A Simple Synthetic Approach to Trachylobane, Beyerane, and Atisane Diterpenoids from Carvone

Antonio Abad,* Consuelo Agulló, Ana C. Cuñat, Ismael Navarro, M. Carmen Ramírez de Arellano[1]

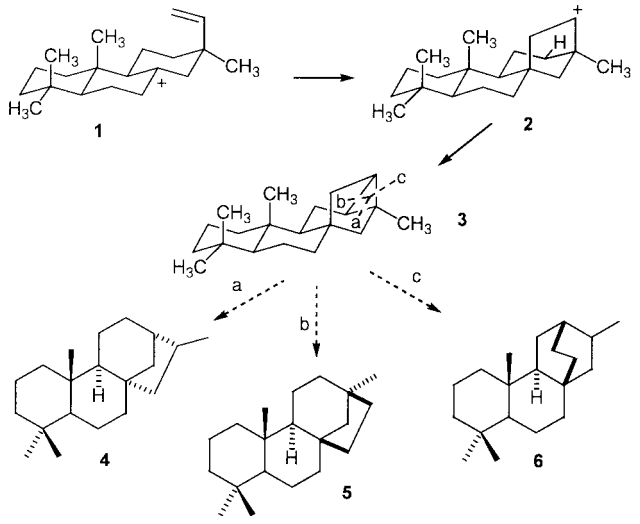
Departamento de Química Orgánica, Universitat de Valencia, Dr. Moliner 50, 46100-Burjassot (Valencia), Spain
Fax +34(6)3864328; E-mail: Antonio.Abad@uv.es

Received 4 January 2001

Abstract: A stereoselective general synthetic approach to trachylobane-, beyerane-, and atisane-type polycyclic diterpenoids from carvone is described. Key steps in this approach are an IMDA reaction, an intramolecular diazo ketone cyclopropanation of an unsaturated ketone, and a controlled regioselective opening of a cyclopropyldiketone moiety.

Key words: terpenoids, Diels-Alder reaction, diazo compounds, ring opening, cyclopropane

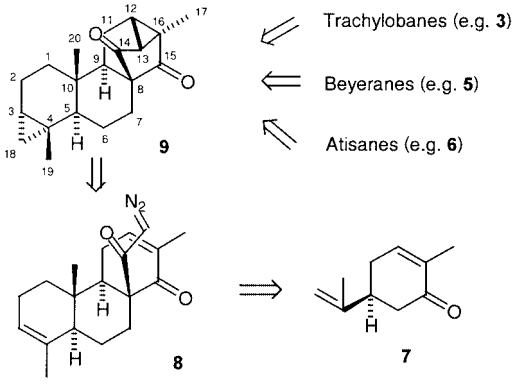
Trachylobane-, beyerane-, atisane- and kaurane-type polycyclic diterpenoids[2] constitute an important group of natural compounds of terrestrial origin that displays a broad spectrum of biological activity, including antimicrobial, antitumor, antifeedant, gibberellin-like, and anti-HIV properties. All of them are biogenetically related, and it is now widely accepted that the tetracyclic carbon skeletons of beyeranes, atisanes and kauranes arise from the cyclization of an intermediate pimaranyl cation **1** that produces the tetracyclic cation **2** (Scheme 1).[3] Closure of this species occurs by either formation of a protonated cyclopropane or by loss of a proton forming the pentacyclic trachylobane skeleton **3**. The three possible cleavage modes of the cyclopropane ring lead to the skeletons of kaurane **4** (path a), beyerane **5** (path b) or atisane **6** (path c).



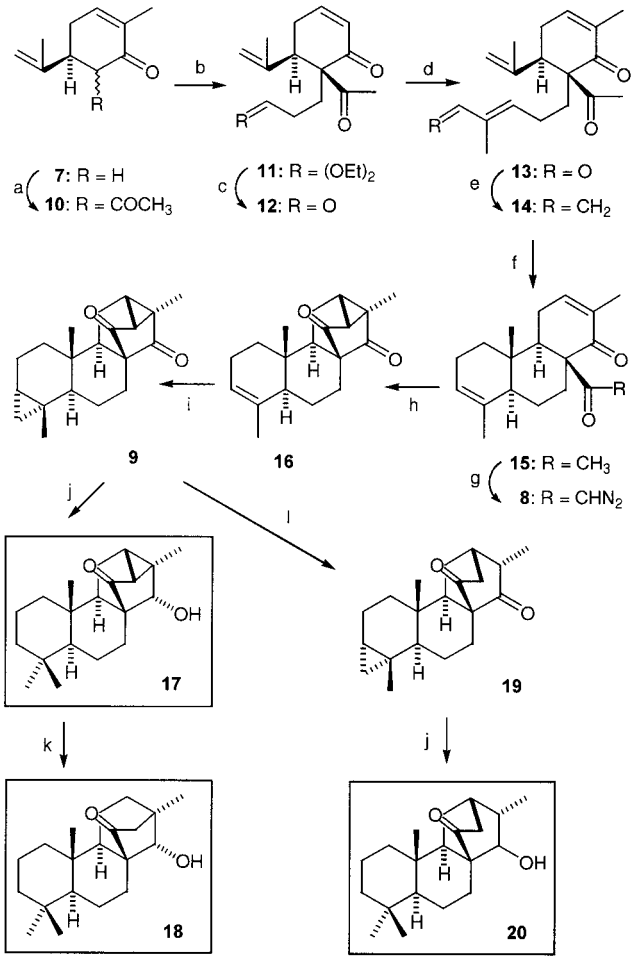
Scheme 1

The synthesis of these compounds has attracted the attention of numerous organic synthetic chemists due to the difficulties associated with the construction of the bridged carbocyclic system,[3b,4] and several synthetic strategies have been developed for the construction of the tricyclo[3.2.1.0^{2,7}]-, bicyclo[3.2.1]- and bicyclo[2.2.2]-octane moieties, characteristic for trachylobanes, beyeranes/kauranes and atisanes respectively.[5]

As part of our research related to the utilization of readily available chiral building blocks for the synthesis of polycyclic terpenoids,[6] we wish to describe in this paper a stereoselective general approach to the carbocyclic skeleton of trachylobanes, beyeranes and atisanes from the monoterpene carvone. As shown in the retrosynthetic analysis in Scheme 2, the key feature of the synthesis involves the preparation of a polycyclic diketone **9**, containing the tricyclo[3.2.1.0^{2,7}]octane moiety incorporated into ring C. This is prepared by the intramolecular addition of a α-diazo carbonyl group to the enone double bond of a homochiral phenanthrenone system **8**, which, in turn, is prepared from carvone **7** following the methodology previously used by us[6] and others[7] for the preparation of related systems. The completion of the trachylobane skeleton from **9** only requires the introduction of the geminal dimethyl group at C-4, while its conversion into the beyerane and atisane frameworks requires, as in the biogenetic route, additional regioselective fragmentation of the C12-C13 or C13-C16 bond.



Scheme 2



Scheme 3 (a) i: LDA, THF, -78 ºC then CH_3CHO; ii: $(ClCO)_2$-DMSO, Cl_2CH_2, -30 ºC then Et_3N, 85%; (b) NaH, THF, 0 ºC then Bu_4NHSO_4 and $ICH_2CH(EtO)_2$, 78%; (c) PPTS, H_2O-acetone, 92%; (d) Ph_3P=C(Me)CHO, benzene, ref, 86%; (e) Ph_3P=CH_2, THF, -78 ºC, 87%; (f) toluene, 185 ºC, propylene oxide, 6 days, 89%; (g) i: LiHMDS, THF, -78 ºC then $CF_3CO_2CH_2CF_3$; ii: MsN_3, CH_3CN, H_2O-Et_3N, 87%; (h) bis(*N*-*tert*-Butyl salicylaldiminate) Cu(II), toluene, ref, 95%; (i) CH_2I_2, $ZnEt_2$, toluene, 0 ºC, 94%; (j) H_2, PtO_2, AcOH, 4 atm, 95% for **17** and 83% for **20**; (k) Li, NH_3-THF, -78 ºC, 83%; (l) SmI_2, THF-MeOH, -78 ºC, 75%.

The synthesis of the key intermediate **9** commences with the preparation of β-diketone **10** from commercial (*S*)-(+)-carvone (**7**) (Scheme 3). This was made by reaction of the kinetic enolate of carvone with acetaldehyde and followed by Swern oxidation of the resulting β-hydroxyketone. The β-diketone **10** is thus obtained in 85% overall yield as a mixture of inseparable epimers. Alkylation of its tetrabutylammonium enolate, obtained by treatment of **10**, first with two equivalents of NaH in THF and then with Bu_4NHSO_4, with 3-iodopropanaldehyde diethyl acetal, afforded diastereoselectively compound **11** in 78% yield. Direct alkylation of the sodium enolate of **10** under different reaction conditions always afforded a much lower yield of **11**, together with significant amounts of O-alkylated products.[8] Removal of the acetal protecting group with pyridinium *p*-toluenesulfonate in aqueous acetone provided the aldehyde **12** in 92% yield. Chemoselective homologation of the aldehyde group of **12** by Wittig reaction with (α-formylethylidene)triphenyl phosphorane provided stereoselectively the chain extended α,β-unsaturated aldehyde **13**, which, by subsequent Wittig methylenation, afforded the 1,3,9-triene **14** in 75% overall yield.

Heating a solution of this compound in toluene and a small amount of propylene oxide in a sealed tube at 185 °C for 6 days afforded stereoselectively the tricyclic compound **15** in very high yield. Having efficiently completed the preparation of the ABC-ring system common to the target diterpenes, the stage was now set for the construction of the tricyclo[3.2.1.$0^{2,7}$]octane moiety of key intermediate **9**. Treatment of the lithium enolate of **15** with 2,2,2-trifluoroethyltrifluoroacetate, followed by diazo-transfer reaction using mesylazide as reagent, provided the tricyclic α-diazoketone **8** in 87% overall yield for the two steps. Intramolecular addition of the α-diazoketone to the enone double bond was accomplished in 95% yield using bis(N-*tert*-butyl salicylaldiminate) copper(II) as the catalyst.[9] In order to complete the construction of the characteristic geminal dimethyl group at the C-4 position of the diterpene skeleton, the A-ring double bond was stereoselectively cyclopropanated, using standard Simmons-Smith cyclopropanation conditions. This reaction cleanly and stereoselectively afforded the key intermediate **9** in 94% yield, the structure of which was firmly established by an X-ray crystallographic analysis (Figure 1).[10]

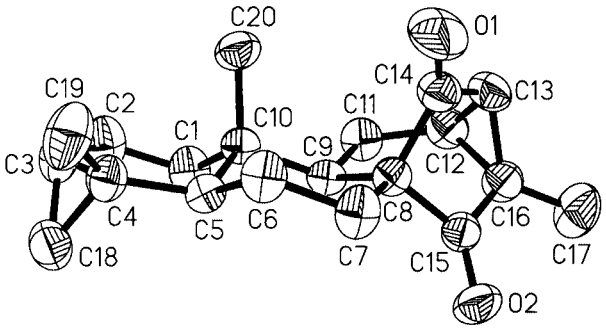


Figure 1 Thermal ellipsoids plot of **9** (50% probability levels)

This compound was then directly converted into the trachylobane-type compound **17** through regioselective cyclopropane hydrogenolysis on stirring under H_2 (4 atm)/Pt in AcOH at room temperature.[11] This treatment not only releases the latent geminal dimethyl group at C-4 but also produces the stereoselective reduction of the C-15 carbonyl group, thus facilitating the eventual elaboration of the peripheral substitution patterns of the trachylobane system.

Completion of the synthesis of the beyerane and atisane frameworks was also efficiently accomplished from **9** as follows. Regioselective cleavage of the C12-C13 bond of **17** by lithium-liquid ammonia reduction furnished the beyerane diterpene **18** in 83% yield. Alternatively, regioselective cleavage of the C13-C16 bond of the cyclopropane moiety of diketone **9** with samarium iodide afforded the compounds **19**, from which the atisane-type compound **20** was obtained after cyclopropane hydrogenolysis. As in the catalytic hydrogenation of **9**, a selective reduction of the carbonyl group at C-15 also occurs, but in this case to give a mixture of epimeric alcohols at this position.[12]

In summary, we have developed a highly efficient and stereoselective approach to trachylobane, beyerane and atisane diterpenoids, via common synthetic intermediates, from carvone. The final diterpene systems prepared by this approach (e.g. **17**, **18** and **20**) are potential precursors of some relevant naturally occurring compounds. Work is currently in progress in our laboratory for the adaptation of this approach to the synthesis of more functionalized members (particularly around A- and B-rings) of this group of natural products.

Acknowledgement

We are grateful to the Ministerio de Educación y Cultura of Spain for financial support (Project PB98-1421-C02-01). M.C.R.A. thanks the Generalitat Valenciana for financial support (Project GVDOC99-22). We also thank Professor M. Doyle for his comments on the addition of diazo compounds to conjugated ketones.

References and Notes

(1) X-ray crystal structure determination (E-mail: mcra@uv.es)

(2) (a) Connolly, J. D., Hill R. A. In *Dictionary of Terpenoids*, 1st ed; Chapman and Hall: London, 1991; Vol. 2, pp 906-970. (b) Faulkner, D. J. *Nat. Prod. Rep*. **2000**, *17*, 165 and previous reviews of this series.

(3) (a) Wenker, E. *Chem. Ind. (London)* **1955**, 282. (b) Goldsmith, D. In *The Total Synthesis of Natural Products*, Vol. 8; Apsimon J., Ed.; John Wiley & Sons: New York, 1992, p 101.

(4) Recent synthesis: (a) Toyota, M.; Wada, T.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 4565. (b) Toyota, M.; Wada, T.; Fukumoyo, K.; Ihara, M. *J. Am. Chem. Soc*. **1998**, *120*, 4916. (c) Berettoni, M.; De Chiara, G.; Iacoangeli, T.; Lo Surdo, P.; Bettolo, R. M.; di Mirabello, L. M.; Nicolini, L.; Scarpelli, R. *Helv. Chim. Acta* **1996**, *79*, 2035. (d) Abad, A.; Agulló, C.; Arnó, M.; Marín, M. L.; Zaragozá, R. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2987.

(5) (a) Cory, R. M.; Chan, D. M. T.; Naguib, Y. M. A.; Rastall, M. H.; Renneboog, R. M. *J. Org. Chem*. **1980**, *45*, 1852. (b) Basu, B.; Mukherjee, D. *Tetrahedron Lett.* **1984**, *25*, 4445. (c) Ihara, M.; Toyota, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2151. (d) Toyota, M.; Yokota, M.; Ihara, M. *Org. Lett.* **1999**, *1*, *1627*.

(6) (a) Abad, A.; Agulló, C.; Castelblanque, L.; Cuñat, A. C.; Navarro, I.; Ramírez de Arellano, M. C. *J. Org. Chem.* **2000**, *65*, 4189. (b) Abad, A.; Agulló, C.; Cuñat, A. C. Llosá, M. C. *Chem. Commun*. **1999**, 427 and literature cited therein.

(7) (a) Shing, T. K. M.; Jiang, Q. *J. Org. Chem*. **2000**, *65*, 7059. (b) Rawal, V. H.; Iwasa, S. Abstracts of Papers; 204th National Meeting of the American Chemistry Society, Washington, DC; American Chemical Society: Washington, 1992; ORGN 35.

(8) This procedure represents a simple alternative for the generation of tetrabutylammonium enolates of β-dicarbonyl compounds. See, Shono, T.; Kashimura, S.; Sawamura, M.; Soejima, T. *J. Org. Chem.* **1988**, *53*, 907.

(9) Although the addition of α-ketocarbenoids to olefinic bonds has extensively been used in synthesis, very few examples have been reported of addition to conjugated ketones (see : Davies, H. M. L. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4 (Semmelhach, M. F. Ed.), Chap. 8, p 103). To our knowledge this is the first example that utilizes this reaction for the construction of a natural polycyclic framework. The high yield obtained in the cyclopropanation reaction of **8** contrasts with the poor results obtained in the few examples of this reaction described so far (see: Burke, S. D.; Grieco, P. A. *Organic Reactions*, Vol. 26, Chap. 2; Dauben, W. G., Ed; John Wiley & Sons: New York, 1979; p 361).
It is unknown if the cyclopropanation reaction occurs via a ketocarbenoid intermediate, an unfavourable process due to the electrophilic character of this species and the adverse electron-withdrawing effect of the carbonyl group on the reactivity of the double bond, or by dipolar cycloaddition of the diazocarbonyl moiety to the α,β-unsaturated system followed by dinitrogen extrusion (see: Doyle, M. P.; Dorow, R. L.; Tamblyn, W. H. *J. Org. Chem*. **1982**, *47*, 4059). In any case, control experiments showed that the reaction (conversion of **8** into **16**) also takes place in the absence of the copper catalyst but at 190 °C in toluene and in no useful synthetic yield.

(10) *Crystal data for compound* **9**: colourless plate of $0.62 \times 0.60 \times 0.10$ mm size, monoclinic, C2, a = 10.4259(9), b = 7.8156(6), c = 20.720(2) Å, β = 104.004(7)°, V = 1638.1(2) Å^3, Z = 4, $2\theta_{max}$ = 56°, diffractometer Nonius CAD4, Mo Kα (λ = 0.71073 Å), ω-scan, 5230 reflections collected of which 3970 (R_{int} = 0.019) were independent, refinement on F^2 using SHELX97 program (Sheldrick, G.M., University of Göttingen, 1997), 201 refined parameters, riding hydrogen atoms, absolute structure could not be determined, R1[I > 2σ(I)] = 0.0421, wR2 (all data) = 0.1188, residual electron density 0.30 eÅ^{-3}.

(11) It should be mentioned that no hydrogenolysis of the other cyclopropane ring was observed, even under more forcing hydrogenation conditions.

(12) All compounds were characterised by ^{1}H NMR, ^{13}C NMR, IR and HRMS. Selected data of more significant compounds are given. *Compound* **9**: mp 143-144 °C (from MeOH); $[\alpha]_D$+73.9° (*c* 3.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.56 (1H, d, *J* = 8 Hz, H-13), 2.44 (1H, ddd, *J* = 8, 5 and 2 Hz, H-12),1.39 (3H, H-17), 0.94 (3H, H-19), 0.79 (3H, H-20), 0.59 (1H, m, H-3), 0.4 (1H, dd, *J* = 9, 4 Hz, H-18β); -0.05 (1H, dd, *J* = 6, 4 Hz, H-18α); HRMS m/z (M^+) calcd 298.1933, obsd 298.1932.
Compound **17**: mp 154-156 °C (from MeOH); $[\alpha]_D$+49.8° (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.61 (1H, br s, H-15); 1.87 (1H, m, H-12),1.80 (1H, d, *J* = 8 Hz, H-13), 1.34 (3H, H-17), 0.87 (3H, H-18), 0.819 (3H, H-19), 0.75 (3H, s, H-20), 0.7 (H-5, dd, *J* = 13, 4.5 Hz); HRMS m/z (M^+) calcd 302.2246, obsd 302.2244.
Compound **18**: mp 164-166 °C (from pentane); $[\alpha]_D$ −44° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.17 (1H, br s, H-15), 2.25 (1H, d, *J* = 19 Hz, H-13), 1.87 (1H, d, *J* = 19 Hz, H´-13), 1.07 (3H, s, H-17), 0.86 and 0.83 (6H, each s, H-18 and H-19), 0.80 (3H, s, H-20); HRMS m/z (M^+) calcd 304.2402, obsd 304.2397.
Compound **20**. A 2:1 mixture of β− and α− epimers at C-15 is

obtained in the reduction of **19**. Both epimeric alcohols are easily separable by column chromatograph using hexane:ethyl acetate 7:3 as eluent; only data of the main epimer (15β-OH) are given: mp 164.5-166.5 °C (from cold pentane); $[\alpha]_D$ −14.5º (*c* 0.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 3.18 (1H, d, *J* = 3 Hz, H-14), 2.54 (1H, ddd, *J* = 13, 4 and 3 Hz, H-7β), 2.27 (1H, dd, *J* = 19 and 3 Hz, H-16), 2.20 (1H, ddd, *J* = 19, 5 and 3 Hz, H´-16), 1.16 (3H, d, *J* = 7 Hz, H-17), 0.85 (3H, H-19), 0.78 (3H, H-18), 0.69 (3H, H-20); HRMS m/z (M^+) calcd 304.2402, obsd 304.2399.

Article Identifier:
1437-2096,E;2001,0,03,0349,0352,ftx,en;L22000ST.pdf