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Stereospecific Rearrangements in Tricyclopentanoid Sesquiterpenes: The Absolute Configuration of (−)-Isocomene, (−)-β-Isocomene, and (−)-Silphinene[1]

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Summary: The determination of the absolute configuration of (−)-isocomene ((−)-**9**), (−)-β-isocomene ((−)-**3**), and (−)-silphinene ((−)-**15**) by correlation with (−)-modhephene ((−)-(3a*R*,4*R*,6a*S*)-**4**) via stereospecific rearrangements is described.

Since their detection, the cyclopentanoid sesquiterpenes (−)-modhephene ((−)-**4**),[2] (−)-isocomene ((−)-**9**),[3] (−)-β-isocomene ((−)-**3**),[4] (−)-silphinene ((−)-**15**),[5] and (−)-silphiperfolene ((−)-**10**)[6] have been the focus of considerable interest. A large number of ingenious syntheses[2–6] have emerged, but only five are enantioselective. These concern (−)-modhephene[2k,o] and (−)-silphiperfolene[6a,d,f] and established their absolute configurations as (−)-(3a*R*,4*R*,6a*S*)-**4** and (−)-(3*R*,3a*S*,5a*S*,8a*S*)-**10**, respectively. This is in accord with their proposed biosynthesis from (−)-β-caryophyllene ((−)-(1*R*,9*S*)-**2**) via cations **7**[2a,7] [to give (−)-**4**] and **13**[5a,8] [to give (−)-**10**], respectively.

In order to determine the hitherto unknown absolute configurations of (−)-isocomene ((−)-**9**), (−)-β-isocomene ((−)-**3**), and (−)-silphinene ((−)-**15**), and hence their relation to (−)-caryophyllene ((−)-(1*R*,9*S*)-**2**), we took advantage of the fact that both **4** and **9**(**3**) and **10** and **15** may formally be derived from each other by three consecutive 1,2-shifts [**4**–**5**–**6**–**7**–**8**–**9**(**3**) and **10**–**11**–**12**–**13**–**14**–**15**, respectively]. We therefore rearranged not only optically active dispirane (−)-(5*S*,6*R*,7*R*)-**1** beyond the stage of (−)-modhephene ((−)-(3a*R*,4*R*,6a*S*)-**4**)[2o] ($\Delta H_f = -25.6$ kcal/mol[9]) but also natural (−)-silphinene[10] ((−)-**15**) ($\Delta H_f = -25.2$ kcal/mol). In the first case, previous experiments with (±)-**1** had shown[21] that isocomene ((1*R*,3a*S*,5a*S*,8a*R*)-**9**) ($\Delta H_f = -26.9$ kcal/mol) would be formed. In the second case, we expected the formation of silphiperfolene (**10**) ($\Delta H_f = -31.7$ kcal/mol).

Experimentally, dispirane (−)-(5*S*,6*R*,7*R*)-**1** (0.075 M) and (−)-silphinene ((−)-**15**) (0.082 M) were rearranged by treatment with 1 equiv of 5% (w/w) of concentrated

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[1] Polyspiranes. 22. Cascade Rearrangements. 16. For parts 21 and 15 see ref 2o.

[2] Systematic name (Chemical Abstracts): (−)-(3a*R*,4*R*,6a*S*)-5,6-dihydro-1,1,3,4-tetramethyl-1*H*,4*H*-3a,6a-propanopentalene. Isolation: (a) Zalkow, L. H.; Harris, R. N., III; Van Derveer, D. *Chem. Soc., Chem. Commun.* **1978**, 420. Zalkow, L. H.; Harris, R. N., III; Burke, N. I. *J. Nat. Prod.* **1979**, *42*, 96. Syntheses: (b) Karpf, M.; Dreiding, A. S. *Tetrahedron Lett.* **1980**, *21*, 4569. Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta* **1981**, *64*, 1123. (c) Smith, A. B., III; Jerris, P. J. *J. Am. Chem. Soc.* **1981**, *103*, 194. Smith, A. B., III; Jerris, P. J. *J. Org. Chem.* **1982**, *47*, 1845. (d) Schostarez, H.; Paquette, L. A. *J. Am. Chem. Soc.* **1981**, *103*, 722. Schostarez, H.; Paquette, L. A. *Tetrahedron* **1981**, *37*, 4431. (e) Oppolzer, W.; Marazza, F. *Helv. Chim. Acta* **1981**, *64*, 1575. Oppolzer, W.; Bättig, K. *Helv. Chim. Acta* **1981**, *64*, 2489. (f) Wender, P. A.; Dreyer, G. B. *J. Am. Chem. Soc.* **1982**, *104*, 5805. (g) Wrobel, J.; Takahashi, K.; Honkan, V.; Lannoye, G.; Cook, J. M.; Bertz, S. H. *J. Org. Chem.* **1983**, *48*, 139. (h) Tobe, Y.; Yamashita, S.; Yamashita, T.; Kakiuchi, K.; Odaira, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1259. (i) Wilkening, D.; Mundy, B. P. *Tetrahedron Lett.* **1984**, *25*, 4619. Mundy, B. P.; Wilkening, D.; Lipkowitz, K. B. *J. Org. Chem.* **1985**, *50*, 5727. (j) Mehta, G.; Subrahmanyam, D. *J. Chem. Soc., Chem. Commun.* **1985**, 768. Mehta, G.; Subrahmanyam, D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 395, 2289. (k) Mash, E. A.; Math, S. K.; Flann, C. J. *Tetrahedron Lett.* **1988**, *29*, 2147. Mash, E. A.; Math, S. K.; Flann, C. J. *Tetrahedron Lett.* **1989**, *30*, 2. Mash, E. A.; Math, S. K.; Flann, C. J. *Tetrahedron* **1989**, *45*, 4945. (l) Fitjer, L.; Kanschik, A.; Majewski, M. *Tetrahedron Lett.* **1988**, *29*, 5525. (m) Sha, C. K.; Jean, T. S.; Wang, D. C. *Tetrahedron Lett.* **1990**, *31*, 3745. (n) Jasperse, C. P.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 5601. Curran, D. P.; Shen, W. *Tetrahedron* **1993**, *49*, 755. (o) Fitjer, L.; Monzó-Oltra, H.; Noltemeyer, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1492.

[3] Systematic name (Chemical Abstracts): (−)-(1*R*,3a*S*,5a*S*,8a*R*)-1,-3a,4,5a-tetramethyl-1,2,3,3a,5a,6,7,8-octahydrocyclopenta[*c*]pentalene. Isolation: (a) Zalkow, L. H.; Harris, R. N., III; Van Derveer, D.; Bertrand, J. A. *J. Chem. Soc., Chem. Commun.* **1977**, 456 and ref 2a. (b) Bohlmann, F.; Le Van, N.; Pickardt, J. *Chem. Ber.* **1977**, *110*, 3777. Syntheses: (c) Paquette, L. A.; Han, Y. K. *J. Org. Chem.* **1979**, *44*, 4014. Paquette, L. A.; Han, Y. K. *J. Am. Chem. Soc.* **1981**, *103*, 1835. (d) Oppolzer, W.; Bättig, K.; Hudlicky, T. *Helv. Chim. Acta* **1979**, *62*, 1493. Oppolzer, W.; Bättig, K.; Hudlicky, T. *Tetrahedron* **1981**, *37*, 4359. (e) Pirrung, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 7130. Pirrung, M. C. *J. Am. Chem. Soc.* **1981**, *103*, 82. (f) Dauben, W. G.; Walker, D. M. *J Org. Chem.* **1981**, *46*, 1103. (g) Wender, P. A.; Dreyer, G. B. *Tetrahedron* **1981**, *37*, 4445. (h) Wenkert, E.; Arrhenius, T. S. *J. Am. Chem. Soc.* **1983**, *105*, 2030. (i) Ranu, B. C.; Kavka, M.; Higgs, L. A.; Hudlicky, T. *Tetrahedron Lett.* **1984**, *25*, 2447. (j) Tobe, Y.; Yamashita, T.; Kakiuchi, K.; Odaida, Y. *J. Chem. Soc., Chem. Commun.* **1985**, 898. (k) Manzardo, G. G. G.; Karpf, M., Dreiding, A. S. *Helv. Chim. Acta* **1986**, *69*, 659. (l) Lee, H. W.; Lee, J. H.; Lee, I. Y. C. *Bull. Korean Chem. Soc.* **1991**, *12*, 392, and ref 2m.

[4] Systematic name (Chemical Abstracts): (1*R*,3a*S*,5a*S*,8a*R*)-1,3a,5a-trimethyl-4-methylenedecahydrocyclopenta[*c*]pentalene. Isolation: (a) Bohlmann, F.; Le Van, N.; Pham, T. V. C.; Jakupovic, J.; Schuster, A.; Zabel, V.; Watson, W. H. *Phytochemistry* **1979**, *18*, 1831. Syntheses: (b) Willmore, N. D.; Goodman, R.; Lee, H. H.; Kennedy, R. M. *J. Org. Chem.* **1992**, *57*, 1216, and ref 2d, e, i, k.

[5] Systematic name (Chemical Abstracts): (−)-(1*R*,3a*S*,5a*S*,8a*S*)-1,4,4,5a-tetramethyl-1,2,3,3a,4,5,5a,6-octahydrocyclopenta[*c*]pentalene. Isolation: (a) Bohlmann, F.; Jakupovic, J. *Phytochemistry* **1980**, *19*, 259. Syntheses: (b) Leone-Bay, A.; Paquette, L. A. *J. Org. Chem.* **1982**, *47*, 4173. Paquette, L. A.; Leone-Bay, A. *J. Am. Chem. Soc.* **1983**, *105*, 7352. (c) Tsunoda, T.; Kodama, M.; Ito, S. *Tetrahedron Lett.* **1983**, *24*, 83. (d) Sternbach, D. D.; Hughes, J. W.; Burdi, D. F.; Banks, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 2149. (e) Wender, P. A.; Ternansky, R. J. *Tetrahedron Lett.* **1985**, *26*, 2625. (f) Crimmins, M. T.; Mascarella, S. W. *J. Am. Chem. Soc.* **1986**, *108*, 3435. (g) Crimmins, M. T.; Mascarella, S. W. *Tetrahedron Lett.* **1987**, *28*, 5063. (h) Rao, Y. K.; Nagarajan, M. *Tetrahedron Lett.* **1988**, *29*, 107. Rao, Y. K.; Nagarajan, M. *J. Org. Chem.* **1989**, *54*, 5678. (i) Franck-Neumann, M.; Miesch, M.; Lacroix, E. *Tetrahedron Lett.* **1989**, *30*, 3533. (j) Shizuri, Y.; Ohkubo, M.; Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 3797. Yamamura, S.; Shizuri, Y.; Shigemori, H.; Okuno, Y.; Ohkubo, M. *Tetrahedron* **1991**, *47*, 635.

[6] Systematic name (Chemical Abstracts): (−)-(3*R*,3a*S*,5a*S*,8a*S*)-3,-5a,7,8-tetramethyl-1,2,3,3a,4,5,5a,6-octahydrocyclopenta[*c*]pentalene. Isolation: ref 4a. Syntheses: (a) Paquette, L. A.; Roberts, R. A.; Drtina, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 6690. (b) Wender, P. A.; Singh, S. K. *Tetrahedron Lett.* **1985**, *26*, 5987. (c) Curran, D. P.; Kuo, S. C. *J. Am. Chem. Soc.* **1986**, *108*, 1106. Curran, D. P.; Kuo, S. C. *Tetrahedron* **1987**, *43*, 5653. (d) Meyers, A. I.; Lefker, B. A. *Tetrahedron* **1987**, *43*, 5663. (e) Kakiuchi, K.; Ue, M.; Tsukahara, H.; Shimizu, T.; Miyoa, T.; Tobe, Y.; Odaira, Y.; Yasuda, M.; Shima, K. *J. Am. Chem. Soc.* **1989**, *111*, 3707. (f) Dickson, J. K., Jr.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1990**, 1440.

[7] Roberts, J. S. In *Terpenoids and Steroids;* Hanson, J. R., Ed.; The Royal Society Press: London, 1981; Vol. 10, p 105.

[8] (a) Bohlmann, F.; Zdero, C.; Jakupovic, J.; Robinson, H.; King, R. M. *Phytochem.* **1981**, *20*, 2239. (b) Klobus, M.; Zhu, L.; Coates, R. M. *J. Org. Chem.* **1992**, *57*, 4327.

[9] The heats of formation of **3**, **4**, **9**, **10**, and **15** were calculated using PCMODEL (version 4.0): Serena Software, P.O. Box 3076, Bloomington, IN 47402. The structure of carbenium ion **14** was optimized using MMP2: Sprangue, J. T.; Tai, J. C.; Allinger, N. L. *J. Comput. Chem.* **1987**, *8*, 581. The parameters for carbenium ions were taken from UNICAT 2: Müller, P.; Mareda, *J. Helv. Chim. Acta* **1987**, *70*, 1017. The p-orbital was defined as orthogonal to the plane of the three neighboring carbon atoms, and the distance of the cationic center to the center of each lobe set to 1.50 Å.

[10] Natural (−)-silphinene ((−)-**15**) and natural (−)-isocomene ((−)-**9**) were isolated from the roots of *Otanthus maritimus*: de Pascual Teresa, J.; San Feliciano, A.; Barrero, A. F.; Medarde, M.; Tomé, F. *Phytochemistry* **1981**, *20*, 166. Natural (−)-**9** was used to check the chemical identity (^{1}H-NMR) and optical purity (GC) of synthetic (−)-**9** isolated from incompletely rearranged samples of (−)-**1** and (−)-**15**.

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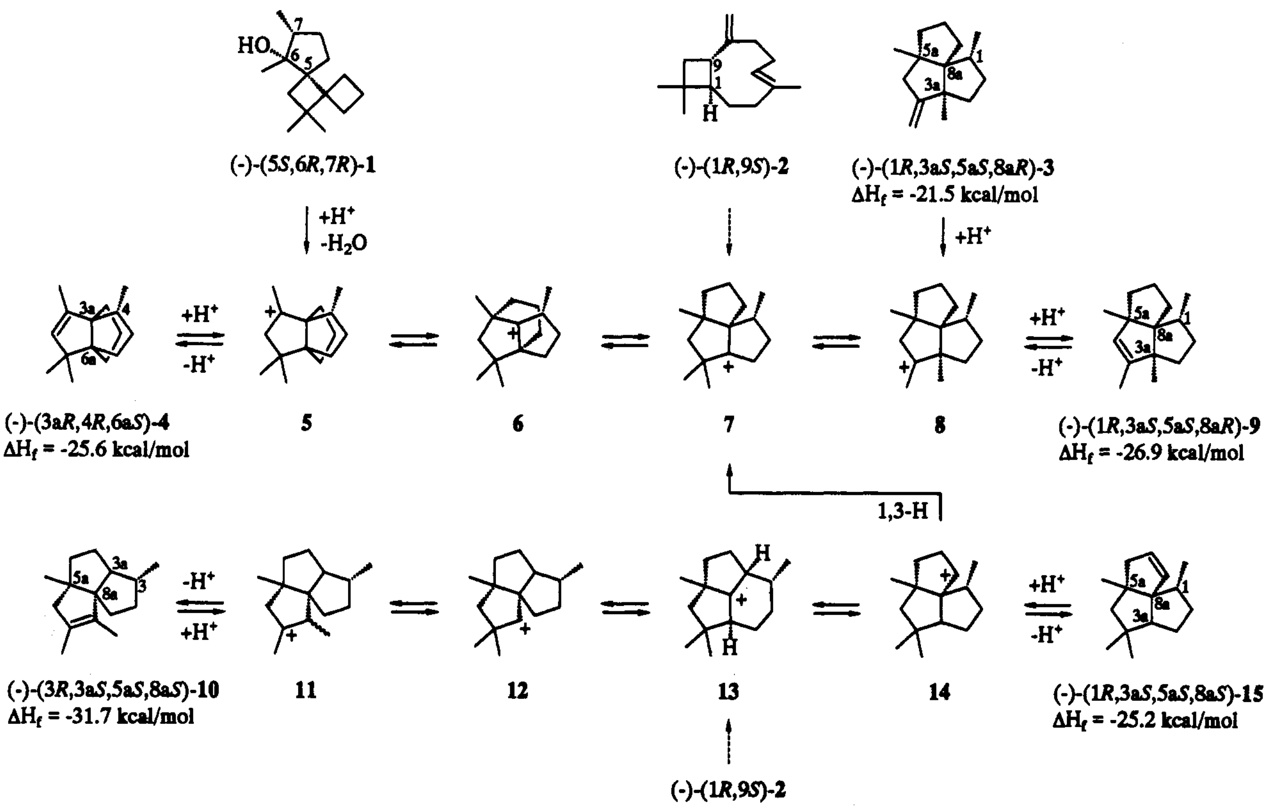
Scheme I



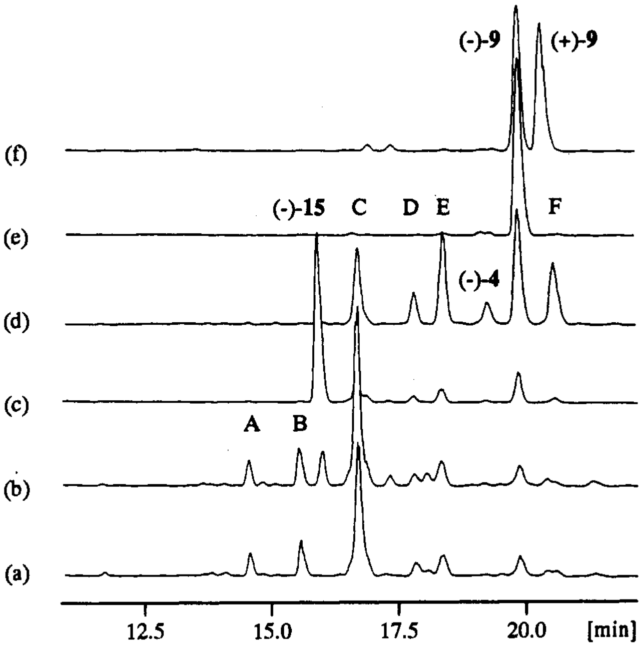
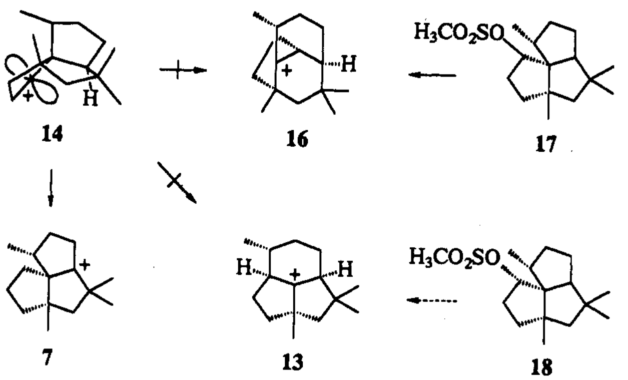


Figure 1. Capillary gas chromatograms (25-m × 0.25-i.d. deactivated fused-silica capillary column coated with heptakis-(2,3,6-tri-*O*-methyl)-β-cyclodextrin in OV-1701 (0.07 M), at 110 °C, carrier gas 0.6 bar H_2). Product distribution after rearrangement with 1 equiv of 5% (w/w) of H_2SO_4 on silica gel in benzene at 70 °C: (−)-1 (0.075 M) after 3 h (a) and 40 min (d); (−)-15 (0.082 M) after 3 h (b) and 30 min (c); (e) natural (−)-9; (f) synthetic (±)-9.

sulfuric acid on silica gel in benzene for 3 h at 70 °C. To our surprise, capillary gas chromatography on permethylated β-cyclodextrin revealed that the outcome in both cases was virtually the same (Figure 1a,b). This indicated that (−)-silphinene ((−)-15) had largely rearranged via an initial 1,3-hydrogen shift (14–7), yielding the same enantiomer of isocomene ((1*R*,3a*S*,5a*S*,8a*R*)-9) as formed from (−)-modhephene ((−)-(3a*R*,4*R*,6a*S*)-4), a known intermediate of the rearrangement of dispirane (−)-(5*S*,6*R*,7*R*)-1.[2o]

Scheme II



To confirm this result and to determine the sign of rotation, isocomene ((1*R*,3a*S*,5a*S*,8a*R*)-9), as formed from both (−)-1 and (−)-15, was isolated from incompletely rearranged samples (Figure 1d,c) by chromatography on silica gel doped with 20% (w/w) silver nitrate using pentane as eluent. First, ^{1}H-NMR confirmed the structural assignment,[10] and then capillary gas chromatography on permethylated β-cyclodextrin proved the identity with natural (−)-isocomene[10] (Figure 1e,f). Thus, it became clear that the absolute configurations of (−)-isocomene and (−)-silphinene are (1*R*,3a*S*,5a*S*,8a*R*)-9 and (−)-(1*R*,3a*S*,5a*S*,8a*S*)-15, respectively. As natural (−)-β-isocomene (ΔH_f = 21.5 kcal/mol) has formerly been rearranged to (−)-isocomene,[10] its absolute configuration is (−)-(1*R*,3a*S*,5a*S*,8a*R*)-3.

As to the unusual 1,3-hydrogen shift in protonated (−)-silphinene (14) (Scheme II), inspection of the geometryoptimized structure[9] reveals that the close proximity (d) of the bridgehead hydrogen to the center of one lobe of the lone pair orbital together with a favorable dihedral angle (θ) may well account for the effective discrimination between the 1,3-hydrogen shift observed (**14**–**7**; d = 1.50 Å, θ = 31.7°), the 1,2-alkyl shift expected (**14**–**13**; d = 2.17 Å, θ = 27.4°), and a second 1,2-alkyl shift (**14**–**16**; d = 2.08 Å, θ = 23.7°) originally not taken into account. It is interesting to note that this last shift occurs exclusively upon solvolysis of silphin-2α-yl methanesulfonate (**17**).[8b] It is therefore tempting to speculate that its epimer **18** could rearrange via cation **13** to silphiperfolene (**10**).

In summary, stereospecific rearrangements have been used to establish the absolute configuration of (−)-silphinene ((−)-**15**), (−)-isocomene ((−)-**9**), and (−)-β-isocomene ((−)-**3**) by correlation with (−)-modhephene ((−)-(3aR,4R,6aS)-**4**). (−)-Silphiperfolene ((−)-(3*R*,3a*S*,5a*S*,8a*S*)-**10**), albeit not found,[11] correlates with the other sesquiterpenes as well. This indicates that (−)-β-caryophyllene ((−)-(1*R*,9*S*)-**2**) might well be the precursor of all five sesquiterpenes, entering the tricycloundecane energy surface at **7**[2a,7] and/or **13**.[5a,8] A reinvestigation of its acid-catalyzed rearrangement[12] is in progress.

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(11) Compounds A–F have been isolated from rearranged samples of (±)-**1**, and compound C has been isolated from a rearranged sample of (−)-**15**. C–F have been fully characterized and A–F shown by ^{1}H-NMR to be not identical with (−)-silphiperfolene (−)-**10**).[4a] Details will be published elsewhere.

(12) No less than 13 compounds have been detected by GC in the hydrocarbon fraction obtained from the sulfuric acid catalyzed rearrangement of (−)-β-caryophyllene ((−)-**2**): Parker, W.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc. C* **1969**, 2634. However, the structure of all compounds with the exception of two (clovene and neoclovene) remained unknown.