Pergamon

Tetrahedron Letters 42 (2001) 8965–8968

TETRAHEDRON LETTERS

Stereoselective synthesis of polyoxygenated atisane-type diterpenoids

Antonio Abad,* Consuelo Agulló, Ana C. Cuñat and Ismael Navarro

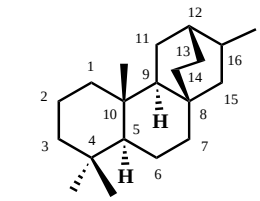
Departamento de Química Orgánica, Universitat de Valencia, Dr. Moliner 50, 46100-Burjassot Valencia, Spain

Received 30 July 2001; revised 15 October 2001; accepted 17 October 2001

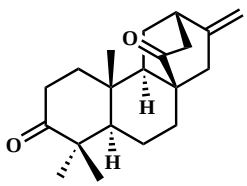
Abstract—A new stereoselective approach to polyoxygenated atisane-type diterpenes starting from (*S*)-(+)-carvone is described. The key steps involve an intramolecular Diels–Alder reaction, an unusual intramolecular diazo ketone cyclopropanation of an unsaturated ketone, and a regioselective endocyclic cleavage of a cyclopropyl carbinyl radical as key synthetic steps. The synthesis of the bioactive polyoxygenated atisanes atis-16(17)-en-3,14-dione (**2**) and 3*R*-hydroxy-atis-16(17)-en-2,14-dione (**3**) following this approach is presented.

A large number of diterpenes with the atisane skeleton (**1**) have been isolated from different natural sources.[1] Many of these tetracyclic diterpenoids, and particularly those containing several oxygenated functions, display a wide spectrum of biological activity.

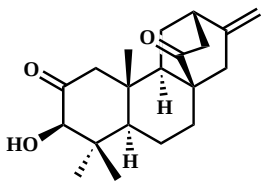
Some examples are shown below.[2] Compound **3**, isolated from the Samoan ethnobotanical tree *Homalanthus acuminatus*, shows AIDS-antiviral activity[3] and compounds **2** and **4** isolated from the Fijian medicinal plant *Euphorbia fidjiana Boiss*,[4a] are active against L1210 mouse leukaemia.[4b]



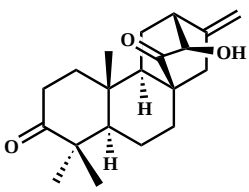
1



2



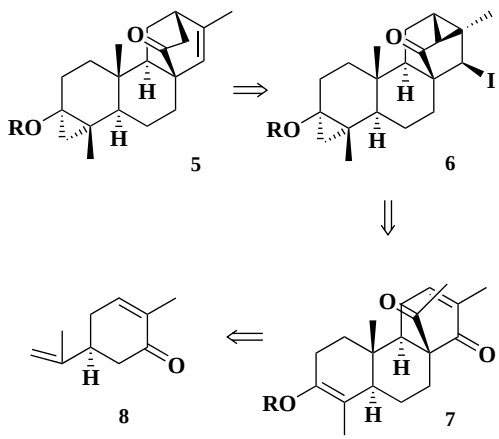
3



4

As a continuation of our studies on the synthesis of tetracyclic diterpenes[5] we report here a new approach towards these compounds from carvone. Explicitly, we describe the preparation of atisanes **2** and **3** via the common key intermediate pentacyclic compound **5** (Scheme 1), which is efficiently prepared from carvone using an IMDA reaction, an unusual intramolecular diazo ketone cyclopropanation of an unsaturated ketone, and a regioselective endocyclic cleavage of a cyclopropyl carbinyl radical as the key synthetic steps.[6]

The easy preparation of **5** in enantiomerically pure form not only allows the synthesis of these and other related natural atisanes, but also offers an excellent opportunity for the preparation of other polyoxy-



R = TBDMS

Scheme 1.

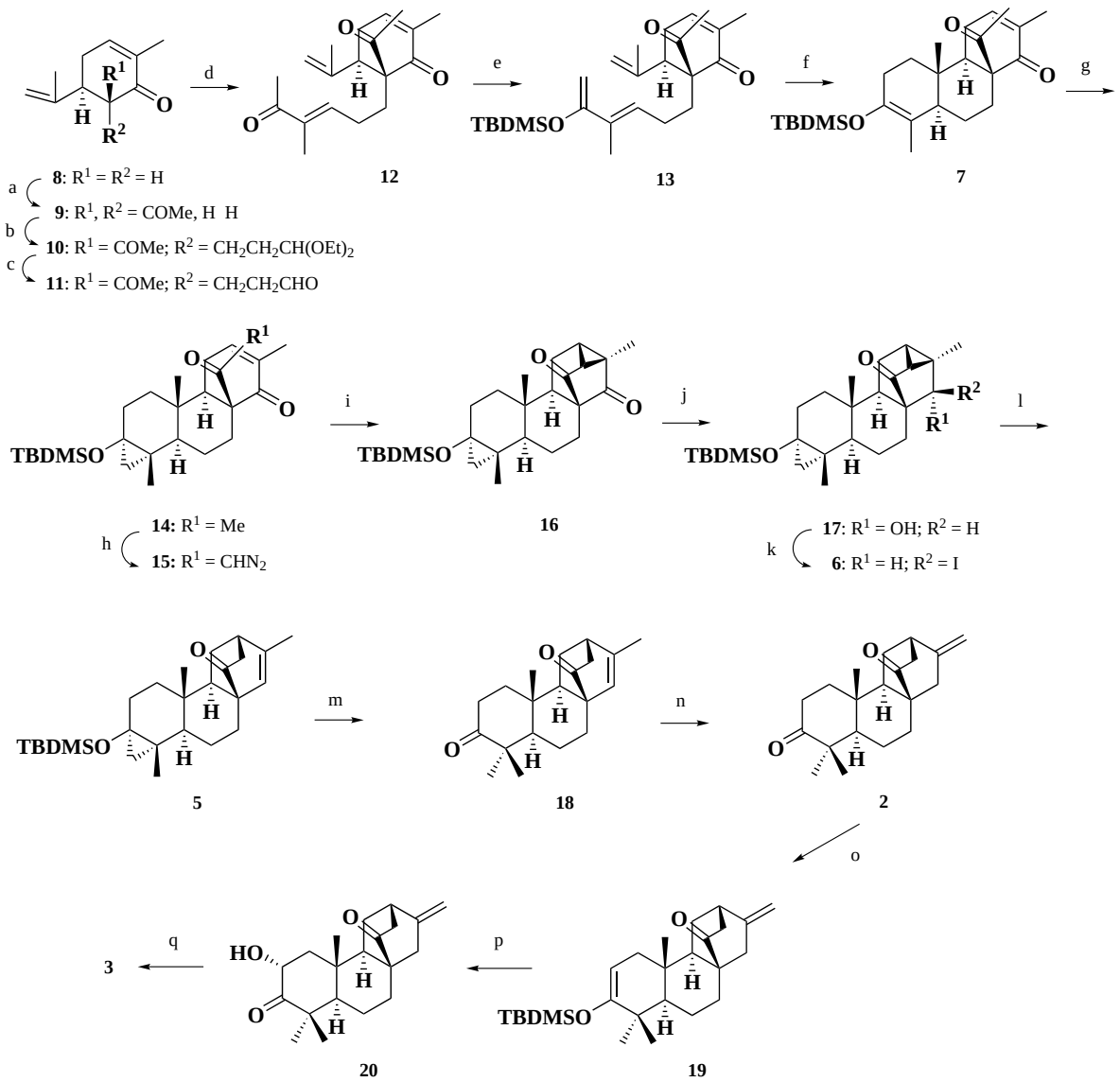
Keywords: terpene; carvone; atisane; cyclopropanation; Diels–Alder reaction; radical cleavage.

* Corresponding author. Tel.: 34-6-3864509; fax: 34-6-3864328; e-mail: antonio.abad@uv.es

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01953-0

genated non-natural atisane-type compounds that may provide new candidates for evaluation of biological activity.

The synthesis of compound **5** commences with the preparation of the 1,3,9-triene **13**, precursor of the IMDA reaction that allows the construction of the ABC rings (Scheme 2).[7] Thus, the reaction of the kinetic enolate of commercial (*S*)-(+)-carvone (**8**) with acetaldehyde, followed by Swern oxidation of the resulting β-hydroxyketone to the β-diketone **9** and alkylation of its tetrabutylammonium enolate with the 3-iodopropanaldehyde diethyl acetal, afforded diastereoselectively the compound **10** in 66% overall yield. Removal of the aldehyde acetal function of **10** with pyridinium *p*-toluenesulfonate (PPTS) in aqueous acetone provided the aldehyde **11** in 92% yield. Homologation of this aldehyde with the α-phosphonate carbanion generated from diethyl 2-oxobutane-3-phosphonate[8] and NaH in THF at room temperature gave the desired (*E*)-enone **12** in 83% yield after column chromatography. The synthesis of the IMDA precursor



Scheme 2. (a) i LDA, THF, −78°C then CH_3CHO, ii $(ClCO)_2$–DMSO, CH_2Cl_2, −30°C then Et_3N, 85%; (b) NaH, THF, 0°C then Bu_4NHSO_4 and $ICH_2CH_2CH(EtO)_2$, 78%; (c) PPTS, H_2O–acetone, 92%; (d) $(EtO)_2P(O)C(Na)(Me)COMe$, THF, rt; 83%; (e) Et_3N, TBDMSOTf, CH_2Cl_2, −78°C; 90%; (f) PhMe, propylene oxide, 190°C; 95%; (g) CH_2I_2, $ZnEt_2$, toluene, 0°C, 89%; (h) i LiHMDS, THF, −78°C then $CF_3CO_2CH_2CF_3$, ii MsN_3, CH_3CN, THF–H_2O–Et_3N, 80%; (i) bis(*N-tert*-butylsalicylaldiminate)Cu(II), toluene, reflux, 90%; (j) H_2, 10% Pt/C, AcOEt, 4 atm, 95%; (k) i MsCl, Et_3N, CH_2Cl_2, rt, ii NaI, acetone, 40°C, 93%; (l) SmI_2, THF–MeOH, rt, 95%; (m) PTSA, $CHCl_3$, reflux, 86%; (n) i NBS, CH_2Cl_2–MeOH, 0°C, ii: $CrCl_3$–$LiAlH_4$, *i*-PrOH, DMF, 91%; (o) TBDMSOTf, Et_3N, CH_2Cl_2, −78°C; 98%; (p) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0°C then $(COOH)_2$, MeOH, rt, 88%; (q) i $(ClCO)_2$–DMSO, Cl_2CH_2, −30°C then Et_3N, ii TBDMSOTf, Et_3N, CH_2Cl_2, 0°C, iii $LiAlH_4$, THF, −78°C then acid workup, 65%.

13 was completed in 90% yield by treatment of the enone **12** with TBDMS triflate and triethylamine in dichloromethane at −78°C. The dienol silyl ether **13** underwent a stereospecific IMDA reaction upon heating in toluene and a small amount of propylene oxide at 190°C for seven days to give the *trans–anti–trans* fused adduct **7** in 95% yield.

Having accomplished the synthesis of the ABC-ring system, attention was turned towards the construction of the bicyclo[2.2.2]octane moiety. First, **7** was submitted to Simmons–Smith cyclopropanation conditions to afford stereoselectively the tetracyclic compound **14** in 89% yield.[9] Treatment of the lithium enolate of **14** with 2,2,2-trifluoroethyltrifluoroacetate, followed by a diazo-transfer reaction using mesylazide as reagent,[10] provided the tetracyclic α-diazoketone **15** in 80% overall yield for the two steps. Cooper(II)-catalyzed intramolecular addition of the α-diazoketone moiety of **15** to the enone double bond afforded the hexacyclic compound **16** in 90% yield. Transformation of the tricyclo[3.2.1.$0^{2,7}$]octane system of **16** into the bicyclo[2.2.2]octane moiety of key intermediate **5** was effected using a radical ring opening of the cyclopropane ring.[11] Accordingly, the carbonyl group at C-15 of diketone **16** was chemo- and stereoselectively hydrogenated to give the α-hydroxyketone **17**, which in turn was converted into the β-iodoketone **6** via the corresponding mesylate, in an overall yield for the three steps of 88%. Finally, samarium(II)-mediated regioselective cleavage of the C13–C16 bond of the cyclopropane moiety of **6** occurred smoothly to afford compound **5** in very high yield.

After successful synthesis of the pentacyclic diketone **5**, which incorporates the requisite atisane skeletal framework, the stage was set for further elaboration into the naturally occurring compounds. Thus, treatment of **5** with *p*-toluenesulfonic acid (PTSA) in refluxing chloroform promoted concomitant ring cleavage of the cyclopropane moiety and hydrolysis of the *tert*-butyldimethylsilyl protecting group to afford the tetracyclic diketone **18** in 86% yield.

Completion of the synthesis of the less functionalised atisane **2** from **18** only required isomerization of the endocyclic double bond to the less substituted position. This was achieved very efficiently by a sequence of allylic bromination, by reaction of **18** with *N*-bromosuccinimide (NBS) in a MeOH–CH_2Cl_2 medium, and chromium(II)/*i*-PrOH reduction.[12] The global yield for this conversion was 91%.

For the synthesis of atisane **3**, advantage was taken of the thermodynamically favorable formation of the silyl enol ether of the carbonyl group at C-3 of diketone **2**, which allowed the selective functionalisation of the methylene group at C-2. Thus, enolization of **2** with TMSOTf and Et_3N in CH_2Cl_2 at −78°C yielded exclusively the silyl enol ether **19** in 98% yield. This compound was treated sequentially with *m*-CPBA in the presence of $NaHCO_3$ in CH_2Cl_2 at 0°C and methanolic oxalic acid giving rise to a 88% overall yield of the α-hydroxy ketone **20**. Final isomerization of the α-hydroxycarbonyl moiety of **20** was executed by an adaptation of the method of Mori.[13] This involved, Swern oxidation of **20** to the corresponding triketone, protection of C-2 and C-14 carbonyl groups by conversion into the corresponding *tert*-butyldimethylsilyl enol ethers under the conventional silylation conditions, stereoselective reduction of the carbonyl group at C-3 with lithium aluminum hydride and acid workup. The whole sequence could be effected without purification of intermediates affording compound **3** in 65% overall yield after chromatographic purification.

The synthetic samples of **2** and **3** have physical and spectral characteristics completely identical to those previously reported for the natural products. The only difference was in the sign of the optical rotation, which establishes that the natural compounds have the absolute stereochemistry antipodal of that represented here (e.g. for natural **2**: 5*S*,8*S*,9*S*,10*R*,12*R;* for natural **3**: 3*S*,5*S*,8*S*,9*S*,10*R*,12*R*).[14]

In conclusion, we have developed a stereoselective approach to polyoxygenated atisane diterpenes starting from (*S*)-(+)-carvone, which has allowed the efficient preparation of atisanes **2** and **3** in enantiomerically pure form. Work is currently in hand to further elaborate the key intermediate of the syntheses (**5**) towards other natural and unnatural more highly functionalised atisane-type compounds.

Acknowledgements

Financial support from the Dirección General de Enseñanza Superior e Investigación Científica (Grant PB98-1421-C02-01) is gratefully acknowledged. We are grateful to the Conselleria d'Educació i Ciència de la Generalitat Valenciana for providing a research fellowship to I.N.

References

1. (a) Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*, 1st ed.; Chapman and Hall: London, 1991; Vol. 2, p. 963; (b) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 165 and previous reviews of this series.
2. The absolute configuration illustrated in structures **2**, **3** and **4** corresponds to that of the atisane series. As it is deduced from the synthesis described in this paper, vide infra, the absolute configuration of the natural compounds **2** and **3** belong to the enantiomeric *ent*-atisane series, viz. *ent*-**2** and *ent*-**3**.
3. Gustafson, K. R.; Munro, M. H. G.; Blunt, J. W.; Cardellina, II, J. H.; McMahon, J. B.; Gulakowski, R. J.; Cragg, G. M.; Cox, P. A.; Brinen, L. S.; Clardy, J.; Boyd, M. R. *Tetrahedron* **1991**, *47*, 4547.
4. (a) Lal, A. R.; Cambie, R. C.; Rutledge, P. S.; Woodgate, P. D. *Tetrahedron Lett.* **1989**, *30*, 3205; (b) Lal, A. R.; Cambie, R. C.; Rutledge, P. S.; Woodgate, P. D. *Phytochemistry* **1990**, *29*, 1925.

5. Abad, A.; Agulló, C.; Cuñat, A. C.; Navarro, I.; Ramírez de Arellano, M. C. *Synlett* **2001**, 349.
6. For recent syntheses of atisane-type compounds, see: (a) Toyota, M.; Wada, T.; Fukumuto, K.; Ihara, M. *J. Am. Chem. Soc.* **1998**, *120*, 4916; (b) Toyota, M.; Wada, T.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 4565; (c) Toyota, M.; Yokota, M.; Ihara, M. *J. Am. Chem. Soc.* **2001**, *123*, 1856.
7. For previous works which use carvone and an IMDA reaction for the construction of other polycyclic natural products, see: (a) Shing, T. K. M.; Tang, Y.; Malone, J. F. *J. Chem. Soc., Chem. Commun.* **1988**, 1294; (b) Shing, T. K. M.; Jiang, Q. *J. Org. Chem.* **2000**, *65*, 7059; (c) Abad, A.; Agulló, C.; Castelblanque, L.; Cuñat, A. C.; Navarro, I.; Ramírez de Arellano, M. C. *J. Org. Chem.* **2000**, *65*, 4189 and references cited therein.
8. Corbel, B.; Medinger, L.; Haelters, J. P.; Sturtz, G. *Synthesis* **1985**, 1048.
9. Nishimura, J.; Kawabata, N.; Furukawa, J. *Tetrahedron* **1969**, *25*, 2647.
10. Danheiser, R.-L.; Miller, R. F.; Bribois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959.
11. (a) *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987; Vols. I and II; (b) Lee, H. P.; Lee, B.; Lee, J.; Park, S. K. *Tetrahedron Lett.* **1999**, *40*, 3427.
12. Omoto, M.; Kato, N.; Sogon, T.; Moei, A. *Tetrahedron Lett.* **2001**, *42*, 939.
13. Yajima, A.; Mori, K. *Eur. J. Org. Chem.* **2000**, 4079.
14. All compounds were characterized by ^{1}H, ^{13}C NMR, IR and HRMS. Selected data of more significant compounds are given. Compound **2**: mp 153.5–155°C (from ethyl ether); $[\alpha]_D^{25}$ −5.5 (0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.89 (1H, br s), 4.68 (1H, bs), 2.73 (1H, m), 2.57 (1H, ddd), 2.17–2.38 (6H, m); 1.95 (1H, m), 1.08 (3H, s), 1.01 (3H, s), 0.87 (3H, s). Compound **3**: mp 164–164.5°C (from cold ethyl ether); $[\alpha]_D^{26}$ +14 (1.0, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6): δ 4.75 (1H, dd), 4.55 (1H, dd), 3.64 (1H, dd), 3.60 (1H, d), 2.33 (1H, dddd), 2.17 (1H, quint.), 2.01 (1H, d), 1.97 (1H, dt), 1.85 (1H, dd), 1.79 (1H, dt), 1.34 (1H, br d), 1.08 (3H, s), 0.61 (3H, s), 0.47 (3H, s). Compound **5**: mp 213.5–215.5°C (from MeOH); $[\alpha]_D^{20}$ −50.8° (1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.33 (1H, br s), 2.6 (1H, m), 2.44 (1H, dt), 2.14 (1H, dt), 1.99 (1H, dd), 1.77 (3H, d), 1.00 (3H, s), 0.85 (9H, s), 0.66 (3H, s), 0.49 (1H, dd), 0.24 (1H, d), 0.09 (3H, s), 0.04 (3H, s). Compound **7**: $[\alpha]_D^{18}$ +60.5 (0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.87 (1H, br s), 3.07 (1H, dddd), 2.84 (dt, 1H, 2.30 (1H, dtd), 2.18 (3H, s), 1.72 (3H, s), 1.54 (3H, s), 0.93 (9H, s), 0.71 (3H, s), 0.10 (3H, s), 0.09 (3H, s). Compound **16**: mp 186.5–188°C (from MeOH); $[\alpha]_D^{25}$ +40 (2.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.58 (1H, d), 2.46 (1H, dt), 2.12 (1H, ddd), 2.02 (ddd), 1.38 (3H, s), 1.01 (3H, s), 0.84 (9H, s), 0.75 (3H, s), 0.49 (1H, dd), 0.22 (1H, d), 0.07 (3H, s), 0.02 (3H, s).