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A sequential RCM/fragmentation protocol towards chiral, stereodefined medium ring sesquiterpenoids. A carvone route to *E*- and *Z*-germacrenes

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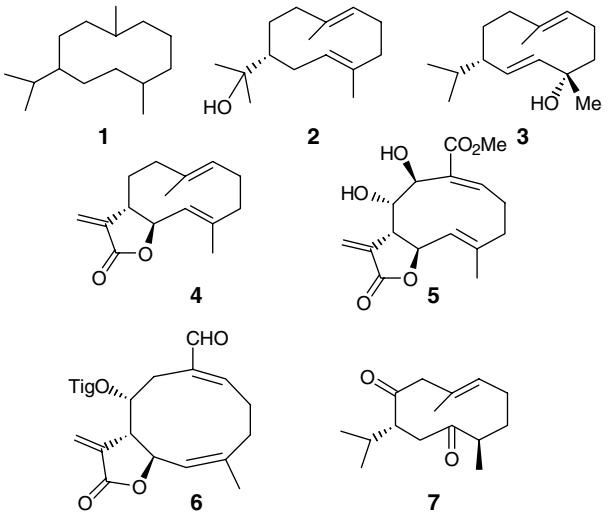
Abstract—A short, flexible and enantioselective approach towards 10-membered germacratrienones, from the commercially available monoterpene chiron (−)-carvone, involving RCM and Grob-type fragmentation as the pivotal steps is delineated.

Among sesquiterpenoid natural products, the monocyclic germacranes, embodying a 10-membered medium ring skeleton **1** occupy a special position in view of their widespread occurrence and their role as biosynthetic progenitors of several polycyclic frameworks.[1] Notable examples of germacrane natural products are the biogenetically important sesquiterpenoid hedycaryol **2**,[2a] biologically active 1,6-germacradien-5-ol **3**[2b] and a prototypical germacranolide represented by costunolide **4**.[2c] An interesting structural feature of germacrane natural products is the presence of either *E*,*E*- (as in **2** and **4**) or *E*,*Z*- (as in **5**)[2d] or somewhat rare *Z*,*Z*- (as in **6**)[2e] configuration of the double bonds in the 10-membered ring. There are also examples of germacranes like sielbodianine A **7**[2f] wherein only one double bond, generally in the *E*-configuration, is present.



For reasons of structural diversity and historical importance, germacrane natural products have attracted[3,4a–d] and continue to engage considerable attention[4e–i] from the synthetic chemistry community. Several interesting strategies[3] have been devised for accessing the 10-membered ring of these natural products with appropriate positioning and stereocontrol of the olefinic bonds. We delineate here a new approach to germacranes from the readily available monoterpene chiron *R*-(−)-carvone by tactically sequencing ring-closing metathesis (RCM) and C–C bond fragmentation on appropriately crafted decalinic platforms to generate a 10-membered cyclic alkene.[5] Since, Grob-type heterolytic fragmentations are under tight stereocontrol (the central C–C bond undergoing cleavage is antiperiplanar to the electrofuge and nucleofuge groups),[6] the substrates can be programmed to deliver either an *E*- or *Z*-cyclodecene thereby rendering this approach both flexible and stereoselective. It is the relative stereochemical positioning of the electrofuge and the nucleofuge on the (−)-carvone derived eudesmane platforms that has enabled access to *E*- or *Z*-germacrenes through fragmentation protocols and it is the execution of this strategy that forms the main thrust of this letter.

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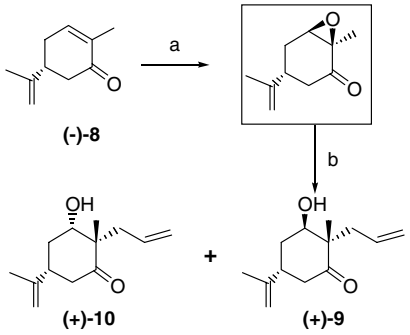
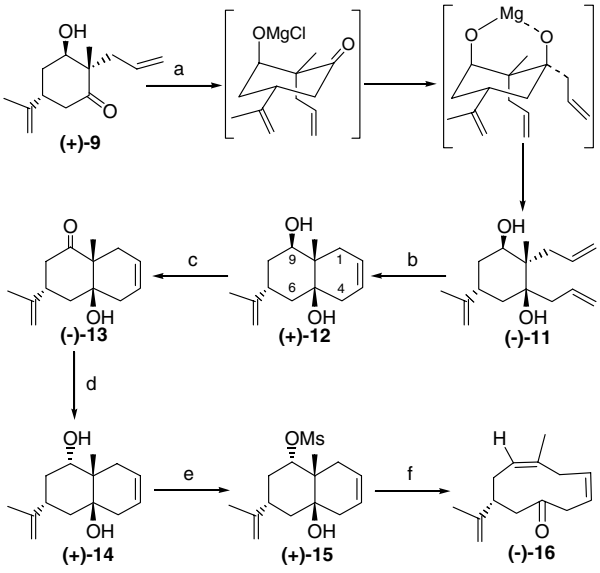
Recently, we described[7] the elaboration of *R*-(−)-carvone **8** to diastereomeric aldol products **9** and **10** in preparatively useful yields, through the intermediacy of an α,β-epoxy ketone as shown in Scheme 1. The substrates **9** and **10** appeared very well suited for executing the contemplated RCM-fragmentation protocol to access 10-membered germacranes. In this context, it was considered more prudent to implement an initial model study. Addition of the Grignard reagent derived from allyl chloride to the β-hydroxy aldol product **9** was stereoselective, directed by the chelating interactions on the axial face, due to the presence of the β-hydroxy group, and gave the diallylated compound **11** in very good yield, Scheme 2.[8] A RCM reaction on **11** using the Grubbs' first generation catalyst[9] proceeded in excellent yield to give bicyclic 1,3-*cis*-diol **12**, its stereochemistry being secured through an X-ray crystal structure determination.[10] While acquisition of the 1,3-diol moiety (as in **12**) was a good omen, their trans relationship was a pre-requisite for the orchestration of a fragmentation protocol and mandated an inversion of the C9 β-hydroxy stereochemistry in **12**. As the Mitsunobu-like inversion protocols on the C9 hydroxyl group in **12** were unsuccessful, it was oxidized to the hydroxy-ketone **13** and further reduced with $NaBH_4$ to furnish a mixture (2:3) of the desired *trans*-1,3-diol **14** and **12**, Scheme 2. The *trans*-diol **14** was readily converted to the mesylate **15** and its activation with base induced smooth fragmentation to furnish *Z*,*Z*-nor-germacratrienone **16**[8] in good yield, Scheme 2.



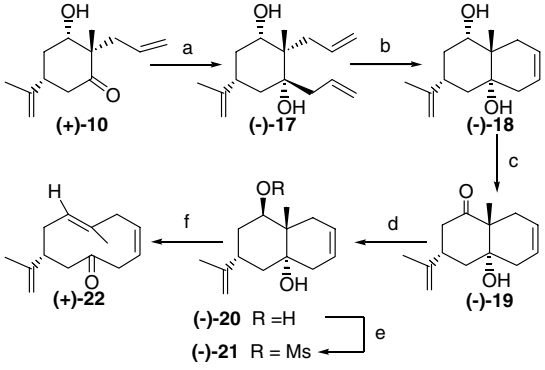
Scheme 1. Reagents and conditions: (a) 30% H_2O_2, 6 N NaOH, MeOH, 0 °C, 92%; (b) Li, liq. NH_3, CH_2=$CHCH_2Br$, Et_2O, −78 °C, 60%.

With the successful acquisition of **16**, implementation of the RCM-fragmentation sequence in the α-hydroxy aldol product **10** was undertaken next. Addition of the allyl Grignard reagent to **10** was moderately stereoselective (6:1) and in the absence of the directive influence of the axial hydroxyl group (cf. **9**) furnished the *cis*-1,3-diol **17**[8] as the major product with favoured addition from the axial face, Scheme 3. A RCM reaction in **17** with Grubbs' catalyst proceeded uneventfully and led to the bicyclic *cis*-diol **18**. Once again, implementation of the fragmentation reaction to generate the 10-membered ring required a trans-disposition of the 1,3-diol moiety to ensure antiperiplanar geometry.[6] Subsequently, **18** was oxidized to the hydroxy-ketone **19** and reduced with $LiAlH_4$ to furnish a mixture (1:2) of *trans*-1,3-diol **20** and **18**, Scheme 3. Mesylation of **20** led to **21** and subsequent exposure to NaH resulted in fragmentation to the *E*,*Z*-nor-germacratrienone **22**,[8] Scheme 3.[11]

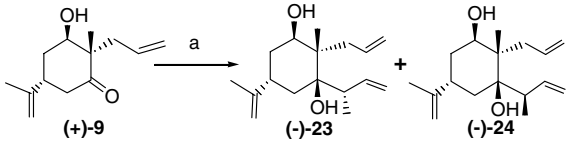
Enthused by the success in accessing the nor-germacratrienones **16** and **22**, we ventured to extend our studies towards the complete C_{15} skeleton of the germacranes. Addition of the Grignard reagent derived from 3-chloro-1-butene to the β-hydroxy-ketone **9** in the presence of Ce^{+3} furnished two diastereomeric addition products **23** and **24** (α- and β-methyl isomers, 55:45) as reported previously, Scheme 4.[7] Both, **23** and **24** were formed through stereoselective addition of the Grignard reagent to **9** from the equatorial face (vide supra) and further elaborated to *Z*,*Z*-germacratrienones as described below.



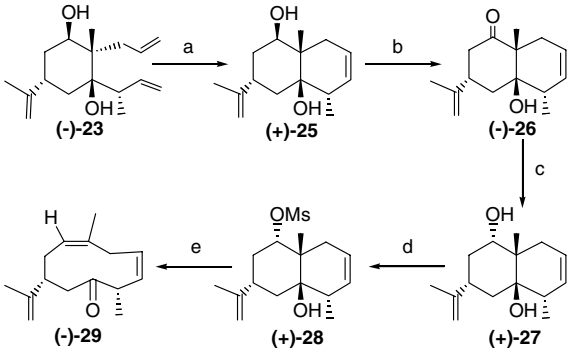
Scheme 2. Reagents and conditions: (a) 2.5 equiv CH_2=$CHCH_2MgCl$, THF, −78 °C, 90%; (b) 5 mol % Grubbs' catalyst, C_6H_6, 80 °C, 94%; (c) PCC, DCM, rt, 71%; (d) $NaBH_4$, MeOH, 0 °C, **12** (54%) and **14** (35%) in a ratio of 3:2; (e) MsCl, Et_3N, DMAP, DCM, 0 °C, 92%; (f) NaH, C_6H_6, 65 °C, 79%.



Scheme 3. Reagents and conditions: (a) 2.5 equiv CH_2=$CHCH_2MgCl$, THF, −78 °C, 93%; (b) 10 mol % Grubbs' catalyst, C_6H_6, 80 °C, 78%; (c) PCC, DCM, rt, 75%; (d) LAH, THF, 0 °C, **18** (55%) and **20** (27%) in a ratio of 2:1; (e) MsCl, Et_3N, DMAP, DCM, 0 °C, 90%; (f) NaH, C_6H_6, 65 °C, 67%.

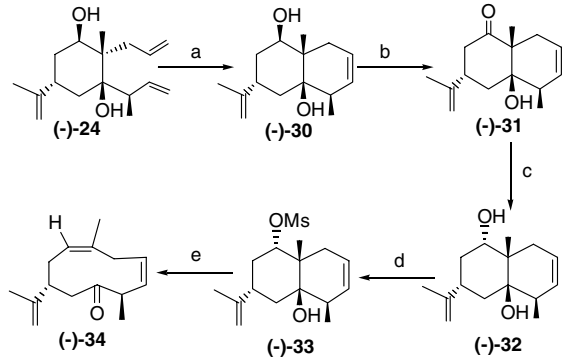


Scheme 4. Reagents and conditions: (a) anhyd $CeCl_3$, 2.5 equiv $CH_2{=}CHCH(CH_3)MgCl$, THF, −78 °C, 95%.

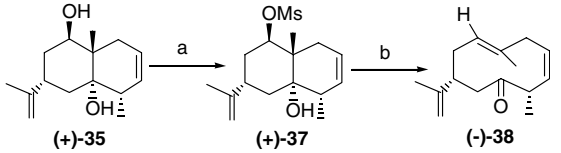


Scheme 5. Reagents and conditions: (a) 8 mol % Grubbs' catalyst, C_6H_6, 80 °C, 92%; (b) PCC, DCM, rt, 80%; (c) $NaBH_4$, MeOH, 0 °C, **25** (51%) and **27** (34%) in a ratio of 1.5:1; (d) MsCl, Et_3N, DMAP, DCM, 0 °C, 90%; (e) NaH, C_6H_6, 65 °C, 62%.

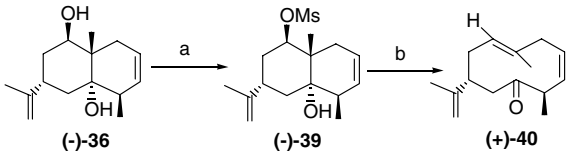
A RCM reaction on **23** was efficient and led to the eudesmane derivative **25**, Scheme 5. The *cis*-1,3-diol moiety in **25** was modified to set up the fragmentation by oxidation to the hydroxy-ketone **26** and reduction to epimeric alcohols **25** and **27** (1.5:1). The *trans*-1,3-diol **27** was converted to the mesylate **28** and careful exposure to NaH in the complete absence of moisture and air led to the fragmented product *Z*,*Z*-germacratrienone **29**, Scheme 5.[8,12] An identical sequence starting from the diastereomer **24** involved RCM to the bicyclic eudesmane derivative **30**, PCC oxidation to **31** and $NaBH_4$ reduction to obtain the *trans*-1,3-diol **32** as a minor product along with **30** (1:4), Scheme 6. The mesylate **33** resulting from **32**, on exposure to NaH under a rigorous moisture and air free regime, led to the diastereomeric *Z*,*Z*-germacratrienone **34**, Scheme 6.[8,12]



Scheme 6. Reagents and conditions: (a) 5 mol % Grubbs' catalyst, C_6H_6, 80 °C, 89%; (b) PCC, DCM, rt, 78%; (c) $NaBH_4$, MeOH, 0 °C, **30** (72%) and **32** (18%) in a ratio of 4:1; (d) MsCl, Et_3N, DMAP, DCM, 0 °C, 80%; (e) NaH, C_6H_6, 65 °C, 70%.



Scheme 7. Reagents and conditions: (a) MsCl, Et_3N, DMAP, DCM, 0 °C, 95%; (b) NaH, C_6H_6, 65 °C, 60%.



Scheme 8. Reagents and conditions: (a) MsCl, Et_3N, DMAP, DCM, 0 °C, 92%; (b) NaH, C_6H_6, 65 °C, 62%.

To further amplify the potential of our RCM/fragmentation based strategy to access stereochemically diverse *E*- and/or *Z*-configured germacrenes, we also implemented the fragmentation protocols on the *trans*-1,3-diols **35** and **36**, obtained from the α-hydroxy aldol product **10** (vide supra) following the steps outlined for the diastereomeric product **9**, Schemes 7 and 8.

Thus **35** was converted into its mesylate **37** and treatment with NaH led to the fragmented *E*,*Z*-germacratrienone **38**, Scheme 7.[8,11] Similarly, the *trans*-1,3-diol **36** was derivatized to its mesylate **39** and base mediated fragmentation led to the *E*,*Z*-germacratrienone **40**, Scheme 8.[8,11]

In summary, we have outlined a short and versatile approach to germacratrienes based on sequential RCM and fragmentation protocols from the readily available monoterpene chiron (−)-carvone. By manipulating the precursor *trans*-1,3-diol moiety on the eudesmane platform into different stereochemical settings, it was possible to generate either *E*- or *Z*-alkene in the 10-membered ring in a predictable manner.

Acknowledgements

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8. All new compounds were characterized on the basis of IR, ^{1}H and ^{13}C NMR and HRMS data. Spectral data for selected compounds: (−)-**16**: $[\alpha]_D^{24}$ −170.4 (*c* 1.2, $CHCl_3$); IR 1702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88 (ddt, $J = 10.5$, 5.7, 1.8 Hz, 1H), 5.62–5.54 (m, 1H), 5.04 (t, $J = 8.4$ Hz, 1H), 4.75 (s, 1H), 4.53 (s, 1H), 3.13 (td, $J = 5.4$, 2.1 Hz, 1H), 3.09–3.00 (m, 2H), 2.86 (dd, $J = 13.8$, 10.2 Hz, 1H), 2.73 (m, 1H), 2.52 (dd, $J = 14.1$, 5.4 Hz, 1H), 2.25–2.19 (m, 2H), 2.06 (dd, $J = 15.0$, 2.4 Hz, 1H), 1.78 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.8, 147.2, 135.4, 130.7, 122.4, 121.8, 109.7, 44.1, 41.2, 39.8, 31.3, 28.5, 23.6, 22.4; HRMS (ES): *m*/*z* calcd for $C_{14}H_{20}ONa$ (M+Na): 227.1412; found: 227.1427. Compound (+)-**22**: $[\alpha]_D^{24}$ (+)-6.0 (*c* 1.0, $CHCl_3$); IR 1704 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.2, 148.7, 133.0, 130.0, 129.7, 122.2, 109.4, 48.2, 47.5, 43.0, 39.4, 34.0, 21.1, 18.2; HRMS (ES): *m*/*z* calcd for $C_{14}H_{20}ONa$ (M+Na): 227.1412; found: 227.1418. Compound (−)-**29**: $[\alpha]_D^{23}$ −20.0 (*c* 0.8, $CHCl_3$); IR 1701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.78 (ddt, $J = 10.8$, 5.4, 2.1 Hz, 1H), 5.34 (dd, $J = 10.8$, 5.4 Hz, 1H), 5.04 (t, $J = 8.4$ Hz, 1H), 4.76 (s, 1H), 4.51 (s, 1H), 3.35–3.26 (m, 1H), 3.08 (dd, $J = 15.3$, 12.0 Hz, 1H), 2.97 (dd, $J = 13.5$, 11.4 Hz, 1H), 2.74–2.66 (m, 1H), 2.38–2.22 (m, 2H), 2.14 (t, $J = 6.0$ Hz, 1H), 2.03 (dd, $J = 15.3$, 1.8 Hz, 1H), 1.78 (s, 6H), 1.23 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.2, 147.3, 135.4, 130.4, 128.9, 121.5, 109.8, 47.8, 40.9, 37.4, 31.8, 28.1, 23.6, 22.5, 18.8; HRMS (ES): *m*/*z* calcd for $C_{15}H_{22}ONa$ (M+Na): 241.1568; found: 241.1568. Compound (−)-**34**: $[\alpha]_D^{23}$ −326.7 (*c* 1.0, $CHCl_3$); IR 1705 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.72 (dd, $J = 17.4$, 10.2 Hz, 1H), 5.57 (t, $J = 10.2$ Hz, 1H), 5.06 (t, $J = 8.4$ Hz, 1H), 4.75 (s, 1H), 4.56 (s, 1H), 3.17 (qui, $J = 6.9$ Hz, 1H), 2.98 (dd, $J = 15.9$, 11.1 Hz, 1H), 2.70–2.54 (m, 3H), 2.32–2.26 (m, 3H), 1.79 (s, 3H), 1.77 (s, 3H), 1.15 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.9, 147.3, 135.9, 130.4, 127.3, 121.4, 109.6, 47.1 (2C), 40.1, 31.1, 28.0, 23.2, 22.7, 15.7; HRMS (ES): *m*/*z* calcd for $C_{15}H_{22}ONa$ (M+Na): 241.1568; found: 241.1580. Compound (−)-**38**: $[\alpha]_D^{23}$ −23.2 (*c* 0.8, $CHCl_3$); IR 1698 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$): δ 213.5, 148.5, 136.4, 133.9, 129.3, 126.8, 110.0, 46.6, 44.3, 41.2, 40.0, 33.1, 31.3, 20.4, 17.6; HRMS (ES): *m*/*z* calcd for $C_{15}H_{22}ONa$ (M+Na): 241.1568; found: 241.1584. Compound (+)-**40**: $[\alpha]_D^{23}$ +68.2 (*c* 1.1, $CHCl_3$); IR 1702 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.5, 148.9, 134.1, 130.8, 129.6, 127.9, 109.2, 47.8, 47.0, 46.1, 38.8, 33.8, 21.3, 18.7, 18.5; HRMS (ES): *m*/*z* calcd for $C_{15}H_{22}ONa$ (M+Na): 241.1568; found: 241.1568.
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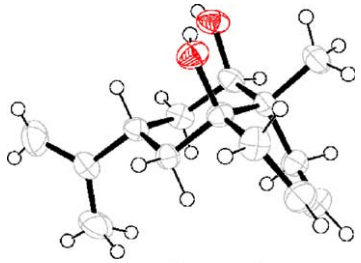
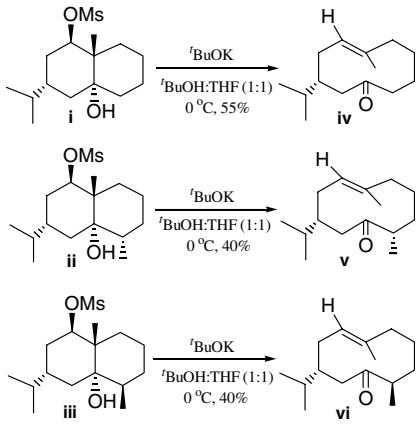
10. X-ray data for **12**: $C_{14}H_{22}O_2$, MW = 222.32, colourless crystal, crystal system: orthorhombic, space group: $P2_12_12_1$, cell parameters: $a = 6.7810(40)$, $b = 8.2778(49)$, $c = 22.5066(14)$ Å, $V = 1263.34(13)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.17$ g cm^{-3}, $F(000) = 487.9$, $\mu = 0.076$ mm^{-1}, total no. of l.s. parameters = 149, $R_1 = 0.043$ for 1999 reflections with $F_0 > 4\sigma(F_0)$ and 0.047 for all 2147 reflections. $wR_2 = 0.116$, GOF = 0.999, restrained GOF = 0.999 for all data (CCDC 282317).

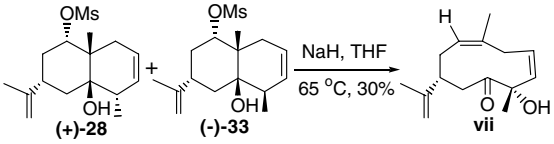


ORTEP diagram of **12**

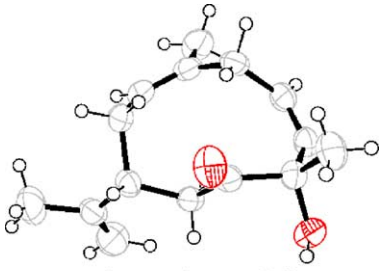
11. We observed that whenever there was an *E*-double bond present in the germacratrienes, as in **22**, **38** and **40**, considerable line broadening and partial doubling of signals were observed in the ^{1}H NMR spectra due to the presence of conformational isomers. Recording the spectra even at (−50 °C) did not help much although reversible changes were noticed. On the other hand, the ^{13}C NMR spectra were quite clean. Attributing the presence of conformers to the *Z*-disubstituted double bond in the germacratrienes, we also prepared the corresponding germacraenones (iv–vi) from the saturated mesylates (i–iii), respectively. Germacraenones (iv–vi) exhibited clean, clear cut ^{1}H and ^{13}C NMR spectra.



12. When the fragmentation reactions were performed without adequate precautions to avoid oxygen and moisture, the main product from either **28** or **33** was the α-ketol **i**, a product of unusual oxidation at the activated doubly allylic tertiary carbon and its structure was determined by X-ray crystallography.



X-ray data for **vii**: $C_{15}H_{22}O_2$, MW = 234.33, colourless crystal, crystal system: trigonal, space group: $P3_1$, cell parameters: $a = 12.9950(30)$, $c = 7.1599(33)$ Å, $V = 1047.10(6)$ Å^3, $Z = 3$, $\rho_{calcd} = 1.04$ g cm^{-3}, $F(000) = 360.0$, $\mu = 0.063$ mm^{-1}, total no. of l.s. parameters = 242, $R_1 = 0.038$ for 2526 reflections with $F_0 > 4\sigma(F_0)$ and 0.043 for all 2783 reflections. $wR_2 = 0.091$, GOF = 1.058, restrained GOF = 1.058 for all data (CCDC 282316).



ORTEP diagram of **vii**