *cis, anti, cis*-3b,4,4,7a-tetramethyldecahydroindeno[1,2-c]furan moiety, incorporating three contiguous quaternary carbon atoms. Generation of three contiguous quaternary carbon atoms in hydrindane framework in order to build the thapsane skeleton poses a considerable synthetic challenge. First attention was focussed[9,10] on the construction of the crucial 3a,4,4,7a-tetramethylhydrindane system, *e.g.*, **29** containing three contiguous quaternary carbon atoms.



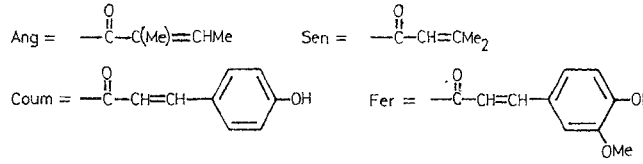
X = Y = H, Z = OAng
X = Y = H, Z = OSen
X = Y = H, Z = OCoum
X = Y = H, Z = OFer
X = Z = H, Y = OSen
Y = Z = H, X = OAng
X = Y = Z = H



X = OSen, R = H
X = R = H
X = H · R = Fer

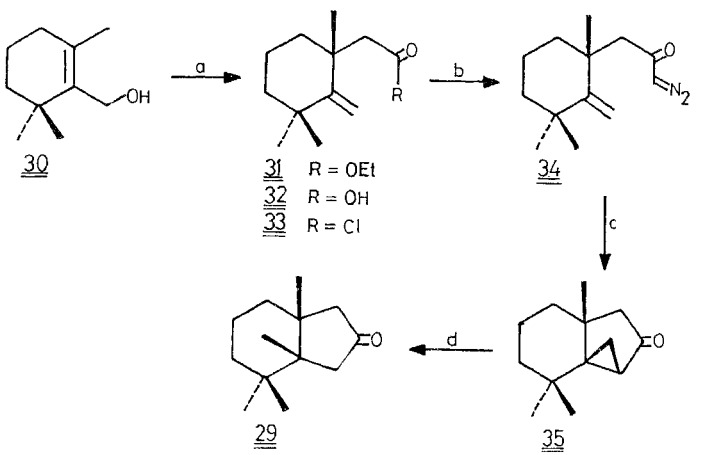


R = H
R = Ac



The methodology described in the previous sections readily identified cyclogeraniol **30**[20] as the starting material, containing one quaternary carbon atom. The synthetic sequence is depicted in Scheme 4. The *ortho* ester Claisen rearrangement of cyclogeraniol **30** with triethyl *ortho* acetate and propionic acid followed by base-catalysed hydrolysis of the resultant ester **31** furnished the ene-acid **32.** Treatment of the acid chloride **33**, obtained from the acid **32** and oxalyl chloride, with an excess of ethereal diazomethane furnished the key diazo ketone **34**. Anhydrous copper sulfate-catalysed intramolecular cyclopropanation reaction of the diazo ketone **34**, stereospecifically generated the cyclopropyl ketone **35**, a known degradation product[21] of the sesquiterpene thujopsene.

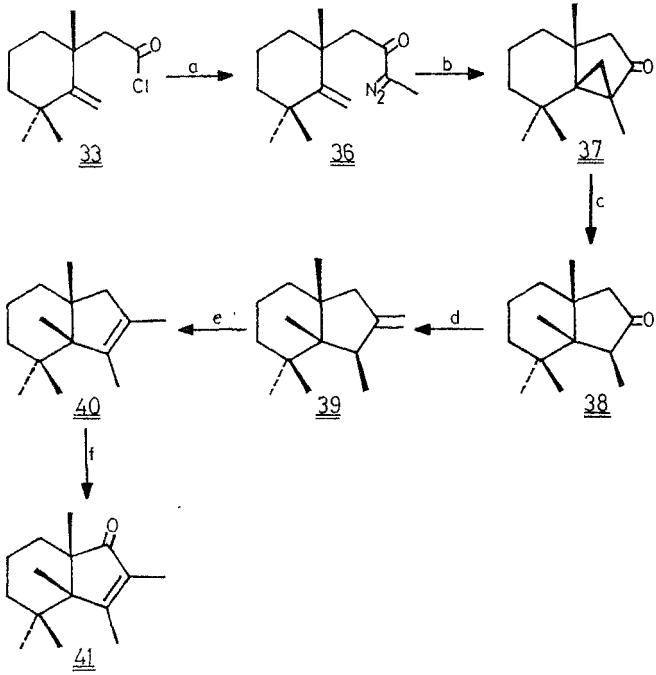
Finally, the regiospecific cleavage of the C_2–C_3 cyclopropane bond by using lithium in liquid ammonia transformed the cyclopropyl ketone **35** into hydrindanone **29**, thus creating two vicinal quaternary carbon atoms in addition to the one present in cyclogeraniol (**30**) in a contiguous manner. However, for the construction of the thapsane skeleton, further elaboration of the hydrindanone **29** posed serious regiochemical



SCHEME 4. (a) (i) $MeC(OEt)_3$, EtCOOH, sealed tube, 180°C, (ii) MeOH, aq. NaOH, reflux; (b) (i) $(COCl)_2$, C_6H_6, RT; (ii) CH_2N_2, Et_2O RT; (c) $CuSO_4$; c-$C_{16}H_{32}$, $h\nu$; (d) Li, liquid NH_3

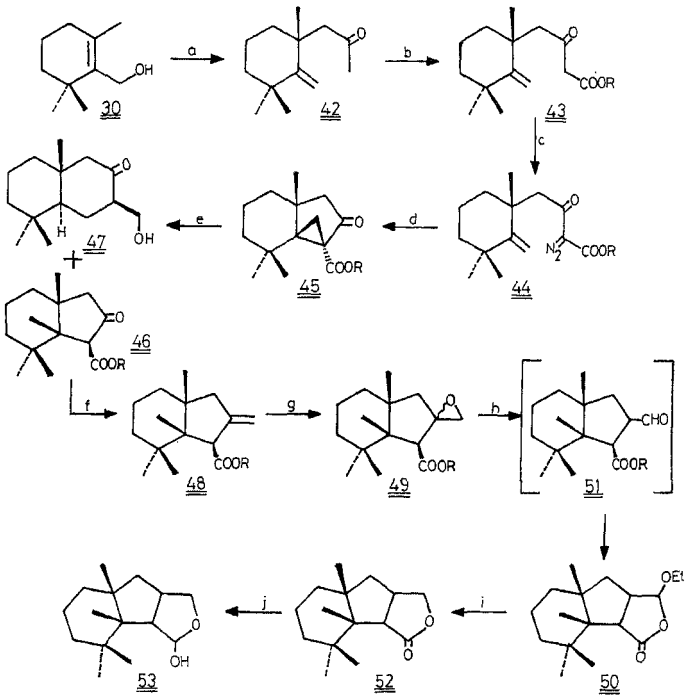
problems as the two methylenes α to carbonyl group in **29** are not easily distinguishable. To overcome this, the sequence was slightly modified and diazoethane was used instead of diazomethane as depicted in Scheme 5. Thus, treatment of the acid chloride **33** with an excess of ethereal diazoethane 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 pentamethylhydrindanone **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 hydrindanone **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[9,10].

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 rearrangement[22] 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 $LiN(Me_3Si)_2$ and quenching



SCHEME 5. (a) $MeCHN_2$, Et_2O, RT; (b) $CuSO_4$; *c*-C_6H_{12}, hν(NV); (c) Li, liq. NH_3; (d) $Ph_3P^+CH_3{}^-Br$, $K^+{}^-O$*t*-Am, C_6H_6, *t*-AmOH; (e) PTSA, CH_2Cl_2, RT; (f) CrO_3, ^tBuOOH, CH_2Cl_2, 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[23] 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 derivatve **47**. Formation of the two products **46** and **47** can be rationalised as follows[3]: 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



SCHEME 6. (a) CH_2=C(OMe)Me, EtCOOH, toluene, sealed tube, 160°C, (b) (i) $LiN(TMS)_2$, THF, −70°C; (ii) ClCOOEt, RT; (c) TsN_3, NEt_3, MeCN, RT; (d) $Rh(OAc)_2$, C_6H_6, RT; (e) Li, liquid NH_3, THF, −33°C; (f) $Ph_3P^+CH_3\ ^-Br$, $K^+\ ^-O$-*t*-Am, C_6H_6, *t*-AmOH, reflux; (g) magnesium monoperphthalate, EtOH, RT; (h) $BF_3.OEt_2$, CH_2Cl_2, RT; (i) Et_3SiH, CF_3COOH, reflux; (j) DIBAH, toluene, −70°C.

by Witting 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, (±)β-cuparenone, (±)-albene and (±)-thapsanes. The recent discovery[24] on the dramatic acceleration of the *ortho* ester Claisen rearrangement of allyl alcohols by employing microwave heating technique enhances the versatility of this methodology.

Acknowledgement

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