Pergamon

Tetrahedron Letters 43 (2002) 7933–7936

TETRAHEDRON LETTERS

Synthesis of oxygenated spongiane-type diterpenoids from carvone

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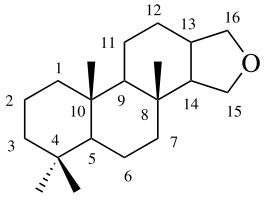
Received 6 June 2002; accepted 5 September 2002

Abstract—A new diastereoselective approach to oxygenated spongiane diterpenes starting from (*R*)-(−)-carvone is described. The carvone is incorporated as the B ring in the final spongiane framework using a B→AB→ABC→ABCD approach, which involves an intramolecular Diels–Alder reaction and the regioselective ring-opening of a dihydrofuran ring as key synthetic steps. The structure of the key intermediate in this approach has been verified by X-ray crystallography.

The spongianes are a group of diterpenes isolated from various species of sponges and sponge-eating marine nudibranchs, which have structures based on the hypothetical spongiane tetracyclic skeleton (**1**).[1] Many of these compounds show a wide spectrum of biological properties[2] that may be associated in some cases with the presence of an electrophilic unsaturated γ-lactone moiety.[3] Such is the case of dorisenones A (**2**), B (**3**), C (**4**) and D (**5**), four spongiane diterpenoids recently isolated together with other related saturated compounds (e.g. **6** and **7**) from the Japanese marine mollusc *Chromodoris obsoleta* (Chromodorididae). These dorisenones showed strong cytotoxic activity against several cell lines.[4] As has been previously suggested for related systems,[5] the enhanced biological activity of these and other polyoxygenated spongiane diterpenes may be due to the presence of polar groups (i.e. OH, acetate, epoxide, etc.) in the region of the Michael acceptor centre.[6]



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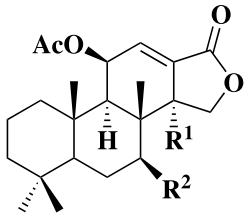
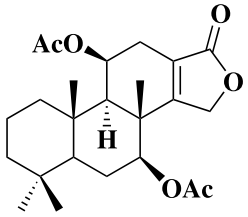


2: R^1=OH, R^2=OAc

3: R^1=OH, R^2=H

5: R^1=H, R^2=OAc



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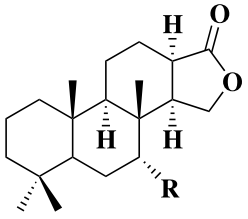

6: R=OH

7: R=OAc

In connection with our previous work on the synthesis of spongianes[7] and the use of the monoterpene carvone as chiral building block for the synthesis of polycyclic terpenes,[8] in this communication we present a simple and practical method for the preparation of enantiomerically pure spongiane-type diterpenoids structurally and functionally related to dorisenones.[9]

The strategy we followed for the synthesis of the spongiane framework, a B→AB→ABC→ABCD approach, was based on the initial preparation of an epoxy decalone (AB rings, compound **11**) from carvone (Scheme 1), followed by an intramolecular Diels–Alder reaction for the construction of the C ring (compound **17**) and further manipulation of the Diels–Alder adduct functionality for elaboration of the D ring (compound **18**).

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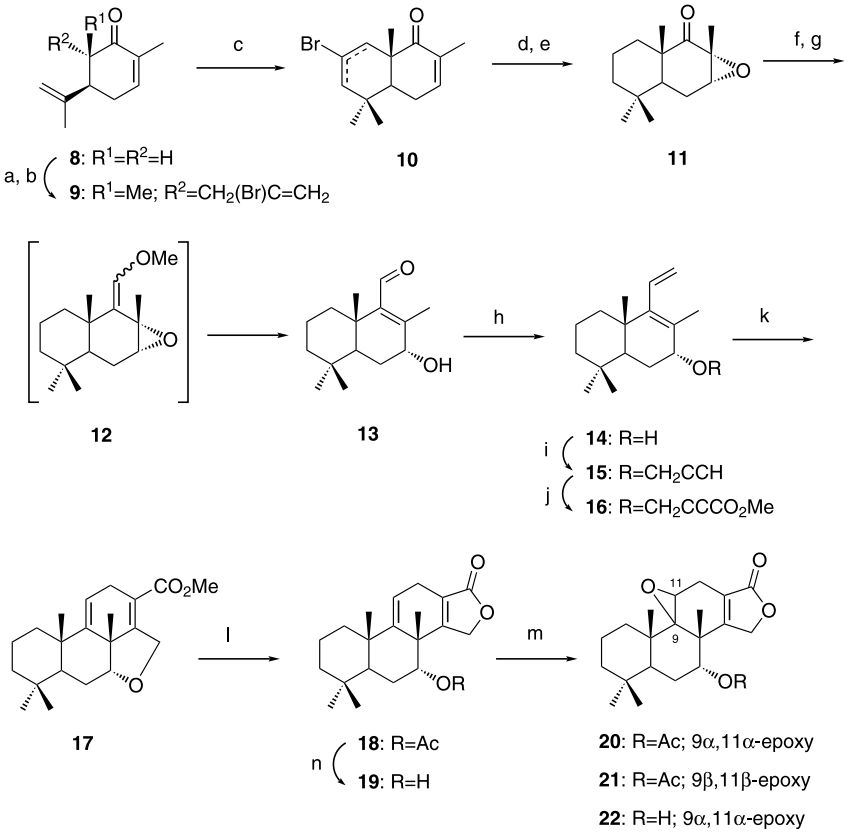
0040-4039/02/$ - see front matter
PII: S0040-4039(02)01891-9



Scheme 1. *Reagents and conditions*: (a) LDA, THF, 0°C, then MeI (89%); (b) LDA, THF–HMPA, −10°C, then $BrCH_2(Br)C{=}CH_2$ (86%); (c) CF_3CO_2H, rt, 48 h (78%); (d) H_2O_2, NaOH, MeOH, 0°C, overnight (92%); (e) H_2, Pd/C, EtOH–Et_3N (95%); (f) $Ph_2P(O)CH(Li)OMe$, THF, −78°C (99%); (g) NaH, DMF, rt, 3 h, then at 0°C, H_2O and HCO_2H, 30 min at rt (87% from **11**); (h) $Ph_3P{=}CH_2$, THF, −20°C to rt (94%); (i) $BrCH_2CCH$, 60% NaOH, Bu_4NI (74%); (j) BuLi, THF, −78°C, then $CNCO_2Me$ (84%); (k) toluene, 112°C, 17 h, 95%; (l) ZnI_2, Ac_2O, 48 h (quant.); (m) from **18**: *m*-CPBA, CH_2Cl_2; rt, 24 h (86% of a 1:1 mixture of **20** and **21**); from **19**: *tert*-BuOOH, $VO(acac)_2$, C_6H_6; rt, 24 h (70%); (n) KOH, MeOH, rt, 30 min (92%).

The synthesis commences with the diastereoselective preparation of **9** by two consecutive alkylations of (*R*)-carvone (**8**) with MeI and 2,3-dibromopropene.[10] Treatment of **9** with CF_3COOH at room temperature afforded an inseparable mixture of two isomeric vinylic bromides **10**, in a 60/40 ratio as deduced by ^1H NMR analysis of the mixture, which were stereoselectively converted into the α-epoxy decalone **11** by successive treatment with alkaline hydrogen peroxide and hydrogenation using 10% Pd/C as the catalyst in EtOH–Et_3N. The global yield for the transformation of carvone into **11** via this five-step reaction sequence was around 50%. Treatment of ketone **11** with the lithium derivative of α-methoxymethyldiphenylphosphine oxide in THF at low temperature afforded a mixture of crystalline β-hydroxyphosphine oxides, which, despite being partially separable by column chromatography, were jointly subjected to *syn* elimination by treatment with sodium hydride in DMF at room temperature to give a mixture of isomeric vinyl ethers **12**. These were not isolated but treated in situ with aqueous formic acid to effect hydrolysis of the vinyl ether moiety and subsequent opening of the initially formed β,γ-epoxy aldehyde, providing the desired unsaturated hydroxy aldehyde **13** in 87% overall yield for the three-step reaction sequence from epoxy ketone **11**. Methylenation of **13** using standard Wittig conditions furnished the bicyclic diene **14** in 94% yield.

With the diene **14** now at hand, we first tried to construct the C ring through an intermolecular Diels–Alder reaction with dimethyl acetylenedicarboxylate (DMAD). However, the reaction was very sluggish, providing a very low yield of the Diels–Alder adduct, which was, anyway, identified as the adduct formed by β-approach of the dienophile, *syn* to the angular methyl group at C-10, thus affording the opposite configuration at C-8 of the spongiane framework.[11] Consequently, our attention then turned to the utilization of an intramolecular Diels–Alder (IMDA) reaction for the construction of the C ring. First, treatment of the dienol **14** with propargyl bromide under phase-transfer conditions provided the propargyl ether derivative **15** in 75% yield, which was then converted in high yield to the acetylenic ester **16** by sequential treatment with butyl lithium and methyl cyanoformate. The triene **16** underwent a smooth and clean IMDA cycloaddition upon heating in a sealed tube at 112°C overnight in anhydrous toluene to afford the expected *trans–anti–trans* fused ABC ring system **17** in 95% yield after column chromatography.

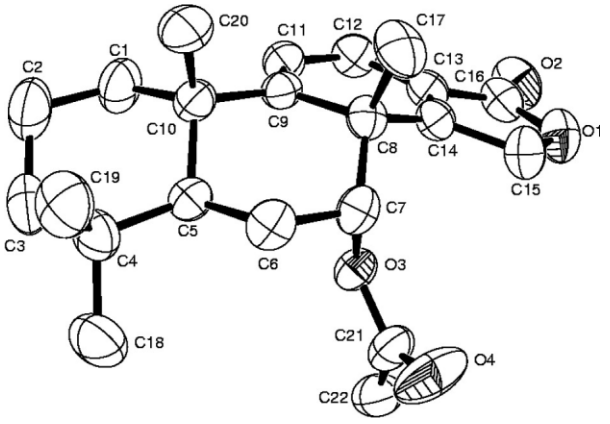


Figure 1. X-Ray structure of compound **18** showing 50% probability displacement ellipsoids. The H atoms are omitted for clarity.

The final part of the synthesis involved the regioselective ring-opening of the dihydrofuran ring of **17**, which was smoothly effected by treatment with acetic anhydride and zinc iodide.[12] Under these conditions, the presumed 7-acetoxy-15-iodo-derivative formed initially rapidly underwent lactonization to give the spongiane-type compound **18** in nearly quantitative overall yield for the last two steps. The structure and stereochemistry of **18** was verified by X-ray crystallography (Fig. 1).[13]

The readily prepared compound **18** seems adequately functionalized around the B and C ring to undertake the preparation of more highly oxygenated spongianes of the type represented by dorisenones A–B. With respect to this, we carried out a brief exploration into the possibility of carrying out further oxygenation of some of the C ring positions of **18**. As expected, the 9,11-double bond can be stereo- and quimioselectively functionalized without affecting the γ-butenolide moiety. For example, direct epoxidation of **18** with *m*-chloroperbenzoic acid took place non-stereoselectively, affording a roughly 1:1 mixture of easily separable epoxides **20** and **21** in 86% combined yield. In contrast, previous hydrolysis of the acetate group of **18**, followed by hydroxyl-directed peracid epoxidation of the resulting alcohol **19** with *tert*-butyl hydroperoxide in the presence of catalytic vanadyl acetylacetonate afforded exclusively the α-epoxide **20**.[14]

In summary, we have developed an efficient and stereoselective approach to spongiane diterpenoids from carvone. The final spongiane systems prepared by this approach (e.g. **18**–**22**) are potential precursors of some relevant naturally occurring compounds. Work is currently in progress in our laboratory in this direction and the results of these and related studies will be reported in due course.

Acknowledgements

Financial support from the Dirección General de Enseñanza Superior e Investigación Científica (Grant PB98-1421-C02-01) is gratefully acknowledged. We express our thanks to Dr. Carlos Jimenez of the Departamento de Química Inorgánica for the X-ray structure determination of **18**. We are also grateful to the Ministerio Español de Ciencia y Tecnología for providing a research fellowship to A.B.G.

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11. The stereochemistry of the Diels–Alder adduct formed was assigned on the basis of intramolecular NOE studies. In particular, no NOE was observed upon irradiation of either the Me-8 (δ 1.25 ppm) or the Me-10 (δ 0.98 ppm) on each other, which strongly suggested the *anti* disposition of both methyl groups.
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13. *Crystal data for compound **18***: colourless prisms of 0.28×0.25×0.22 mm size, orthorhombic, $P2_12_12_1$, $a=9.7500(2)$, $b=12.9360(3)$, $c=15.9630(4)$ Å, $V=2013.35(8)$ Å^3, $Z=4$, theta range for data collection 2.03–27.48°, Nonius

Kappa CCD diffractometer, Mo Kα ($\lambda = 0.71073$ Å), 14582 reflections were collected of which 4614 [R(int) = 0.0349] were independent, refinement on F^2 using the SHELX-97 program (Sheldrick, G. M., University of Göttingen, 1997), 236 refined parameters, riding hydrogen atoms, absolute structure could not be determined, $R_1[I>2\sigma(I)] = 0.0558$, wR_2 (all data) = 0.1558, residual electron density 0.308 e Å^{-3}.

14. All compounds were characterized by ^{1}H and ^{13}C NMR, IR and HRMS. Selected data of more significant compounds are given:

Compound ***11***: mp 72–74°C (from pentane); $[\alpha]_D^{23} = +205.4°$ (0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.34 (1H, dd, $J = 3.2$, 1.7 Hz, H-7), 2.25 (1H, ddd, $J = 15.1$, 3.2, 3.0 Hz, H-6α), 1.92 (1H, ddd, $J = 15.1$, 12.8, 1.7 Hz, H-6β), 1.84 (1H, ddd, $J = 13.4$, 4.9, 3.0 Hz, H-1β), 1.52 (1H, dd, $J = 12.8$, 3.4 Hz, H-5), 1.42 (3H, s, Me-C_8), 1.02 (3H, s, Me-$C_{4\beta}$), 0.93 (3H, s, Me-C_{10}), 0.90 (3H, s, Me-$C_{4\alpha}$).

Compound ***14***: mp 109–110°C (from cold pentane); $[\alpha]_D^{26} = +83.1°$ (1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.11 (1H, dddq, $J = 17.6$, 11.4, 1.0, 0.8 Hz, H-11), 5.29 (1H, dd, $J = 11.2$, 2.5 Hz, H-12$_{cis}$), 4.96 (1H, dd, $J = 17.6$, 2.6 Hz, H-12$_{trans}$), 4.00 (1H, br s, H-7), 1.81 (1H, ddd, $J = 14.1$, 4.2, 1.5 Hz, H-6α), 1.80 (3H, d, $J = 0.8$ Hz, Me-C_8), 1.72 (1H, ddd, $J = 14.1$, 12.3, 4.5 Hz, H-6β), 1.34 (1H, dd, $J = 12.2$, 3.2, H-5), 0.97 (3H, s, Me-C_{10}), 0.92 (3H, s, Me-$C_{4\beta}$), 0.86 (3H, s, Me-$C_{4\alpha}$).

Compound ***18***: mp 183–184°C (from hexane); $[\alpha]_D^{27} = -47.7°$ (1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.76 (1H, dd, $J = 4.5$, 2.7 Hz, H-11), 4.96 (1H, dd, $J = 2.7$, 2.7 Hz, H-7), 4.83 (1H, ddd, $J = 16.8$, 3.3, 1.8 Hz, H-15), 4.49 (1H, ddd, $J = 16.8$, 3.0, 2.4 Hz, H-15′), 2.97 (1H, dddd, $J = 22.5$, 4.5, 3.0, 1.8 Hz, H-12β), 2.82 (1H, dddd, 22.5, 3.3, 2.7, 2.4 Hz, H-12α), 1.98 (3H, s, CH_3CO), 1.44 (3H, s, Me-C_8), 1.21 (3H, s, Me-C_{10}), 0.85 (3H, s, Me-$C_{4\beta}$), 0.77 (3H, s, Me-$C_{4\alpha}$).

Compound ***20***: mp 115–116°C (from ethyl acetate–hexane); $[\alpha]_D^{26} = -16.7°$ (1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.99 (1H, dd, $J = 2.5$, 2.3 Hz, H-7), 4.70 (1H, dd, $J = 17.0$, 2.8 Hz, H-15β), 4.47 (1H, ddd, $J = 17.0$, 2.6, 2.5 Hz, H-15α), 3.36 (1H, dd, $J = 2.3$, 1.1 Hz, H-11), 2.95 (1H, ddd, $J = 18.6$, 2.3, 2.0 Hz, H-12β), 2.47 (1H, dddd, $J = 18.6$, 2.8, 2.6, 1.1 Hz, H-12α), 2.10 (3H, s, CH_3CO), 1.86 (1H, ddd, $J = 14.9$, 12.8, 2.5 Hz, H-6β), 1.71 (1H, dd, $J = 12.8$, 2.3 Hz, H-6α), 1.39 (3H, s, Me-C_8), 1.26 (3H, s, Me-C_{10}), 0.83 (3H, s, Me-$C_{4\beta}$), 0.82 (3H, s Me-$C_{4\alpha}$).

Compound ***21***: mp 114–116°C (from ethyl acetate–hexane); $[\alpha]_D^{26} = -21.0°$ (1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.16 (1H, dd, $J = 3.0$, 2.8 Hz, H-7), 4.71 (1H, ddd, $J = 16.8$, 2.6, 2.6 Hz, H-15), 4.64 (1H, ddd, $J = 16.8$, 3.2, 1.5 Hz, H-15′), 3.89 (1H, dd, $J = 2.1$, 1.7 Hz, H-11), 2.84 (1H, dddd, $J = 19.3$, 2.6, 1.7, 1.5 Hz, H-12), 2.54 (1H, dddd, $J = 19.3$, 3.2, 2.6, 2.1 Hz, H-12′), 1.92 (3H, s, CH_3CO), 1.43 (3H, s, Me-C_8), 1.20 (3H, s, Me-C_{10}), 0.87 (3H, s, Me-C_4), 0.84 (3H, s, Me-$C_{4'}$).