26. Rogiolenyne D, the Likely Immediate Precursor of Rogiolenyne A and B, Branched C_{15} Acetogenins Isolated from the Red Seaweed *Laurencia microcladia* of Il Rogiolo. Conformation and Absolute Configuration in the Whole Series

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It is shown that in the red seaweed *Laurencia microcladia,* collected in the Mediterranean off the torrent Il Rogiolo, the new branched C_{15} acetogenin rogiolenyne D (= *(+)-(2S,3S,7R)-3-(bromomethyl)-7-[(Z)-1-chlorohexen-3-en-5-ynyl)]-2-ethyl-2,3,6,7-tetrahydrooxepin;* (+)-**3**) co-occurs with the already reported rogiolenyne A ((−)-**1**) and B ((−)-**2a**), suggesting the lineage (+)-**3**→(−)-**1**←(−)-**2a**, which is realized here chemically. The relative configurations are established *via* NMR analysis and chemical transformations as regards the seven-membered ring, while recourse is made to conformational analysis for the side chain. The absolute configuration is established *via* the *Mosher*'s NMR method applied to the MTPA esters of (−)-**2a**.

1. Introduction. – As the only examples of acetogenins built on a branched C_{15} chain, we have recently reported on two oxepanes, called rogiolenyne A ((−)-**1**) and B ((−)-**2a**), isolated from the red seaweed *Laurencia microcladia,* collected off the torrent Il Rogiolo in the Mediterranean [1] (*cf.* the *Scheme*).

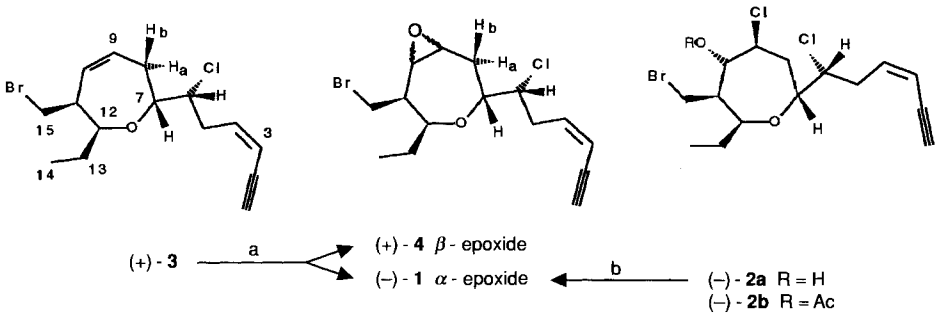
All other C_{15} acetogenins – either *O*-heterocyclic or carbocyclic – are built on a linear C_{15} chain [2]. They have raised general interest for their marked bioactivity, which makes these compounds ecologically important [2], and in regard to the chemistry of medium-sized cyclic ethers. These are difficult to obtain *via* chemical synthesis, as evidenced from the fact that so far only the total syntheses of the oxocanes (−)-laurenyne [3] and (±)-laurencin have been completed – the latter in only 0.003% yield [4] – in spite of much synthetic work with model compounds. These have mainly concerned oxocanes, with structures close to [5a] or remote from naturally-occurring compounds [5b], while models for oxepanes [6] and oxonanes [3] [7] have only been considered briefly.

In this perspective, we thought that the unusual branching of the rogiolenynes [1] merits further consideration. We report here on our accomplishments along these lines, describing the isolation of a novel rogiolenyne, which was previously hypothesized [1] as the parent compound in this series, and establishing their absolute configurations and conformations.

2. Results and Discussion. – 2.1. *Rogiolenyne D* ((+)-**3**). *Structure, Conformation, and Structural Correlation with Rogiolenyne A* ((−)-**1**) *and B* ((−)-**2a**). NMR and MS data (*Table* and *Exper. Part*) indicate for the new product that we have isolated from *L. microcladia* the molecular formula $C_{15}H_{20}BrClO$. This has one O-atom less than, and the same

[1]) Presented in part by *G.G.* at the Giornate di Chimica delle Sostanzze Naturali, Maratea, 2–5 June 1991.

Scheme



a) 1. MCPBA/CH_2Cl_2, 2. HPLC (*Si-60*; α/β-epoxide 3:2). b) 3% K_2CO_3/MeOH, r.t., 1 h.

degree of unsaturation as, rogiolenyne A ((–)-**1**, *Scheme*). The similarity of the NMR spectra of these two compounds, and in particular the replacement of the epoxide NMR signals of (–)-**1** by the cyclic-olefin signals with rogiolenyne D (*Exper. Part*, [1]), suggests structure (+)-**3**[2]) in the planar form. This is fully supported by $^1H,^1H$- and $^1H,^{13}C$-correlation spectra, while differential decoupling and NOE experiments allow us to define, as in the case of (–)-**1** [1], the configuration of the ring attachment for the three side chains.

These conclusions find further support in the chemical transformations outlined in the *Scheme:* peroxy-acid epoxidation of rogiolenyne D ((+)-**3**) gives both the natural rogiolenyne A ((–)-**1**) and the isomeric, unnatural isorogiolenyne A ((+)-**4**) in a 3:2 ratio. It is also seen from the *Scheme* that epoxide closure of the bromohydrin group of rogiolenyne B ((–)-**2a**), under mild basic conditions, gives rogiolenyne A ((–)-**1**). This serves to correlate configurationally at the seven-membered ring rogiolenyne D with rogiolenyne A ((–)-**1**) and B ((–)-**2a**) [2].

The meager stereoselectivity of the epoxidation of rogiolenyne D ((+)-**3**; *Scheme*) contrasts with the appreciable stereoselectivity found in the peroxy-acid epoxidation of *cis*-2,7-disubstituted dialkyl-4,5-dehydrooxepanes, where peroxy-acid attack *anti* to the side chains is favored by 6:1 [8]. The latter finding [8] can be rationalized along a torsion-angle analysis as with chair cycloheptenes [9]: starting clockwise from the C(3)–C(4) bond, the relevant sequence of torsion-angle signs is $-,0,+$. On this basis, peroxy-acid attack at the olefinic bond of *cis*-2,7-disubstituted dialkyl-4,5-dehydro-oxepanes should be favored from the direction *anti* to the side chains, as found experimentally [8].

In the case of rogiolenyne D ((+)-**3**), molecular-mechanics calculations indicate a twist-chair[3]) as the lowest-energy conformer **A** (*Fig. 1*), to which the corresponding torsion-angle sequence $-,0,-$ pertains. For this sequence, a twist-chair cycloheptene free of polar and steric effects would be expected to display no stereoselectivity on epoxidation [9]. Therefore, the non-negligible stereoselectivity observed with rogiolenyne D ((+)-**3**) (*Scheme*) likely reflects steric and polar effects by the side chain at C(11).

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[2]) All experimental data are discussed in terms of the numbering given in the formula (+)-**3**, whereas systematic numbering is only used for retrieval purposes (see *Exper. Part*).

[3]) Which is supported by the NOE data in the *Exper. Part*, in particular the positive enhancement at H_b–C(15) on irradiation at H–C(7).

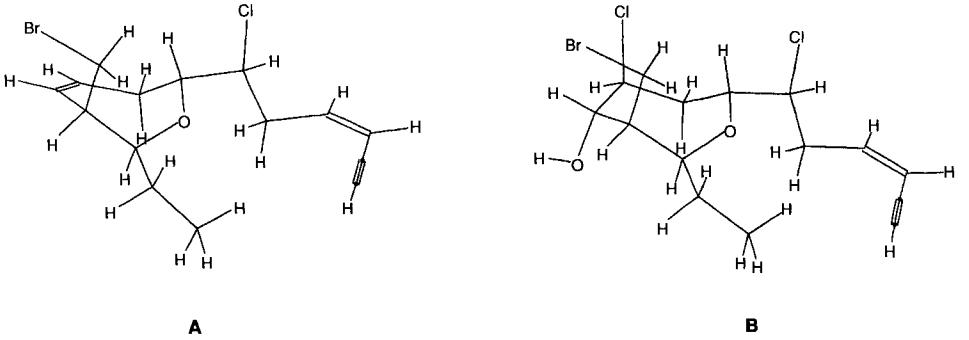

Fig. 1. *Lowest strain-energy conformation of rogiolenyne D* ((+)-**3**) (**A**) *and rogiolenyne B* ((−)-**2a**) (**B**) *from molecular-mechanics calculations*

Molecular-mechanics calculations suggest that also rogiolenyne B ((−)-**2a**) takes preferentially a twist-chair conformation **B** where the OH group and the ring O-atom are in '*transoid*' relationship (*Fig. 1*). This is less strained by *ca.* 4 Kcal·mol^{-1} than a twist-chair where these two groups are in '*cisoid*' relationship.

As far as the chlorinated side chain is concerned, molecular-mechanics calculations have been carried out with (+)-**3** for the various possible values of the H–C(7)–C(6)–H dihedral angle for both the *threo-* and the *erythro-*configuration. According to this analysis, a *threo-*configuration with H–C(7)–C(6)–H dihedral angle of 60° is preferred over all other conformations. Since the energy barriers are low (*ca.* 6 Kcal·mol^{-1}), averaging of the dihedral angle to *ca.* 60° is expected; low $J(7,6)$ values (2.7 Hz) are in accordance with this analysis. For the *erythro-*configuration, the energy minimum occurs at a H–C(7)–C(6)–H dihedral angle of *ca.* 180°, *i.e.* at an average dihedral angle of *ca.* 170°, which would fit for $J(7,6) \approx 10$ Hz [10], in contrast with our ^{1}H-NMR observations.

In conclusion, this analysis of the configuration at the chlorinated side chain represents an attempt to surmount the difficulties caused by freely rotating chains, although the same high degree of confidence can not be attached to this analysis as to that concerning the configurations at the oxepane ring.

2.2. *Absolute Configuration of Rogiolenyne B* ((−)-**2a**) *and the other Rogiolenynes.* The assignment of the absolute configuration for marine medium-sized C_{15} cyclic ethers has been made by the *Bijvoet* X-ray method with the oxocanes laurencin [11a], pinnatifidenynes [11b][4]), and laurenyne [11c], although erroneously in the latter case [3]. Moreover, *Prelog*'s atrolactic method [12] has been used to define the absolute configuration at C(6)–OH in the side chain of octahydro-deacetyl-laurencin, derived *via* hydrolysis and hydrogenation of the oxocane laurencin [13], whose relative configuration was already known from X-ray analysis [14]. This information served to correlate the oxocane laurepinnacin to laurencin [15]. In turn, the oxepane isolaurepinnacin has been related to laurepinnacin through common degradation products [15]. However, these chemical methods for absolute configuration assignment often rely on the stereospecificity of the reactions; conducting, such as with the oxepane laurepinnacin [15], non-stereospecific

[4]) **Added in Proof.** – The original assignment [11b] was erroneous (M. Norte, A. G. Gonzalez, F. Cataldo, M. L. Rodriguez, I. Brio, *Tetrahedron* **1991**, *47*, 9411).

reactions, like the Zn/AcOH cleavage of β-bromo-ethers, may lead to erroneous configurational assignments.

Finally, enantioselective total synthesis has only been carried out with laurenyne [3], leading to reverse the absolute-configuration assignment made through the *Bijvoet* X-ray method [11c].

We have followed a different approach to the absolute-configuration assignment of the rogiolenynes. The secondary OH function of rogiolenyne B ((−)-**2a**) seemed us ideally suited for application of the original *Mosher*'s method for absolute-configuration assignment [16], which has repeatedly proved reliable [17] in its original formulation [16], and which has been recently applied to marine terpenes [18].

To this end, the diastereoisomeric 2-methoxy-2-phenyl-2-(trifluoromethyl)acetic acid (MTPA) esters (−)-**5a** and (+)-**5b** were prepared by reaction of (−)-**2a** with (−)-(*R*)- or (+)-(*S*)-MTPA chloride, respectively, in pyridine. For both structures, the CF_3 group, the ester C=O group, and the carbinyl H-atom lie in a plane [16b] that bisects the oxepane ring, which takes the twist-chair form. This planar arrangement is consistent with molecular-mechanics calculations. The ^{1}H-NMR data for (−)-**5a** (*Exper. Part*) show that the signals of the protons at the ring segment C(11)–C(12) and the C(13)–C(14) side chain on it are shifted upfield with respect to the same protons of (+)-**5b**. Correspondingly, the signals of the protons at the opposite side of the molecule are shifted downfield, as

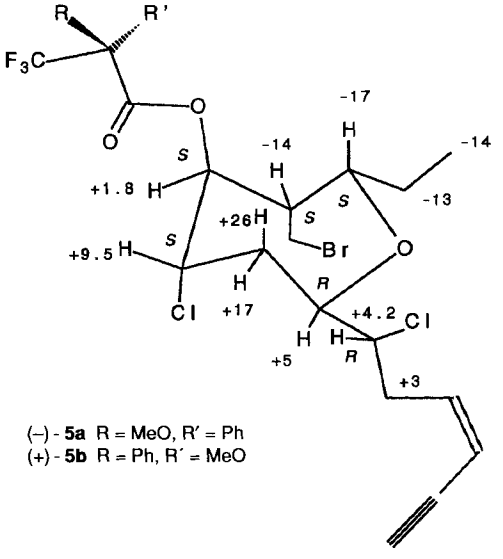

Fig. 2. *^{1}H-NMR Resonance differences* [Hz] *between the (S)-MPTA ester (−)-***5a** *and the (R)-MPTA ester (+)-***5b**

indicated in difference from in *Fig. 2*. Only with (*S*)-configuration at the oxepane C(10) of rogiolenyne B ((−)-**2a**) can the diamagnetic effect of the Ph group [16b] explain these results[5]). All other chiral centers of the oxepane ring of this compound are assigned as in *Fig. 2* from the relative configurations established above.

[5]) A similar analysis of the ^{13}C-NMR signals (*Table*) leads to the same conclusions.

Table. *^{13}C-NMR Data* ($CDCl_3$) *for Rogiolenyne D* ((+)-**3**), *Its MTPA Esters* (−)-**5a** *and* (+)-**5b**, *and Isorogiolenyne A* ((+)-**4**)

C-Atom	(+)-**3**	(+)-**4**	(−)-**5a**[a])	(+)-**5b**[b])
C(1)	82.41 (*d*)	82.44 (*d*)	82.67 (*d*)	82.66 (*d*)
C(2)	79.99 (*s*)	[c])	79.76 (*s*)	79.74 (*s*)
C(3)	110.68 (*d*)	110.85 (*d*)	111.20 (*d*)	111.17 (*d*)
C(4)	141.23 (*d*)	141.00 (*d*)	140.51 (*d*)	140.51 (*d*)
C(5)	34.81 (*t*)	35.43 (*t*)	36.00 (*t*)	36.01 (*t*)
C(6)	64.52 (*d*)	64.95 (*d*)	65.25 (*d*)	65.19 (*d*)
C(7)	76.79 (*d*)	70.00 (*d*)	74.68 (*d*)	74.53 (*d*)
C(8)	29.63 (*t*)	29.69 (*t*)	31.53 (*t*)	31.25 (*t*)
C(9)	132.78 (*d*)	55.94 (*d*)	56.90 (*d*)	56.51 (*d*)
C(10)	128.29 (*d*)	55.99 (*d*)	72.42 (*d*)	72.42 (*d*)
C(11)	47.58 (*d*)	45.03 (*d*)	50.30 (*d*)	50.48 (*d*)
C(12)	77.40 (*d*)	76.76 (*d*)	73.40 (*d*)	73.45 (*d*)
C(13)	25.19 (*t*)	26.51 (*t*)	26.86 (*t*)	26.73 (*t*)
C(14)	11.14 (*q*)	11.30 (*q*)	11.06 (*q*)	11.52 (*q*)
C(15)	33.65 (*t*)	29.34 (*t*)	29.65 (*t*)	29.72 (*t*)

[a]) Detected signals of arom. C: 164.60 (*s*); 129.92 (*d*); 128.72 (*d*); 127.15 (*d*); 55.36 (*q*).
[b]) Detected signals of arom. C: 164.54 (*s*); 129.92 (*d*); 128.74 (*d*); 127.18 (*d*); 55.36 (*q*).
[c]) Not detected.

The absolute configurations at the oxepane ring of both rogiolenyne A ((−)-**1**), C ((−)-**2b**), and D ((+)-**3**) are related to that of (−)-**2a** by the transformations outlined in the *Scheme*.

We thank Mr. *A. Sterni* and Mr. *L. Zuppiroli* for recording mass spectra and both M.P.I. (Progetti 40%) and C.N.R., Roma, for financial support.

Experimental Part

1. *General.* All evaporations were carried out at reduced pressure below 40°. Yields are given on reacted compound. Flash chromatography (FC): *Merck Si-60*, 15–25 μm and *Merck, Lichroprep RP-18*, 40–63 μm. HPLC: *Merck, LiChrosorb Si-60* (7 μm) or *Merck, Lichrosorb CN* (7 μm). All HPLC columns were 25 × 1 cm with 5 ml·min^{-1} solvent flux. Polarimetric data: *JASCO-DP-181* polarimeter. UV: *Perkin-Elmer Lambda 3* spectrophotometer (λ_{max} in nm, ε in mol^{-1}·l·cm^{-1}). NMR: *Varian-XL-300*; δ [ppm] relative to internal TMS (= 0 ppm) and J in Hz; with ^{1}H-NMR spectra (299.94 MHz), the coupling pattern of many protons has been elucidated by differential decoupling irradiations [19], while 90/120 ^{1}H,^{1}H-COSY [20] were carried out with (+)-**3**, (−)-**5a**, and (+)-**5b**, and NOE stands for differential NOE; with ^{13}C-NMR spectra (75.43 MHz), multiplicities are from DEPT [21], and H-bearing C-atoms for compounds (+)-**3** and (+)-**5b** were assigned from ^{13}C,^{1}H-COSY [22]. EI-MS (*m/z*, %): home-built quadrupole mass spectrometer based on the *ELFS-4-162-8 Extranuclear* quadrupole [23] or, for HR-MS, *VG 70-70* mass spectrometer. Molecular-mechanics calculations were carried out with the MMX software, release February 25th, 1980, *J.J. Gajewski* and *K.E. Gilbert, Serena Software*, Bloomington, Indiana.

2. *Isolation.* The residue (0.38 g) from evaporation for the combined *Fr. 4* and *5* of the 54 fractions obtained before from *L. microcladia* extracts [1] was subjected to reversed-phase FC with MeOH/H_2O gradient elution collecting various fractions. The residue from *Fr. 3* (0.03 g) was subjected to HPLC (*CN*) with hexane to give rogiolenyne D ((+)-**3**) (t_R 6.5 min, 22 mg, 0.04%).

3. *Rogiolenyne D* (= *(+)-(2S,3S,7R)-3-(Bromomethyl)-7-[(Z)-1-chlorohex-3-en-5-ynyl]-2-ethyl-2,3,6,7-tetrahydrooxepin*; (+)-**3**). Colorless oil. $[\alpha]_D^{20}$ = +91 (c = 0.28, CCl_4). UV (cyclohexane): 223 (16100). ^{1}H-NMR ($CDCl_3$): 3.13 (*dd*, J(1,3) = 2.3, J(1,4) = 0.9, H–C(1)); 5.59 (*ddt*, J(3,4) = 10.9, J(3,1) = 2.3,

$J(3,5a) \approx J(3,5b) = 1.4$, H–C(3)); 6.11 (*dtd*, $J(4,3) = 10.9$, $J(4,5a) \approx J(4,5b) = 7.0$, $J(4,1) = 0.9$, H–C(4)); 2.94, 2.76 (2*dddd*, $J_{gem} = 15.1$, $J(5a,4) = 7.0$, $J(5a,3) = 1.4$, $J(5a,6) = 4.9$, and $J_{gem} = 15.1$, $J(5b,4) = 7.0$, $J(5b,3) = 1.4$, $J(5b,6) = 9.2$, resp., 2H–C(5)); 3.90 (*ddd*, $J(6,5b) = 9.2$, $J(6,5a) = 4.9$, $J(6,7) = 2.7$, H–C(6)); 4.01 (*ddd*, $J(7,8a) = 10.9$, $J(7,8b) = 1.6$, $J(7,6) = 2.7$, H–C(7)); 2.79 (*m*, H_a–C(8)); 2.19 (*m*, H_b–C(8)); 5.85 (*m*, H–C(9), H–C(10)); 2.74 (*m*, H–C(11)); 4.09 (*ddd*, $J(12,11) = 1.5$, $J(12,13a) = 4.6$, $J(12,13b) = 9.4$, H–C(12)); 1.41 (*ddq*, $J_{gem} = 13.8$, $J(13a,12) = 4.6$, $J(13a,14) = 7.3$, H_a–C(13)); 1.80 (*ddq*, $J_{gem} = 13.8$, $J(13b,12) = 9.3$, $J(13b,14) = 7.3$, H_b–C(13)); 1.00 (*t*, $J(14,13) = 7.3$, 3H–C(14)); 3.63 (*dd*, $J_{gem} = 10.0$, $J(15a,11) = 4.8$, H_a–C(15)); 3.26 (*t*, $J_{gem} = J(15b,11) = 10.0$, H_b–C(15))[6]. NOE (irradiated proton(s)→positive NOE (%) on the observed proton(s)): H–C(12)→8 (H_b–C(8)); H–C(7)→3 (H_b–C(15)); H_a–C(8)→8 (H–C(9)), 4 (H–C(7)), and 4 (H–C(6)). MS: 296,294 (2,2, $[M - HCl]^{+\cdot}$), 253,251 (6,18, $[M - Br]^+$), 219,217 (20,20, $[M - C_6H_6Cl]^+$), 201,199 (8,8), 129 (98), 91 (100).

4. *Epoxidation of (+)-***3**. To 10 mg (0.03 mmol) of (+)-**3** in 1 ml of dry CH_2Cl_2 at r.t. were added 7 mg of 65% *m*-chloroperoxybenzoic acid (MCPBA) and 1 equiv. of $NaHCO_3$ followed by, after 2 h, 1 ml of 5% aq. $NaHCO_3$ soln.; the mixture was percolated through a *Whatman* phase-separation filter, the filtrate was evaporated, and the residue was subjected to HPLC (*Si-60*) with hexane/Et_2O 3:1 obtaining *isorogiolenyne A* ((+)-**4**) (3 mg, 29%, t_R 6.7 min) and (–)-**1** (4.5 mg, 44%, t_R 8.0 min), identical in all respects to natural rogiolenyne A.

Isorogiolenyne A (=(+)-(1R,2R,3S,5R,7S)-2-(Bromomethyl)-5-[(Z)-1-chlorohex-3-en-5-ynyl]-3-ethyl-4,8-dioxabicyclo[5.1.0]octane; (+)-**4**). Colorless oil. $[\alpha]_D^{20} = +11$ ($c = 0.20$, CCl_4). ^{1}H-NMR ($CDCl_3$): 3.13 (*dd*, $J(1,3) = 2.3$, $J(1,4) = 1.0$, H–C(1)); 5.57 (*ddt*, $J(3,4) = 10.9$, $J(3,1) = 2.3$, $J(3,5a) \approx J(3,5b) = 1.4$, H–C(3)); 6.05 (*dtd*, $J(4,3) = 10.9$, $J(4,5a) \approx J(4,5b) = 7.0$, $J(4,1) = 0.9$, H–C(4)); 2.75, 2.88 (2*dddd*, $J_{gem} = 14.6$, $J(5a,6) = 8.8$, $J(5a,4) = 7.0$, $J(5a,3) = 1.3$, and $J_{gem} = 14.6$, $J(5b,6) = 5.5$, $J(5b,4) = 7.0$, $J(5b,3) = 1.3$, resp., 2H–C(5)); 3.86 (*ddd*, $J(6,7) = 2.0$, $J(6,5b) = 5.5$, $J(6,5a) = 8.8$, H–C(6)); 3.92 (*td*, $J(7,6) \approx J(7,8b) = 2.0$, $J(7,8a) = 11.3$, H–C(7)); 2.59 (*dd*, $J(8b,7) = 11.2$, $J_{gem} = 16.2$, H_a–C(8)); 2.25 (*ddd*, $J(8b,7) = 1.9$, $J(8b,9) = 5.0$, $J_{gem} = 16.2$, H_b–C(8)); 3.38 (*m*, H–C(9)); 3.40 (*m*, H–C(10)); 2.47 (*dddd*, $J(11,10) = 4.2$, $J(11,15a) = 5.7$, $J(11,12) = 1.6$, $J(11,15b) = 9.7$, H–C(11)); 3.84 (*ddd*, $J(12,11) = 1.6$, $J(12,13a) = 4.8$, $J(12,13b) = 9.0$, H–C(12)); 1.73, 1.42 (2*ddq*, $J(13a,12) = 4.8$, $J_{gem} = 15.6$, $J(13a,14) = 7.1$, and $J(13b,12) = 9.0$, $J_{gem} = 15.6$, $J(13b,14) = 7.3$, resp., 2H–C(13)); 0.99 (*t*, $J(14,13a) = J(14,13b) = 7.1$, 3H–C(14)); 3.55, 3.45 (2*dd*, $J(15a,11) = 10.0$, $J_{gem} = 10.0$, and $J(15b,11) = 4.4$, $J_{gem} = 10.0$, resp., 2H–C(15)). MS: nearly superimposable to that (–)-**1**.

5. *Treatment of Rogiolenyne B* ((–)-**2a**) *with MTPA-Cl*. To a soln. of (–)-**2** (6 mg, 0.015 mmol) in 0.2 ml of dry pyridine and 0.2 ml of CCl_4 were added 5 mol-equiv. of (–)-(*R*)-MTPA-Cl [2a]. The resulting soln. was allowed to stand at r.t. for 24 h and was then added of 3 ml of a sat. $CuSO_4$ aq. soln. and percolated through a *Whatman* phase-separation filter; the filtrate was evaporated, and the residue was subjected to HPLC (*CN*; hexane/i-PrOH 97.5:2.5) affording the pure MTPA-ester (–)-**5a** (t_R 8.2 min, 3.8 mg, 65%), besides unreacted (–)-**2a** (t_R 14 min, 2 mg). Under otherwise identical conditions, (–)-**2a** (8 mg) was reacted with (+)-(*S*)-MTPA-Cl [2a], leading to the pure MTPA ester (+)-**5b** (t_R 8.5 min, 70%).

*Data of (–)-***5a**. $[\alpha]_D^{20} = -11$ ($c = 0.10$, CCl_4). ^{1}H-NMR ($CDCl_3$): 3.11 (*dd*, $J(1,3) = 2.3$, $J(1.4) = 1.0$, H–C(1)); 5.59 (*ddt*, $J(3,4) = 10.8$, $J(3,1) = 2.3$, $J(3,5a) \approx J(3,5b) = 1.4$, H–C(3)); 6.10 (*dtd*, $J(4,3) = 10.8$, $J(4,5a) \approx J(4,5b) = 7.2$, $J(4,1) = 1.0$, H–C(4)); 2.85 (*m*, 2H–C(5)); 3.83 (*ddd*, $J(6,7) = 2.6$, $J(6,5a) = 6.0$, $J(6,5b) = 8.4$, H–C(6)); 4.29 (*ddd*, $J(7,6) = 2.6$, $J(7,8b) = 3.6$, $J(7,8a) = 11.7$, H–C(7)); 2.75 (*ddd*, $J(8a,7) = 11.7$, $J(8a,9) = 1.6$, $J_{gem} = 15.8$, H_a–C(8)); 1.85 (*ddd*, $J(8b,7) = 3.6$, $J(8b,9) = 6.0$, $J_{gem} = 15.8$, H_b–C(8)); 4.40 (*ddt*, $J(9,10) = 3.1$, $J(9,8b) = 6.0$, $J(9,11) \approx J(9,8a) = 1.6$, H–C(9)); 5.88 (br. *t*, $J(10.9) \approx J(10,11) = 3.1$, H–C(10)); 2.15 (*dddd*, $J(11,10) = 2.7$, $J(11,15a) = 11.0$, $J(11,12) = 1.6$, $J(11,15b) = 4.4$, H–C(11)); 3.96 (br. *t*, $J(12,13a) = J(12,13b) = 7.3$, H–C(12)); 1.76, 1.39 (2 *ddq*, $J_{gem} = 15.6$, $J(13a,14) = 7.5$, $J(13a,12) = 7.3$, and $J_{gem} = 15.6$, $J(13b,14) = 7.5$, $J(13b,12) = 7.3$, resp., 2H–C(13)); 0.80 (*t*, $J(14,13a) = J(14,13b) = 7.5$, 3H–C(14)); 3.86, 3.64 (2*dd*, $J_{gem} = 11.0$, $J(15a,11) = 10.8$, and $J_{gem} = 11.0$, $J(15b,11) = 4.5$, resp., 2H–C(15)); 3.55 (*q*, $J = 1.1$, MeO); 7.6–7.4 (series of *m*, 5 arom. H). MS: nearly superimposable to that of (+)-**5b** below.

*Data of (+)-***5b**. $[\alpha]_D^{20} = +17$ ($c = 0.24$, CCl_4). ^{1}H-NMR ($CDCl_3$): 3.11 (*dd*, $J(1,3) = 2.3$, $J(1.4) = 1.0$, H–C(1)); 5.59 (*ddt*, $J(3,4) = 10.8$, $J(3,1) = 2.3$, $J(3,5a) \approx J(3,5b) = 1.4$, H–C(3)); 6.09 (*dtd*, $J(4,3) = 10.8$, $J(4,5a) \approx J(4,5b) = 7.2$, $J(4,1) = 1.0$, H–C(4)); 2.85 (*m*, 2H–C(5)); 3.81 (*ddd*, $J(6,7) = 2.6$, $J(6,5a) = 6.0$, $J(6,5b) = 8.4$, H–C(6)); 4.27 (*ddd*, $J(7,6) = 2.6$, $J(7,8b) = 3.6$, $J(7,8a) = 11.7$, H–C(7)); 2.66 (*ddd*, $J(8a,7) = 11.7$, $J(8a,9) = 1.6$, $J_{gem} = 15.8$, H_a–C(8)); 1.79 (*ddd*, $J(8b,7) = 3.6$, $J(8b,9) = 6.0$, $J_{gem} = 15.8$, H_b–C(8)); 4.36 (*ddt*, $J(9,10) = 3.1$, $J(9,8b) = 6.0$, $J(9,11) \approx J(9,8a) = 1.6$, H–C(9)); 5.88 (br. *t*, $J(10,9) \approx J(10,11) = 3.1$, H–C(10)); 2.20 (*dddd*, $J(11,10) = 2.7$, $J(11,15a) = 11.0$, $J(11,12) = 1.6$, $J(11,15b) = 4.4$, H–C(11)); 4.02 (br. *t*,

[6]) The position of H_a–C(15) and H_b–C(15) is indicated in *Fig. 1* (**A**).

$J(12,13a) = J(12,13b) = 7.3$, H–C(12)); 1.79, 1.46 (2*ddq*, $J(13a,12) = 7.3$, $J_{gem} = 15.6$, $J(13a,14) = 7.5$, and $J(13b,12) = 7.3$, $J_{gem} = 15.6$, $J(13b,14) = 7.5$, resp. 2H–C(13)); 0.85 (*t*, $J(14,13a) = J(14,13b) = 7.5$, 3H–C(14)); 3.88, 3.66 (2*dd*, $J_{gem} = 11.0$, $J(15a,11) = 10.8$, and $J_{gem} = 11.0$, $J(15b,11) = 4.5$, resp., 2H–C(15)); 3.51 (*q*, $J = 1.1$, MeO); 7.6–7.4 (series of *m*, 5 arom. H). NOE (irradiated protons(s)→positive NOE (%) on the observed proton(s)): H–C(10)→10 (H–C(9)) and 5 (H–C(11)); H–C(7)→6 (H–C(6)), and 5 (H_b–C(8)); H–C(11)→9 (H–C(10)), 5 (H–C(12)), and 4 (H_a–C(15)); H_a–C(8)→4 (H–C(9)), and 10 (H–C(12)). MS: 602, 600, 598 (0.7, 1.3, 0.9, M^+), 566, 564, 562 (3, 14, 10, $[M - HCl]^+$), 521, 519 (15, 21, $[M - Br]^+$), 489, 487, 485 (4, 14, 11, $[M - C_6H_6Cl]^+$), 368, 366, 364 (3, 7, 4, $[M - MTPA - OH]^+$), 287, 285 (5,16) 189 (100), 155 (41), 105 (50). HR-MS: 519.1310 ($C_{25}H_{28}Cl_2F_3O_4$, calc. 519.1355).

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