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Total synthesis of the marine sesquiterpene quinone (−)-cyclozonarone

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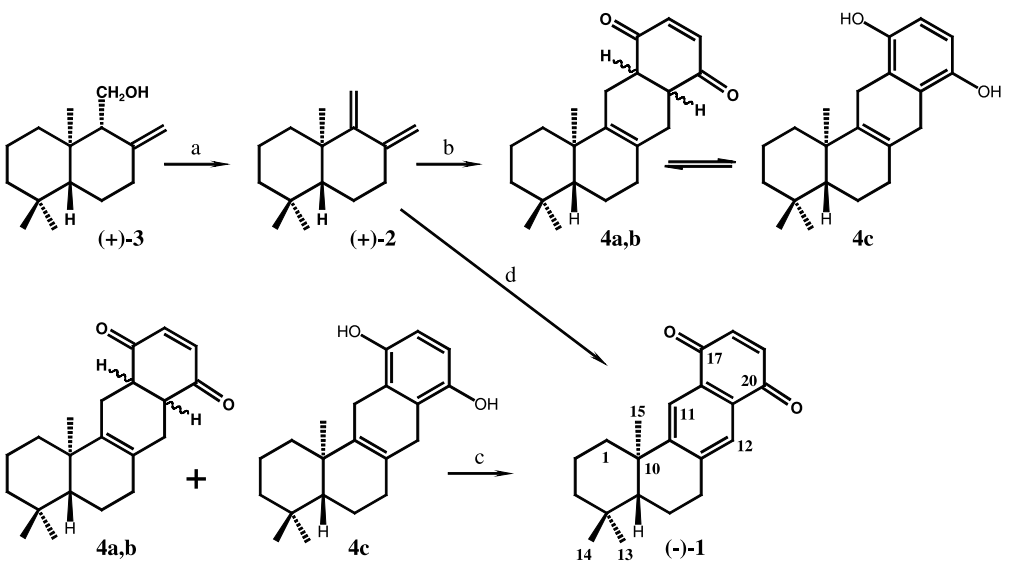
Abstract—The total synthesis of the naturally occurring sesquiterpene quinone (−)-cyclozonarone was achieved starting from (+)-albicanol. Elimination of water led to drima-(8,12),(9,11)-diene, which reacted in the key step of the synthesis—a Diels–Alder reaction—with benzoquinone. Further oxidation led to the target molecule. © 2001 Elsevier Science Ltd. All rights reserved.

The marine (−)-cyclozonarone has been isolated from the Pacific brown algae *Dictyopteris undulata* and possesses a potent feeding-deterrent activity toward young abalones.[1] The absolute configuration of natural (−)-(5*R*,10*R*)-cyclozonarone ((**−**)-**1**) was recently established: A synthesis starting from the commercially available (**−**)-polygodial led to (+)-(5*S*,10*S*)-cyclozonarone.[2] Herein, we describe the synthesis of (**−**)-cyclozonarone ((**−**)-**1**) via (+)-albicanol ((+)-**3**) (Scheme 1). Our synthesis of the chiral building block (+)-**3** was reported earlier.[3]

(+)-Albicanol ((+)-**3**) was dissolved in pyridine and added to a stirred mixture of Tf_2O in pyridine at 0°C.



Scheme 1. Synthesis of (**−**)-(5*R*,10*R*)-cyclozonarone ((**−**)-**1**): (a) pyridine, Tf_2O, 0→20°C, 30 min (68%); (b) benzoquinone, MeOH, AcOH, KOAc, reflux, Ar, 2 h (75–89%); (c) DDQ (92%); (d) benzoquinone, MeOH, AcOH, KOAc, reflux, Ar, 36 h (35%).

Keywords: terpenes; quinones; Diels–Alder reaction.

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Table 1. ^{1}H and ^{13}C NMR-data of (−)-**1** and (+)-**2** in $CDCl_3$

	(−)-**1**		(+)-**2**	
Position	δ ^{1}H (ppm)	δ ^{13}C (ppm)	δ ^{1}H (ppm)	δ ^{13}C (ppm)
1	2.40 m (1H) 1.38 m (1H)	38.5	1.62 m (1H) 1.43 m (1H)	37.5
2	1.73 m (1H) 1.62 m (1H)	19.0	1.48 m (1H) 1.42 m (1H)	19.1
3	1.47 m (1H) 1.19 m (1H)	41.4	1.40 m (1H) 1.18 m (1H)	42.3
4	–	33.5	–	33.8
5	1.27 m (1H)	49.6	1.11 m (1H)	52.5
6	1.90 m (1H) 1.69 m (1H)	18.5	1.71 m (1H) 1.45 m (1H)	22.7
7	3.05 m (1H) 2.93 m (1H)	30.6	2.45 m (1H) 2.11 m (1H)	35.9
8	–	142.8	–	150.0
9	–	156.9	–	161.8
10	–	38.6	–	40.2
11	7.94 s (1H)	123.0	4.78 m (1H) 4.63 m (1H)	103.1
12	7.69 s (1H)	127.3	4.72 d (1.8 Hz; 1H) 4.52 d (1.8 Hz; 1H)	101.8
13	0.94 s (3H)	33.3	0.87 s (3H)	33.4
14	0.92 s (3H)	21.6	0.85 s (3H)	22.0
15	1.17 s (3H)	24.4	0.94 s (3H)	20.7
16	–	129.0[a]		
17	–	185.2[c]		
18	6.85 m (1H)[c]	138.8[b]		
19	6.85 m (1H)[c]	138.5[b]		
20	–	185.2[c]		
21	–	129.7[a]		

[a] Exchangeable signals.
[b] Exchangeable signals.
[c] Isochron signals. (^{1}H: 500 MHz; ^{13}C: 125 MHz).

The reaction yielded 68% drima-(8,12),(9,11)-diene ((+)-**2**)[4] purified by flash chromatography through SiO_2 (cyclohexane). Diels–Alder reaction of the diene (+)-**2** with an excess of benzoquinone gave a mixture of **4a**,**b** and **c** with 75–89% yield after 2 h. If the reaction time was extended to 36 h the desired (**–**)-(5*R*,10*R*)-cyclozonarone ((**–**)-**1**)[5] could be obtained with 35% yield after MPLC (LiChrospher® Si 60, *n*-hexane/ethylacetate 9:1). In this case the oxidizing agent was benzoquinone. Oxidation of the mixture of **4a**,**b** and **c** with DDQ led to (**–**)-**1**[5] (92% yield). A comparison of optical rotation and the spectroscopic data (MS, NMR) (Table 1) of (**–**)-**1** with natural (**–**)-cyclozonarone[1] showed good agreement.

Acknowledgements

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References

1. Kurata, K.; Taniguchi, K.; Suzuki, M. *Phytochemistry* **1996**, *41*, 749–752.
2. Cortes, M.; Valderrama, J. A.; Cuellar, M.; Armstrong, V.; Preite, M. *J. Nat. Prod.* **2001**, *64*, 348–349.
3. Schröder, J.; Magg, C.; Seifert, K. *Tetrahedron Lett.* **2000**, *41*, 5469–5473.
4. (+)-**2**: Colourless liquid, $[\alpha]_D^{25}$ +181° (*c* 1.00, $CHCl_3$). Ref. 2 for (**–**)-**2**: $[\alpha]_D^{16}$ −189° (*c* 5.07, $CHCl_3$). **MS** *m*/*z* (%): 204 (100, $M^{+\bullet}$), 189 (67), 175 (17), 161 (57), 147 (42), 133 (96), 119 (97), 105 (95), 91 (86), 79 (48), 69 (37). **HRMS**: calcd for $C_{15}H_{24}$ 204.1878. Found 204.1878.
5. (**–**)-**1**: Yellow oil, $[\alpha]_D^{25}$ −87° (*c* 1.00, $CHCl_3$). Ref. 1: $[\alpha]_D^{19}$ −89° (*c* 0.33, $CHCl_3$). **MS** *m*/*z* (%): 308 (59, $M^{+\bullet}$), 293 (99), 265 (4), 251 (7), 237 (12), 225 (72), 211 (100), 197 (21), 181 (5), 152 (5), 115 (4), 69 (14). **HRMS**: calcd for $C_{21}H_{24}O_2$ 308.1776. Found 308.1776.