



Pergamon

Tetrahedron Letters 41 (2000) 5469–5473

TETRAHEDRON
LETTERS

Total synthesis of the marine sesquiterpene hydroquinones zonarol and isozonarol and the sesquiterpene quinones zonarone and isozonarone

Jörg Schröder, Christine Magg and Karlheinz Seifert*

Lehrstuhl für Organische Chemie I/2, NW II, Universität Bayreuth, D-95440 Bayreuth, Germany

Received 2 May 2000; accepted 30 May 2000

Abstract

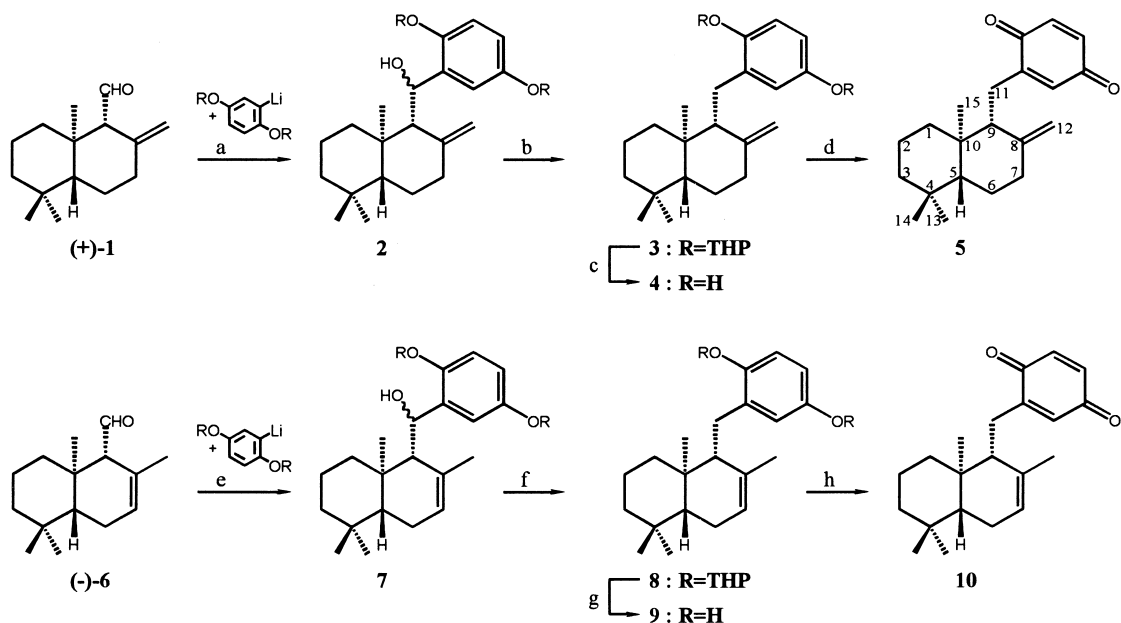
The total synthesis of the naturally occurring sesquiterpene hydroquinones zonarol and isozonarol and the sesquiterpene quinones zonarone and isozonarone was achieved starting from β -ionone, which was transformed via (+)-albicanic acid to (+)-albicanal and (–)-drim-7-en-11-al. Coupling of the aldehydes with lithiated hydroquinone ethers and further modification of the coupling products led to the target molecules.
© 2000 Elsevier Science Ltd. All rights reserved.

Keywords: terpenes; phenols; quinones.

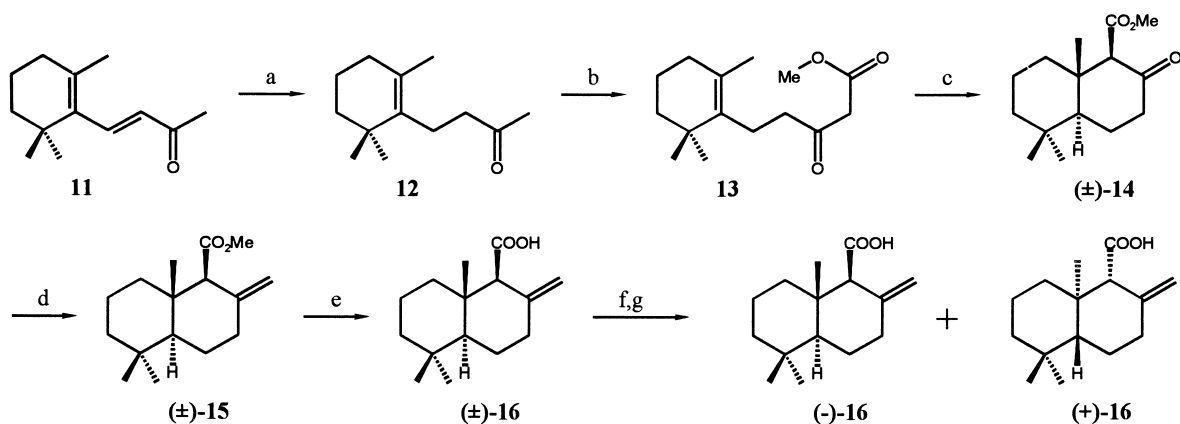
Sesquiterpene quinones represent a substance class with increasing pharmacological interest. Among other properties, antitumour activity,¹ inhibition of the HIV 1 reverse transcriptase² and immunomodulation³ have been reported. Our aim is the synthesis and the investigation of biological properties of these compounds. Zonarone⁴ (**5**), zonarol⁴ (**4**) and isozonarol⁵ (**9**) have been synthesized before starting from geranylacetone and the Wieland–Miescher ketone. Herein we wish to report an efficient and general access to sesquiterpene quinones of the drimane type. The marine natural products zonarol (**4**), zonarone (**5**), isozonarol (**9**) and isozonarone (**10**) have been isolated from algae.⁶ Compounds **4**, **5**, **9** and **10** have been synthesized by coupling (+)-albicanal ((+)-**1**) and (–)-drim-7-en-11-al ((–)-**6**) with lithiated hydroquinone-di-THP-ether and transforming the coupling products into the desired natural compounds (Scheme 1). The chiral aldehydes (+)-**1** and (–)-**6** have been prepared starting from β -ionone via a known route.^{7–9} The total yield of ($\pm$)-albicanic acid (($\pm$)-**16**) could be improved from 30% to 54% (Schemes 2 and 3).

The most important step in the synthesis of zonarone (**5**) and isozonarone (**10**) (Scheme 1) was the coupling of the sesquiterpene part of the molecule with the arene unit. According to standard procedures,¹⁰ we lithiated the di-THP-ether of hydroquinone with *sec*-butyllithium and added

* Corresponding author. Tel: 0921 553396; fax: 0921 555358; e-mail: karlheinz.seifert@uni-bayreuth.de



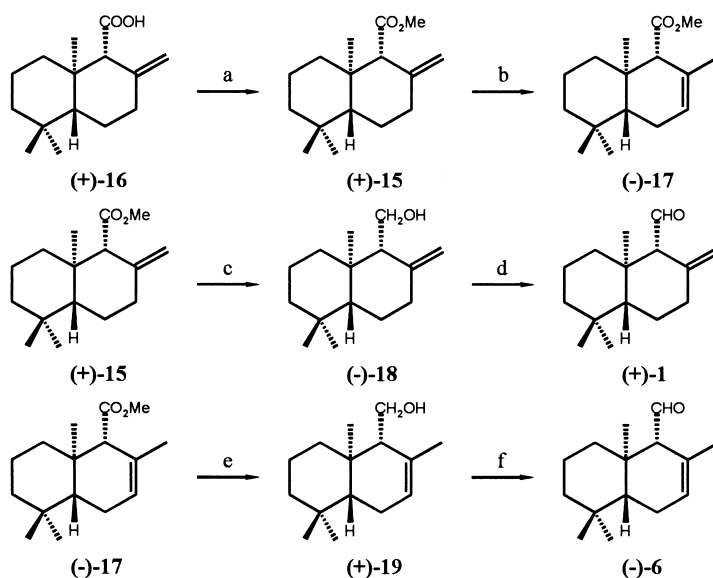
Scheme 1. (a) R=THP, ether, 0°C, (80%); (b) 10 equiv. Li, NH₃, THF, NH₄Cl, -78°C, (94%); (c) oxalic acid, H₂O, MeOH, ethyl acetate, (80%); (d) 3.0 equiv. CAN, MeCN/H₂O (1:1), (95%); (e) R=THP, ether, room temperature, (85%); (f) 10 equiv. Li, NH₃, THF, NH₄Cl, -78°C, (95%); (g) oxalic acid, H₂O, MeOH, ethyl acetate, (86%); (h) 3.5 equiv. CAN, DMF/MeCN/H₂O (1:1:1), (81%)



Scheme 2. (a) (i) Et₃SiH, (Ph₃P)₃RhCl (0.5%), 55°C, (ii) MeOH, K₂CO₃ (99%); (b) dimethyl carbonate, NaH, toluene, 100°C (97%); (c) 2 equiv. SnCl₄, CH₂Cl₂ (72%); (d) methylenetriphenylphosphorane, toluene (99%); (e) NaSEt, DMF, reflux (79%); (f) and (g) separation of the racemate according to the literature⁹ using (+)- and (-)-α-phenylethylamine as chiral auxiliary

(+)-albicanal ((+)-1), respectively (-)-drim-7-en-11-al ((-)-6) to the formed lithium organyl. The reaction afforded high yields of the benzyl alcohols 2 and 7 as coupling products, which were mixtures of diastereoisomers.

Removal of the hydroxyl group in position 11 using the Li/NH₃/NH₄Cl-system¹¹ led quantitatively to the deoxygenated species 3, zonarol-di-THP-ether, and 8, isozonarol-di-THP-ether,



Scheme 3. (a) (i) $[\text{Et}_4\text{N}]^+\text{OH}^-$, MeOH, (ii) dimethyl sulfate, THF (99%); (b) Pd/CaCO₃ (5%), Ph₃P (2%), hydrogen atmosphere, room temperature, ethyl acetate (71%); (c) DIBAH, CH₂Cl₂, 0°C (98%); (d) PCC, CH₂Cl₂, room temperature (98%); (e) DIBAH, CH₂Cl₂, 0°C (95%); (f) PCC, CH₂Cl₂, room temperature (97%)

respectively. Deprotection in the presence of oxalic acid¹² gave zonarol (**4**) and isozonarol (**9**). Optimized oxidation of **4** and **9** with cerium (IV) ammonium nitrate (CAN) yielded the desired sesquiterpene quinones zonarone (**5**) and isozonarone (**10**). The structures of compounds **1–19** have been determined by means of mass spectra and one and two dimensional NMR techniques. A comparison of NMR data and optical rotations of synthetic **4**, **5**, **9** and **10**^{13–16} with natural **4**, **5**, **9** and **10** shows good agreement.

The chiral aldehydes (+)-**1** and (–)-**6** have been obtained starting from β-ionone (**11**) (Scheme 2). **11** was transformed to dihydro-β-ionone (**12**) by using Et₃SiH in the presence of Wilkinson's catalyst, followed by solvolysis with MeOH/K₂CO₃ instead of hydrogenation with Bu₃SnH.^{7,8} Claisen condensation of **12** with dimethyl carbonate led to the monocyclic β-ketoester **13**, which was cyclized with two equivalents of SnCl₄ in dichloromethane to 8-oxo-12-nordriman-11-acid methyl ester (±)-**14**. Methylenation of (±)-**14** led to (±)-albicanic acid methyl ester (±)-**15**, which had to be hydrolysed to the corresponding racemic albicanic acid (±)-**16**. This reaction is somewhat difficult; we obtained (±)-**16** in a yield of 55% by using the described procedure (NaI, DMF, 3 days).⁹ However, we found that the reaction of (±)-**15** with NaSEt in DMF (150°C, 1 h) yielded 79% of (±)-**16** after two recrystallizations from methanol. (±)-**16** was separated into the two enantiomers (–)-albicanic acid ((–)-**16**) and (+)-albicanic acid ((+)-**16**), as described in the literature.⁹ According to this procedure (±)-**16** was mixed with chiral (+)- or (–)-α-phenylethylamine and the resulting salt was purified by several recrystallizations from ethanol. For the synthesis of (+)-albicanal ((+)-**1**) and (–)-drim-7-en-11-al ((–)-**6**), (+)-albicanic acid ((+)-**16**) was used.

(+)-**16** was quantitatively transformed to the methyl ester (+)-**15** (Scheme 3). Isomerisation of (+)-**15** in the presence of Pd/CaCO₃ and triphenylphosphane under hydrogen atmosphere yielded 71% of (–)-drim-7-en-11-acid methyl ester (–)-**17**. The two esters (+)-**15** and (–)-**17** were reduced with diisobutylaluminium hydride (DIBAH) to the corresponding alcohols (–)-albicanol ((–)-**18**)

and (+)-drim-7-en-11-ol ((+)-**19**), respectively. Oxidation with pyridinium chlorochromate (PCC) led to the desired aldehyds (+)-albicanal ((+)-**1**) and (–)-drim-7-en-11-al ((–)-**6**).

Acknowledgements

Support of this research by a grant of the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

References

- Barrero, A. F.; Alvarez-Manzaneda, E. J.; Mar Herrador, M.; Chahboun, R.; Galera, P. *Bioorg. Med. Lett.* **1999**, *9*, 2325–2328.
- Loya, S.; Tal, R.; Kashman, R. Y.; Hizi, A. *Antimicrobial Agents and Chemotherapy* **1990**, *34*, 2009–2012.
- Bourguet-Kondracki, M.-L.; Longeon, A.; Morel, E.; Guyot, M. *Int. J. Immunopharmac.* **1991**, *13*, 393–399.
- Mori, K.; Komatsu, M. *Bull. Soc. Chim. Belg.* **1986**, *95*, 771–781.
- Welch, S. C.; Rao, A. S. C. P. *J. Org. Chem.* **1978**, *43*, 1957–1961.
- Fenical, W.; Sims, J. J.; Squatrito, D.; Wing, R. M.; Radlick, P. *J. Org. Chem.* **1973**, *38*, 2383–2386.
- Herlem, D.; Kervagoret, J.; Yu, D.; Khuong-Huu, F.; Kende, A. S. *Tetrahedron* **1993**, *49*, 607–618.
- Liapis, M.; Ragoussis, V.; Ragoussis, N. *J. Chem. Soc., Perkin Trans. 1* **1985**, 815–817.
- Ragoussis, V.; Liapis, M.; Ragoussis, N. *J. Chem. Soc., Perkin Trans. 1* **1987**, 987–992.
- Morey, J.; Costa, A.; Deyá, P. M.; Suner, G.; Saá, J. M. *J. Org. Chem.* **1990**, *55*, 3902–3909.
- Small, G. H.; Engman, A. M.; Hall, S. S. *J. Org. Chem.* **1975**, *40*, 3151–3152.
- Grant, H. N.; Prelog, V.; Sneed, R. P. A. *Helv. Chim. Acta* **1963**, *46*, 415–421.
- 4**: Colourless crystals, mp 154°C (sub.), $[\alpha]_D^{23} +17^\circ$ (c 1.7, CHCl₃). Ref. 17: $[\alpha]_D +18^\circ$ (CHCl₃). MS m/z (%): 314 (68, M⁺), 299 (8), 229 (6), 217 (6), 201 (6), 191 (100), 178 (23), 163 (24), 161 (28), 149 (17), 137 (20), 109 (19), 95 (29), 81 (17). HRMS: Calcd for C₂₁H₃₀O₂ 314.22460. Found 314.2246. ¹H-NMR (500 MHz, C₆D₆): 6.63 (d, 1H, 2.5 Hz, H-6'), 6.31 (dd, 1H, 8.5/2.5 Hz, H-4'), 6.24 (d, 1H, 8.5 Hz, H-3'), 4.87 (s, 2H, H-12), 2.81 (1H, 15.5/10.2 Hz, H-11), 2.73 (1H, 15.5/1.9 Hz, H-11), 2.29 (m, 1H, H-7), 2.17 (1H, 10.2 Hz, H-9), 1.91 (dd, 1H, 12.8/4.6 Hz, H-7), 1.74 (d, 1H, 12.6 Hz, H-1), 1.57 (m, 1H, H-6), 1.52 (m, 1H, H-2), 1.40 (m, 1H, H-2), 1.34 (d, 1H, 13.2 Hz, H-3), 1.26 (dd, 1H, 12.8/4.1 Hz, H-6), 1.14 (m, 1H, H-3), 1.04 (m, 1H, H-1), 1.02 (m, 1H, H-5), 0.84 (s, 3H, H-13), 0.80 (s, 3H, H-15), 0.78 (s, 3H, H-14). ¹³C-NMR (125 MHz, C₆D₆): 150.0 (C-5'), 148.6 (C-8), 147.8 (C-2'), 130.1 (C-1'), 116.9 (C-6'), 115.8 (C-3'), 112.7 (C-4'), 108.2 (C-12), 56.3 (C-9), 55.6 (C-5), 42.4 (C-3), 40.2 (C-10), 39.2 (C-1), 38.5 (C-7), 33.7 (C-13), 33.7 (C-4), 24.6 (C-6), 23.9 (C-11), 21.7 (C-14), 19.8 (C-2), 14.7 (C-15).
- 5**: Yellow crystals, mp 133–134°C (MeOH), $[\alpha]_D^{23} +65^\circ$ (c 0.48, MeOH). Ref. 4: $[\alpha]_D +59^\circ$ (MeOH). MS m/z (%): 312 (58, M⁺), 297 (14), 282 (5), 256 (12), 216 (17), 201 (19), 189 (100), 175 (39), 161 (36), 147 (26), 137 (67), 124 (66), 119 (27), 95 (40), 81 (40). HRMS: Calcd for C₂₁H₂₈O₂ 312.2089. Found 312.2089. ¹H-NMR (500 MHz, CDCl₃): 6.71 (d, 1H, 10.0 Hz, H-3'), 6.64 (dd, 1H, 10.0/2.4 Hz, H-4'), 6.43 (bs, 1H, H-6'), 4.74 (s, 1H, H-12), 4.28 (s, 1H, H-12), 2.55 (m, 2H, H-11), 2.33 (m, 1H, H-7), 1.97 (m, 1H, H-9), 1.73 (m, 1H, H-1), 1.71 (m, 1H, H-7), 1.70 (m, 1H, H-6), 1.55 (m, 1H, H-2), 1.48 (m, 1H, H-2), 1.37 (m, 1H, H-3), 1.31 (m, 1H, H-6), 1.19 (m, 1H, H-3), 1.10 (m, 1H, H-5), 1.06 (m, 1H, H-1), 0.85 (s, 3H, H-13), 0.78 (s, 3H, H-14), 0.74 (s, 3H, H-15). ¹³C-NMR (125 MHz, CDCl₃): 187.8 (C-5'), 187.8 (C-2'), 149.3 (C-1'), 147.1 (C-8), 136.8 (C-3'), 136.0 (C-4'), 132.8 (C-6'), 108.0 (C-12), 55.4 (C-5), 53.9 (C-9), 41.9 (C-3), 39.7 (C-10), 39.1 (C-1), 37.8 (C-7), 33.6 (C-13), 33.6 (C-4), 24.1 (C-6), 23.0 (C-11), 21.1 (C-14), 19.3 (C-2), 14.5 (C-15).
- 9**: Colourless crystals, mp 150–152°C (CHCl₃), $[\alpha]_D^{22} +28^\circ$ (c 1.0, CHCl₃). Ref. 17: $[\alpha]_D +30^\circ$ (CHCl₃). MS m/z (%): 314 (96, M⁺), 191 (100), 175 (18), 161 (13), 135 (17), 123 (36), 109 (37), 95 (27), 69 (13). HRMS: Calcd. for C₂₁H₃₀O₂ 314.22460. Found 314.2246. ¹H-NMR (500 MHz, CDCl₃): 6.72 (d, 1H, 2.7 Hz, H-6'), 6.58 (d, 1H, 8.5 Hz, H-3'), 6.49 (dd, 1H, 8.5/2.7 Hz, H-4'), 5.37 (bs, 1H, H-7), 2.56 (m, 2H, H-11), 2.32 (bs, 1H, H-9), 1.97 (m, 1H, H-6), 1.88 (m, 1H, H-1), 1.87 (m, 1H, H-6), 1.54 (m, 1H, H-2), 1.45 (s, 3H, H-12), 1.41 (m, 1H, H-2), 1.41 (m, 1H, H-3), 1.26 (m, 1H, H-5), 1.17 (m, 1H, H-3), 1.08 (m, 1H, H-1), 0.89 (s, 3H, H-14), 0.86 (s, 3H, H-13), 0.86 (s, 3H, H-15). ¹³C-NMR (125 MHz, CDCl₃): 149.2 (C-5'), 147.0 (C-2'), 135.3 (C-8), 131.3 (C-1'), 122.3 (C-7), 116.5 (C-6'),

- 116.1 (C-3'), 112.8 (C-4'), 54.2 (C-9), 50.3 (C-5), 42.2 (C-3), 39.5 (C-1), 36.8 (C-10), 33.3 (C-13), 33.0 (C-4), 26.2 (C-11), 23.7 (C-6), 22.2 (C-12), 21.9 (C-14), 18.9 (C-2), 13.9 (C-15).
16. **10**: Yellow crystals, mp 130–132°C (MeOH), $[\alpha]_{\text{D}}^{21} +89^{\circ}$ (c 0.1, MeOH). Ref. 6: $[\alpha]_{\text{D}}^{30} +95^{\circ}$ (MeOH). **MS** m/z (%): 314 (4), 312 (2, M⁺), 189 (33), 124 (38), 119 (100), 109 (40), 95 (18), 91 (21), 81 (19), 69 (25). **HRMS**: Calcd. for C₂₁H₂₈O₂ 312.2089. Found 312.2089. **¹H-NMR** (500 MHz, C₆D₆): 6.46 (d, 1H, 0.8 Hz, H-6'), 6.15 (m, 1H, H-3'), 6.11 (m, 1H, H-4'), 5.33 (bs, 1H, H-7), 2.48 (m, 1H, H-11), 2.13 (m, 1H, H-11), 1.94 (m, 1H, H-9), 1.86 (m, 1H, H-6), 1.77 (m, 1H, H-6), 1.56 (m, 1H, H-1), 1.43 (m, 1H, H-2), 1.40 (s, 3H, H-12), 1.34 (m, 1H, H-2), 1.34 (m, 1H, H-3), 1.10 (m, 1H, H-3), 1.10 (m, 1H, H-5), 0.84 (s, 3H, H-13), 0.83 (s, 3H, H-14), 0.80 (m, 1H, H-1), 0.75 (s, 3H, H-15). **¹³C-NMR** (125 MHz, C₆D₆): 187.1 (C-5'), 187.0 (C-2'), 151.1 (C-1'), 136.5 (C-3'), 135.7 (C-4'), 133.8 (C-8), 132.8 (C-6'), 123.4 (C-7), 53.2 (C-9), 50.0 (C-5), 42.3 (C-3), 39.6 (C-1), 36.9 (C-10), 33.3 (C-13), 33.1 (C-4), 25.9 (C-11), 24.0 (C-6), 22.8 (C-12), 22.0 (C-14), 19.1 (C-2), 13.9 (C-15).
17. Ochi, M.; Kotsuki, H.; Muraoka, K.; Tokoroyama, T. *Bull. Chem. Soc. Jap.* **1979**, *52*, 629–630.