J Mol Model (2008) 14:335–342
DOI 10.1007/s00894-008-0274-3

ORIGINAL PAPER

Ab initio analysis of the Cope rearrangement of germacrane sesquiterpenoids

William N. Setzer

Received: 26 November 2007 / Accepted: 17 January 2008 / Published online: 15 February 2008

Abstract The energetics of the Cope rearrangement of 17 germacrane sesquiterpenoids to their respective elemane forms have been calculated using both density functional theory (B3LYP/6-31G*) and post Hartee-Fock (MP2/6-31G**) *ab initio* methods. The calculations are in qualitative agreement with experimentally observed Cope rearrangements, but the two methods give slightly different results. MP2 calculations generally show more favorable elemene energies compared to the respective germacrenes (by around 3–4 kcal mol^{-1}) and smaller activation energies (by 2–3 kcal mol^{-1}). Additionally, neither method is accurate enough to consistently reproduce the germacrene/elemene equilibrium. Apparently, the generally small energy differences between the two forms in these sesquiterpenoids cannot be adequately reproduced at these levels of calculation.

Keywords Density functional theory · *Ab initio* molecular orbital theory · Germacrane sesquiterpenoids · Elemane sesquiterpenoids · Cope rearrangement

Introduction

A number of germacrane sesquiterpenoids have been reported to undergo facile Cope rearrangement to their corresponding elemane derivatives [1, 2]. Thus, for example, germacrene A leads to β-elemene [3], germacrene B to γ-elemene [4], and germacrene C to δ-elemene [5]. Gas chromatographic analyses of essential oils generally show that germacrane sesquiterpenoids are often accompanied by their corresponding elemane Cope rearrangement products, and there has been some concern about whether one or the other may be an artifact due to the high temperatures encountered during hydrodistillation or gas chromatographic analysis [6]. Although the Cope rearrangement has been investigated at many different levels of theory [7–17], a comprehensive investigation of the Cope rearrangement of germacrene derivatives has not been previously undertaken. The different isomeric germacrane and elemane sesquiterpenes, as well as their different substitution patterns, may profoundly affect the equilibrium distribution of these Cope rearrangement products. This report presents the *ab initio* activation barriers and reaction energetics of conversion of 17 different germacrane sesquiterpenoids to their corresponding elemanes using density functional theory (DFT) and post Hartree-Fock (MP2) theory. Houk and co-workers [18, 19] have found that the B3LYP/6-31G* DFT method generally performs better than other DFT or post Hartree-Fock methods for pericyclic reactions. These workers have pointed out that HF and CASSCF methods overestimate activation enthalpies in pericyclic reactions due to neglect of correlation energy in the case of HF [20] and incomplete correlation energy in CASSCF [10, 18]. For model systems of the Cope rearrangement, the B3LYP/6-31G* method performs very well [18, 21] and compares well with computationally more demanding CASPT2 and CBS-QB3 methods [10, 16, 18]. However, the B3LYP functional has been found to give increased errors with increasing molecular size [22, 23], and Schreiner and co-workers [22] have recommended using higher level (e.g., MP2 with a 6-31G** basis set) single-point energy calculations on DFT structures as a confirmation. It has been pointed out, however, that the

W. N. Setzer (✉)
Department of Chemistry, University of Alabama in Huntsville, Huntsville AL 35899, USA
e-mail: wsetzer@chemistry.uah.edu

MP2 method often overcorrects for the lack of correlation in HF calculations, and tends to predict activation energies that are lower than experimental values for pericyclic reactions [18, 24, 25].

Computational studies

All calculations were carried out using SPARTAN '06 for Windows [26]. The hybrid B3LYP functional [27, 28] and the 6-31G* basis set [29] were used for the optimization of all stationary points in the gas phase. Single-point Hartree-Fock *ab initio* energies were calculated using the DFT geometries (above) at the 6-31G** [29] level, followed by a correlation energy calculation using the second-order Møller-Plesset model (MP2) [29]. Frequency calculations were used to characterize stationary points as minima or first-order saddle points. All reactions and activation enthalpies reported are zero-point (ZPE) corrected with unscaled frequencies, but with no thermal corrections; they are, therefore, $\Delta H_{(0K)}$. Entropies were calculated using the linear harmonic oscillator approximation.

Results

DFT (B3LYP/6-31G*) and post-HF (MP2/6-31G**) enthalpies ($\Delta H_{(0K)}$) and free energies (ΔG, based on HF 6-31G** calculated entropies and 220 °C) for the Cope rearrangement of germacrane sesquiterpenoids to their respective elemanes are summarized in Table 1. Calculations were performed on germacrene A, germacrene B, germacrene C, hedycaryol, germacrone, helminthogermacrene, isogermacrene A, bicyclogermacrene, isolepidozene, bacchascandon, furanodiene, furanodienone, linderalactone, neolinderalactone, costunolide, dihydrocostunolide, and guayulin A (Fig. 1). The calculations show that different substitution patterns affect the relative energetics of the germacrene–elemene Cope rearrangement. The transition state energies for these reactions are comparable to those found experimentally [30] and calculated previously for 1,5-hexadiene and substituted 1,5-hexadienes [10, 13, 15, 20, 31].

Discussion

Germacrene A and β-elemene have been detected together, by GC and GC-MS, in a number of essential oils. The concentration of β-elemene is generally higher [32–43], with an average of 9.4:1 (β-elemene : germacrene A). The DFT-calculated enthalpy difference of 2.28 kcal mol^{-1} between germacrene A and β-elemene accounts for the observed greater abundance of β-elemene over germacrene

Table 1 Calculated energies for the Cope rearrangement of germacrane sesquiterpenoids to the respective elemanes[a]

			Germacrene	Transition state
Germacrene A – β-elemene	DFT	ΔH	2.28	31.31
		ΔG	3.01	33.27
	MP2	ΔH	5.97	28.23
		ΔG	6.15	29.53
Germacrene B – γ-elemene	DFT	ΔH	0.99	31.35
		ΔG	2.43	33.70
	MP2	ΔH	3.40	28.58
		ΔG	3.81	29.89
Germacrene C – δ-elemene	DFT	ΔH	7.02	31.72
		ΔG	6.36	32.64
	MP2	ΔH	9.95	28.90
		ΔG	10.38	30.13
Hedycaryol – elemol	DFT	ΔH	2.89	31.14
		ΔG	4.15	32.79
	MP2	ΔH	6.62	28.52
		ΔG	6.86	29.85
Germacrone – *trans*-β-elemenone	DFT	ΔH	−0.87	32.12
		ΔG	−0.36	34.07
	MP2	ΔH	3.19	28.34
		ΔG	4.00	29.68
Helminthogermacrene – *cis*-β-elemene	DFT	ΔH	4.62	36.08
		ΔG	5.23	37.85
	MP2	ΔH	9.66	32.59
		ΔG	9.88	34.08
Isogermacrene A – Iso-β-elemene	DFT	ΔH	−0.44	29.80
		ΔG	−0.33	32.12
	MP2	ΔH	5.23	27.99
		ΔG	5.01	28.93
Bicyclogermacrene – bicycloelemene	DFT	ΔH	−6.14	27.53
		ΔG	−5.65	28.07
	MP2	ΔH	−2.22	26.96
		ΔG	−1.80	27.86
Isolepidozene	DFT	ΔH	−24.36	19.65
		ΔG	−24.18	20.59
	MP2	ΔH	−21.40	20.75
		ΔG	−20.84	21.45
Bacchascandon/ Acoragermacrone – shyobunone	DFT	ΔH	−3.62	24.31
		ΔG	−2.83	26.58
	MP2	ΔH	0.21	24.84
		ΔG	0.87	25.94
Furanodiene – curzerene	DFT	ΔH	−0.56	28.66
		ΔG	0.12	30.76
	MP2	ΔH	3.07	26.34
		ΔG	3.23	27.55
Furanodienone – curzerenone	DFT	ΔH	−2.35	26.44
		ΔG	0.07	29.66
	MP2	ΔH	−4.45	22.25
		ΔG	−3.38	23.86
Linderalactone – isolinderalactone	DFT	ΔH	−2.19	27.72
		ΔG	−1.83	30.45
	MP2	ΔH	0.74	24.15
		ΔG	1.15	25.76
Neolinderalactone – isolinderalactone	DFT	ΔH	−8.20	27.87
		ΔG	−7.63	29.74

Table 1 (continued)

			Germacrene	Transition state
	MP2	ΔH	−4.38	25.54
		ΔG	−4.02	26.73
Costunolide – dehydrosaussurea lactone	DFT	ΔH	−4.35	27.17
		ΔG	−4.19	29.56
	MP2	ΔH	0.48	25.77
		ΔG	0.68	26.85
Dihydrocostunolide – saussurea lactone	DFT	ΔH	−3.69	27.83
		ΔG	−3.99	30.18
	MP2	ΔH	1.10	26.04
		ΔG	1.19	27.12
Guayulin A	DFT	ΔH	−7.15	27.18
		ΔG	−5.70	28.18
	HF[b]	ΔH	−3.07	48.81
		ΔG	−2.68	49.55

[a] Calculated energies, in kcal mol^{-1}, are relative to the elemenes. Free energies were calculated using calculated standard entropies (B3LYP/6-31G* or HF/6-31G**, respectively) and 493K (220 °C, typical GC injection temperature)

[b] For guayulin A, HF/6-31G** calculations were carried out; there was not enough memory available to perform MP2 calculations

A. The MP2 enthalpy is too large (5.97 kcal mol^{-1}), however, and would predict complete conversion to β-elemene at typical GC temperatures (220–280 °C).

GC-MS analyses of most essential oils containing both germacrene B and γ-elemene show a preponderance of germacrene B over γ-elemene [32, 44–54], with an overall ratio of 3.22:1. The DFT calculations, however, indicate germacrene B to be 0.99 kcal mol^{-1} higher in energy than γ-elemene; inconsistent with the observed compound distribution. The MP2 ΔH_r of −3.40 kcal mol^{-1} is even worse. It may be that equilibration via Cope rearrangement does not occur during GC analysis and that the experimental ratios do in fact represent the relative concentrations of the materials in the plants. Li and co-workers have found that GC analysis of microwave-distilled plant material gave greater concentrations of γ-elemene over germacrene B [55]. Recent GC-MS analyses on *Piper* leaf essential oils carried out in our laboratories (unpublished data) show γ-elemene predominating over germacrene B in a 2.35 to 1 ratio.

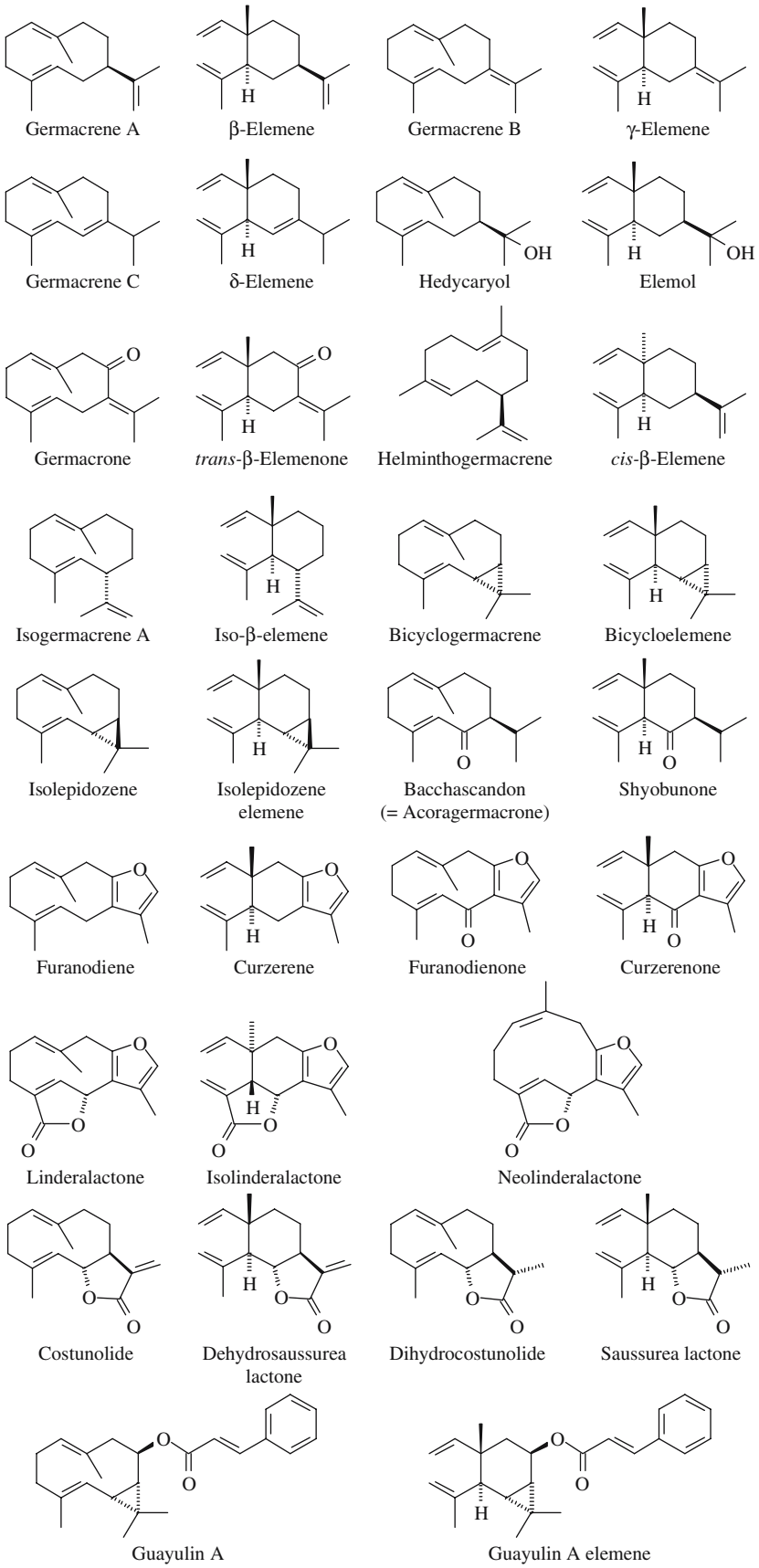
Generally, essential oils obtained by hydrodistillation and analyzed by GC do not show germacrene C, but may have δ-elemene [36, 54, 56, 57]. The calculated energy difference between germacrene C and δ-elemene of 7.08 (DFT) or 9.95 (MP2) kcal mol^{-1} suggests that germacrene C, if present in the essential oil, was converted to δ-elemene either during the hydrodistillation (100 °C) or the GC analysis (GC injector temperatures typically 220–280 °C). Germacrene C was first isolated by Morikawa and Hirose, who found that it readily underwent Cope rearrangement to δ-elemene at 100 °C [58], and other workers have verified the thermal lability of germacrene C [59–62]. Germacrene C can be isolated by solvent extraction at room temperature and analyzed by GC using low injector temperatures (< 100 °C) [63].

Helminthogermacrene was isolated from the liverwort *Scapania undulata* by Adio and co-workers [64], who also found trace amounts of its Cope rearrangement product, *cis*-β-elemene. These workers were able to convert helminthogermacrene to *cis*-β-elemene by preparative GC with an injector temperature of 390 °C, consistent with the DFT-calculated energy difference of 4.62 kcal mol^{-1}. Another liverwort, *Saccogyna viticulosa*, has yielded isogermacrene A as well as its Cope rearrangement product, iso-β-elemene [65]. Isogermacrene A was found to readily undergo Cope rearrangement to give iso-β-elemene, but the product ratio was not reported. DFT calculations show isogermacrene A to be 0.44 kcal mol^{-1} more stable than iso-β-elemene, and would not be consistent with complete conversion of isogermacrene A to iso-β-elemene. However, the MP2 energy difference (isogermacrene A is 5.23 kcal mol^{-1} higher in energy than iso-β-elemene) is in agreement with complete conversion of isogermacrene A to iso-β-elemene.

Bicyclogermacrene has been found to undergo Cope rearrangement to give bicycloelemene at temperatures above 200 °C [66–69]. Interestingly, however, bicyclogermacrene is abundant in many essential oils, especially the Lauraceae, but its Cope rearrangement product, bicycloelemene, is not generally observed [42, 70–72]. Hackl and co-workers [73] and Tesso and co-workers [74], on the other hand, were able to detect trace amounts of bicycloelemene, along with bicyclogermacrene, in *Saccogyna viticulosa* and *Chloranthus spicatus*, respectively. The DFT-calculated energies for bicyclogermacrene and bicycloelemene are inconsistent with a favorable Cope rearrangement; bicyclogermacrene is 6.14 kcal mol^{-1} lower in energy than bicycloelemene. Post-HF calculations show a smaller, but still endothermic, enthalpy of reaction for bicyclogermacrene to bicycloelemene (2.22 kcal mol^{-1}), which is consistent with experimental observations. Isolepidozene, a diastereomer of bicyclogermacrene, has been found in a number of liverworts [64, 75], but its corresponding Cope rearrangement product has apparently never been detected. Both DFT and MP2 calculations show isolepidozene to be much more stable (24.4 and 21.4 kcal mol^{-1}, respectively) than the corresponding elemene, so it is not surprising that the elemene has not been found.

Germacrone has been reported to be thermally labile with respect to Cope rearrangement to *trans*-β-elemenone [6, 76], and the two compounds are often found together in essential oils [32, 47, 77–79], generally with germacrone predominating. The overall germacrone to β-elemenone

Fig. 1 Sesquiterpenoids discussed in this work



ratio from published essential oil compositions is 14.5:1 [32, 47, 77–84]. DFT calculations are in qualitative agreement; germacrone is lower in energy by 0.87 kcal mol^{-1}. MP2 calculations, on the other hand, are contradictory and show germacrone to be 3.19 kcal mol^{-1} higher in energy than β-elemenone.

Bacchascandon (= acoragermacrone) has been isolated by solvent extraction of *Baccharis scandens* [85], *Baccharis latifolia* [86], and *Acorus calamus* [87, 88], and this compound has been found to undergo Cope rearrangement to its elemane derivative, shyobunone [88, 89]. GC-MS analyses of essential oils generally shows evidence of shyobunone without evidence of bacchascandon [90–93]. DFT calculations are not in agreement with these observations, showing bacchascandon to be 3.62 kcal mol^{-1} more stable than shyobunone. MP2 calculations, however, have bacchascandon slightly higher in energy than shyobunone by 0.21 kcal mol^{-1}.

When collected at cooler temperature (e.g., solvent extraction at room temperature), essential oils containing both hedycaryol and elemol generally show higher concentrations of hedycaryol [94–97]. Conversely, essential oils obtained by steam distillation show little if any hedycaryol, but generally only elemol [96–98]. Indeed, hedycaryol has been observed to undergo ready conversion to elemol [99–101], and DFT calculations support this observation. Elemol is 2.89 kcal mol^{-1} more stable than hedycaryol, comparable to values calculated for germacrene A and β-elemene. Interestingly, Adams [102] reports hedycaryol and elemol to have virtually identical retention indices on the non-polar DB-5 GC column (1548 and 1549, respectively) and the two compounds have virtually identical mass spectral fragmentation patterns. It seems likely that hedycaryol, injected under typical GC-MS conditions, rearranges completely to elemol.

DFT calculations show furanodiene to be 0.56 kcal mol^{-1} lower in energy than curzerene (= furanoelemene), and most essential oils containing furanodiene show higher concentrations of that sesquiterpenoid over its Cope rearrangement product curzerene [80, 103–106]. Curzerene has, however, been preparedby Cope rearrangement of furanodiene [6, 107–109], and hydrodistillation and hot (250 °C) GC injection temperatures, result in increasing concentrations of curzerene [6, 47, 81, 110]. DFT total electronic energies of furanodiene and curzerene do not account for this behavior, but post-HF MP2 calculations show curzerene to be 3.07 kcal mol^{-1} more stable than furanodiene. Furanodienone generally predominates over curzerenone in essential oil compositions [80, 105, 106]. The energetics of the furanodienone to curzerenone conversion (DFT, ΔH_r=2.35 kcal mol^{-1}; MP2, ΔH_r= 4.45 kcal mol^{-1}) are consistent with these experimental results.

The sesquiterpenoid linderalactone, isolated from the roots of *Lindera strychnifolia* [111] has been found to undergo Cope rearrangement at 160 °C to give isolinderalactone [111–113]. The isomeric neolinderalactone has also been shown to undergo Cope rearrangement to isolinderalactone [114, 115]. The DFT calculations indicate that linderalactone is 2.19 kcal mol^{-1} more stable than isolinderalactone, and are therefore inconsistent with a Cope rearrangement to give a 2:3 ratio of linderalactone/ isolinderalactone as reported by Takeda et al. [112]. The MP2/6-31G** calculations are in better agreement with the experimental observations, and indicate linderalactone to be 0.74 kcal mol^{-1} less stable than isolinderalactone, consistent with the observed equilibrium ratio. Gopalan and Magnus [115] found that Cope rearrangement of neolinderalactone at 300°C gave isolinderalactone in a 19:1 ratio (i.e., 5% conversion). Again, DFT calculations predict a negligible conversion of neolinderalactone to isolinderalactone (ΔH_r=8.20 kcal mol^{-1}). MP2/6-31G** calculations, on the other hand, show neolinderalactone to be 4.38 kcal mol^{-1} more stable than isolinderalactone, again consistent with the small amount of Cope rearrangement at 300°C that was observed experimentally.

MP2 calculations show the sesquiterpene lactone costunolide to be slightly higher in energy (0.48 kcal mol^{-1}) than its Cope rearrangement product dehydrosaussurea lactone, whereas DFT calculations show it to be 4.35 kcal mol^{-1} lower in energy. Costunolide and dihydrocostunolide are abundant components of Costus Resinoid (*Saussurea lappa* root oil) [116, 117], while dehydrosaussurea lactone and saussurea lactone have been found in the liverwort *Frullania rostrata* [118]. Dehydrosaussurea lactone and saussurea lactone have been shown to readily undergo reversible Cope rearrangement to costunolide and dihydrocostulolide, respectively, with the elemenes slightly predominating over the germacrenes [119–121], in agreement with MP2 results.

Guayulin A, a cinnamic acid ester derivative of bicyclogermacrene, is a major component of guayule (*Parthenium argentatum*) [122–124]. Although the compound adopts a conformation suitable for Cope rearrangement [125], the corresponding elemene has not been reported. B3LYP/6-31G* and HF 6-31G** calculations are consistent with this; the energy difference between guayulin A and the corresponding elemene are 7.14 and 3.07 kcal mol^{-1} in favor of the germacrene.

Conclusions

Ab initio calculations, at the B3LYP/6-31G* or MP2/6-31G** levels are in qualitative agreement with experimentally observed Cope rearrangements of germacrane

sesquiterpenoids to their respective elemanes, but the two methods do give slightly different results. Post Hartree-Fock MP2 calculations generally show more favorable elemene energies compared to the respective germacrenes by around 3–4 kcal mol^{-1}, and smaller activation energies by 2–3 kcal mol^{-1}. The overall lower activation energies obtained with the MP2 method are consistent with what has been observed previously for the Cope rearrangement and has been attributed to overcorrection of the correlation energy [18]. In addition, neither method is accurate enough to consistently predict the germacrene/elemene equilibrium. Apparently, the generally small energy differences between the germacrene form and the elemene form in these sesquiterpenoids cannot be adequately reproduced at these levels of calculation. Very high levels of *ab initio* theory with multireference perturbation theory (e.g., CASPT2N or CBS-QB3) could, in principal, give more accurate results, but such calculations are not practical for molecules such as sesquiterpenoids [16]. Density functional methods are the only practical computational tools because they implicitly include electron correlation but are computationally less demanding [126]. Development of new functionals [127–131] could vastly improve the computational accuracy of density functional theory for chemical reactions such as the Cope rearrangement.

References

1. Takeda K (1974) Tetrahedron 30:1525–1534
2. de Kraker JW, Franssen MCR, de Groot A, König WA, Bouwmeester HJ (1998) Plant Physiol 117:1381–1392
3. Faraldos JA, Wu S, Chappell J, Coates RM (2007) Tetrahedron 63:7733–7742
4. Takeda K, Tori K, Horibe I, Ohtsuru M, Minato H (1970) J Chem Soc (C) 2697–2703
5. Colby SM, Crock J, Dowdle-Rizzo B, Lemaux PG, Croteau R (1998) Proc Natl Acad Sci USA 95:2216-2221
6. Yang FQ, Li SP, Zhao J, Lao SC, Wang YT (2007) J Pharm Biomed Anal 43:73–82
7. Dewar MJS, Jie C (1987) J Am Chem Soc 109:5893–5900
8. Osamura Y, Kato S, Morokuma K, Feller D, Davidson ER, Borden WT (1984) J Am Chem Soc 106:3362–3363
9. Dupuis M, Murray C, Davidson ER (1991) J Am Chem Soc 113:9756–9759
10. Hrovat DA, Morokuma K, Borden WT (1994) J Am Chem Soc 116:1072–1076
11. Kozlowski PM, Dupuis M, Davidson ER (1995) J Am Chem Soc 117:774–778
12. Jiao H, Schleyer PvR (1998) J Phys Org Chem 11:655–662
13. Hrovat DA, Beno BR, Lange H, Yoo HY, Houk KN, Borden WT (1999) J Am Chem Soc 121:10529–10537
14. Sakai S (2000) Int J Quant Chem 80:1099–1106
15. Sakai S (2002) J Mol Struct (Theochem) 583:181–188
16. Ventura E, do Monte SA, Dallos M, Lischka H (2003) J Phys Chem A 107:1175–1180
17. Blavins JJ, Cooper DL, Karadakov PB (2004) J Phys Chem A 108:194–202
18. Guner V, Khuong KS, Leach AG, Lee PS, Bartberger MD, Houk KN (2003) J Phys Chem A 107:11445–11459
19. Ess DH, Houk KN (2005) J Phys Chem A 109:9542–9553
20. Houk KN, Gustafson SM, Black KA (1992) J Am Chem Soc 114:8565–8572
21. Hrovat DA, Chen J, Houk CN, Borden WT (2000) J Am Chem Soc 122:7456–7460
22. Schreiner PR, Fokin AA, Pascal RA, de Meijere A (2006) Org Lett 8:3635–3638
23. Woodrich MD, Corminboeuf C, Schreiner PR, Fokin AA, Schleyer PvR (2007) Org Lett 9:1851–1854
24. Dinadayalane TS, Vijaya R, Smitha A, Sastry GN (2002) J Phys Chem A 106:1627–1633
25. Jones GO, Guner VA, Houk KN (2006) J Phys Chem A 110:1216–1224
26. SPARTAN '06 for Windows (2006) Wavefunction, Irvine, CA
27. Becke AD (1993) J Chem Phys 98:5648–5652
28. Lee C, Yang W, Parr RG (1988) Phys Rev 37:785–789
29. Hehre WJ, Radom L, Schleyer PvR (1986) Ab initio molecular orbital theory. Wiley, New York
30. Doering WvE, Toscano VG, Beasley GH (1971) Tetrahedron 27:5299–5306
31. Wiest O, Black KA, Houk KN (1994) J Am Chem Soc 116:10336–10337
32. Mölleken U, Sinnwell V, Kubeczka KH (1998) Phytochemistry 49:1709–1714
33. Skaltsa HD, Mavrommati A, Constantinidis T (2001) Phytochemistry 57:235–244
34. Skaltsa HD, Demetzos C, Lazari D, Sokovic M (2003) Phytochemistry 64:743–752
35. Zoghbi MGB, Andrade EHA, Lobato RCL, Tavares ACC, Souza APS, Conceicao CCC, Guimaraes EF (2005) Biochem Syst Ecol 33:269–274
36. Oliveira MJ, Campos IFP, Oliveira CBA, Santos MR, Souza PS, Santos SC, Seraphin JC, Ferri PH (2005) Biochem Syst Ecol 33:275–285
37. Singh G, Marimuthu P, de Heluani CS, Catalan CAN (2006) J Agric Food Chem 54:174–181
38. Vundac VB, Pfeifhofer HW, Brantner AH, Males Z, Plazibat M (2006) Biochem Syst Ecol 34:875–881
39. Takaku S, Haber WA, Setzer WN (2007) Biochem Syst Ecol 35:525–532
40. Gudaityte O, Venskutonis PR (2007) Biochem Syst Ecol 35:582–592
41. Werka JS, Boehme AK, Setzer WN (2007) Nat Prod Commun 2:1215–1219
42. Setzer WN, Stokes SL, Penton AF, Takaku S, Haber WA, Hansell E, Caffrey CR, McKerrow JH (2007) Nat Prod Commun 2:1203–1210
43. Moriarity DM, Bansal A, Cole RA, Takaku S, Haber WA, Setzer WN (2007) Nat Prod Commun 2:1263–1268
44. Kobaisy M, Tellez MR, Dayan FE, Duke SO (2002) Phytochemistry 61:37–40
45. Palá-Paúl J, Brophy JJ, Goldsack, RJ, Fontaniella B (2004) Biochem Syst Ecol 32:55–62
46. Siani AC, Garrido IS, Monteiro SS, Carvalho ES, Ramos MFS (2004) Biochem Syst Ecol 32:477–489
47. Ogunwande IA, Olawore NO, Ekundayo O, Walker TM, Schmidt JM, Setzer WN (2005) Int J Aromath 15:147–152
48. Pourmortazavi SM, Ghadiri M, Hajimirsadeghi SS (2005) J Food Compos Anal 18:439–446
49. Tzakou O, Constantinidis T (2005) Biochem Syst Ecol 33:1131–1140
50. Viljoen AM, Demirci B, Baser KHC, Potgieter CJ, Edwards TJ (2006) S Afr J Bot 72:99–104

51. Singh G, Marimuthu P, de Heluani CS, Catalan CAN (2006) J Agric Food Chem 54:174–181
52. Demirci B, Kosar M, Demirci F, Dinc M, Baser KHC (2007) Food Chem 105:1512–1517
53. Stokes SL, Cole RA, Rangelova MP, Haber WA, Setzer WN (2007) Nat Prod Commun 2:1211–1213
54. Cole RA, Haber WA, Setzer WN (2007) Biochem Syst Ecol 35:877–886
55. Li N, Deng C, Li Y, Ye H, Zhang X (2006) J Chromatogr A 1133:29-34
56. Bruni R, Pellati F, Bellardi MG, Benvenuti S, Paltrinieri S, Bertaccini A, Bianchi A (2005) J Agric Food Chem 53:964–968
57. Rouatbi M, Duquenoy A, Giampaoli P (2007) J Food Eng 78:708–714
58. Morikawa K, Hirose Y (1969) Tetrahedron Lett 10:1799–1801
59. König WA, Bülow N, Fricke C, Melching S, Rieck A, Muhle H (1996) Phytochemistry 43:629–633
60. Colby SM, Crock J, Dowdle-Rizzo, B, Lemaux PG, Croteau R (1998) Proc Natl Acad Sci USA 95:2216–2221
61. Feger W, Brandauer H, Ziegler H (2000) Flavour Fragr J 15:281–284
62. Silva-Brandão KL, Solverini VN, Trigo JR (2006) Biochem Syst Ecol 34:291–302
63. Gancel AL, Ollé D, Ollitrault P, Luro F, Brillouet JM (2002) Flavour Fragr J 17:416–424
64. Adio AM, Paul C, Kloth P, König WA (2004) Phytochemistry 65:199–206
65. Hackl T, König WA, Muhle H (2004) Phytochemistry 65:2261–2275
66. Nishimura K, Shinoda N, Hirose Y (1969) Tetrahedron Lett 10:3097–3100
67. Takeda K, Horibe I, Minato H (1971) J Chem Soc, D 308
68. Le Quere JL, Latrasse A (1990) J Agric Food Chem 38:3-10
69. Toyota M, Koyama H, Mizutani M, Asakawa Y (1996) Phytochemistry 41:1347–1350
70. Takaku S, Haber WA, Setzer WN (2007) Biochem Syst Ecol 35:525–532
71. Wu X, Vogler B, Haber WA, Setzer WN (2006) Nat Prod Commun 1:465–468
72. Setzer WN, Haber WA (2007) Nat Prod Commun 2:79–83
73. Hackl T, König WA, Muhle H (2004) Phytochemistry 65:2261–2275
74. Tesso H, König WA, Son PT, Giang PM (2006) Flavour Fragr J 21:592–597
75. Hardt IH, Rieck A, König WA, Muhle H (1995) Phytochemistry 40:605–606
76. Loayza I, Abujder D, Aranda R, Jakupovic J, Collin G, Deslauriers H, Jean FI (1995) Phytochemistry 38:381–389
77. Mölleken U, Sinnwell V, Kubeczka KH (1998) Phytochemistry 47:1079–1083
78. Cao J, Qi M, Fang L, Zhou S, Fu R, Zhang P (2006) J Pharm Biomed Anal 40:552–558
79. Zhou X, Li Z, Liang G, Zhu J, Wang D, Cai Z (2007) J Pharm Biomed Anal 43:440–444
80. Dekebo A, Dagne E, Sterner O (2002) Fitoterapia 73:48–55
81. Marongiu B, Piras A, Porcedda S, Scorciapino A (2005) J Agric Food Chem 53:7939–7943
82. Sylvestre M, Pichette A, Longtin A, Nagau F, Legault J (2006) J Ethnopharmacol 103:99–102
83. Melo RM, Corrêa VFS, Amorim ACL, Miranda ALP, Rezende CM (2007) J Braz Chem Soc 18:179–183
84. Setzer WN, Agius BR, Walker TM, Moriarity DM, Haber WA (2008) Nat Prod Commun 3 (in press)
85. Bohlmann F, Zdero C, Robinson H, King RM (1979) Phytochemistry 18:1993–1996
86. Zdero C, Bohlmann F, Solomon JC, King RM, Robinson H (1989) Phytochemistry 28:531–542
87. Iguchi M, Niwa M, Nishiyama A, Yamamura S (1973) Tetrahedron Lett 14:2759–2762
88. Stahl E, Keller K (1983) Planta Med 47:75–78
89. Frater G (2004) Helv Chim Acta 61:2709–2719
90. Gonny M, Bradesi P, Casanova J (2004) Flavour Fragr J 19:424–433
91. Saad HEA, El-Sharkawy SH, Halim AF (1995) Pharm Acta Helv 70:79–84
92. Nagalakshmi MAH, Thangadurai D, Anuradha T, Pullaiah T (2001) Flavour Fragr J 16:241–244
93. Radusiene J, Judzentiene A, Peciulyte D, Janulis V (2007) Plant Genet Res 5:37–44
94. Kerrola K, Galambosi B, Kallio H (1994) J Agric Food Chem 42:776–781
95. Hieda T, Tazaki M, Morishita Y, Aoki T, Nagahama S (1996) Phytochemistry 42:159–162
96. Cool LG, Hu ZL, Zavarin E (1998) Biochem Syst Ecol 26:899–913
97. Cornwell CP, Reddy N, Leach DN, Wyllie SG (2000) Flavour Fragr J 15:421–431
98. Setzer WN, Whitaker KW, Lawton RO (1992) Castanea 57:209–213
99. Southwell IA (1970) Phytochemistry 9:2243–2245
100. Hasegawa S, Hirose Y (1981) Phytochemistry 20:508–510
101. Nagahama S, Tazaki M, Kobayashi H, Sumimoto M (1993) Phytochemistry 33:879–882
102. Adams RP (2007) Identification of essential oil components by gas chromatography / mass spectrometry, 4th edn. Allured, Carol Stream, IL
103. Weyerstahl P, Marschall-Weyerstahl H, Christiansen C, Oguntimein BO, Adeoye AO (1988) Planta Med 54:546–549
104. Mundina M, Vila R, Tomi F, Cicció JF, Ibañez C, Adzet T, Casanova J, Cañigueral S (2000) Flavour Fragr J 15:201–205
105. Bertoli A, Pistelli L. Morelli I, Fraternale D, Giamperi L, Ricci D (2004) Flavour Fragr J 19:522–525
106. Joshi SC, Padalia RC, Bisht DS, Mathela CS (2007) Nat Prod Commun 2:937–939
107. Brieskorn CH, Noble P (1982) Planta Med 44:87–90
108. Baldovini N, Tomi F, Casanova J (2001) Phytochem Anal 12:58–63
109. Yang FQ, Wang YT, Li SP (2006) J Chromatogr A 1134:226–231
110. Mau JL, Lai EYC, Wang NP, Chen CC, Chang CH, Chyau CC (2003) Food Chem 82:583–591
111. Takeda K, Horibe I, Toraoka M, Minato H (1969) J Chem Soc C 1491–1495
112. Takeda K, Horibe I, Minato H (1970) J Chem Soc C 1142–1147
113. Takeda K, Horibe I, Minato H (1973) J Chem Soc, Perkin Trans I 2212–2220
114. Gopalan A, Magnus P (1980) J Am Chem Soc 102:1756–1757
115. Gopalan A, Magnus P (1984) J Org Chem 49:2317–2321
116. Barrero AF, Oltra JE, Cuerva JM, Rosales A (2002) J Org Chem 67:2566–2571
117. Barrero AF, Rosales A, Cuerva JM, Oltra JE (2003) Org Lett 5:1935–1938
118. Asakawa Y, Toyota M, von Konrat M, Braggins JE (2003) Phytochemistry 62:439–452
119. Jain TC, Banks CM, McClosky E (1970) Tetrahedron Lett 11:841–844
120. Grieco PA, Nishizawa M (1977) J Org Chem 42:1717–1720
121. de Kraker JW, Franssen MCR, Joerink M, de Groot A, Bouwmeester HJ (2002) Plant Physiol 129:257–268
122. Schloman WW, Hively RA, Krishen A, Andrews AM (1983) J Agric Food Chem 31:873–876

123. Zoeller JH, Wagner JP, Sulikowski GA (1994) J Agric Food Chem 42:1647–1649
124. Sidhu OP, Ratti N, Behl HM (1995) J Agric Food Chem 43:2012–2015
125. Watkins SF, Fronczek FR, Chiari G, Reynolds GW, Rodriguez E (1985) J Nat Prod 48:631–633
126. Isobe H, Yamanaka S, Yamaguchi K (2003) Int J Quant Chem 95:532–545
127. Vydrov OA, Scuseria GE, Perdew JP, Ruzsinsky A, Csonka GI (2006) J Chem Phys 124:094108
128. Schwabe T, Grimme S (2007) Phys Chem Chem Phys 9:3397–3406
129. Neese F, Schwabe T, Grimme S (2007) J Chem Phys 126:124115
130. Cohen AJ, Mori-Sánchez P, Yang W (2007) J Chem Phys 126:19119
131. Song JW, Hirosawa T, Tsuneda T, Hirao K (2007) J Chem Phys 126:154105