Absolute Configuration of Some Marine Metabolites from *Cystoseira* spp.

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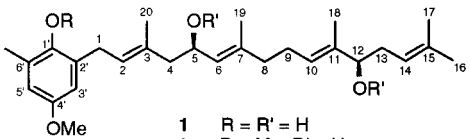
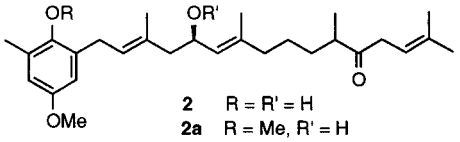
The absolute configuration of meroditerpenoid metabolites isolated from Mediterranean brown algae of the genus *Cystoseira* has been determined using a recent modification of Mosher's method. The data obtained suggest that the compounds examined are interconnected through a stereocontrolled enzymatic reaction. This constitutes another confirmatory step in the validation of a previously proposed biosynthetic pathway for *Cystoseira* metabolites.

The algal genus *Cystoseira* (Order Fucales, Family Cystoseiraceae) is undoubtedly the most important in the Mediterranean ecosystem, due to its number of species (about 30), its abundance, and the conspicuous size of many of the algae. Chemical examination of species collected along the Sicilian coasts has led to the isolation of a vast number of secondary metabolites, including tens of meroditerpenoids. These have been interrelated in a meaningful, although admittedly speculative, biogenetic pathway. In brief, from geranylgeranyltoluquinol, oxidation of the diterpenoid moiety generates compounds containing hydroxyl or carbonyl functions, e.g. **1** and **2**. Further transformations can afford compounds in which the distal isoprene unit has been converted into a tetrahydrofuran ring as in zosterdiol A (**3**), while more complex sequences of biosynthetic steps would lead, through the monocarbocyclic diketone **5**, to polycyclic metabolites exemplified by cystalgerone **4** and balearone **6**. The irregular diterpenoid neobalearone **7** is apparently derived from geranyllavandulyltoluquinol, possibly through a biosynthetic pathway parallel to that leading to balearone and perhaps catalyzed by the same enzymes.[1,2]

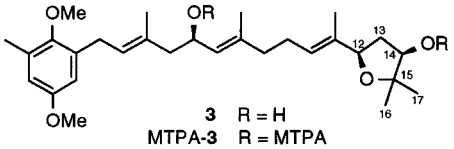
In general, the gross structures of the *Cystoseira* metabolites have been determined largely by spectroscopic means, on occasion with the aid of chemical transformations. The relative stereochemistry of compounds containing more than one chiral center has been assessed, at least in the case of rigid systems, by ^{1}H-NMR spectroscopy (and by X-ray diffraction analysis for balearone). The problem of the absolute configuration remained unsolved, as well as that of the configuration of compounds containing more centers in a flexible structure (e.g. **1**). The recent availability of a modification of the Mosher method for the elucidation of the absolute configuration of secondary alcohols,[3] more reliable than that originally proposed,[4,5] prompted us to apply the new methodology to some representatives of the family of *Cystoseira* meroditerpenoids. The new version of the Mosher technique requires coupling of the chiral secondary alcohol with each of the enantiomeric Mosher acid [2-methoxy-2-phenyl-2-(trifluoromethyl)-acetic acid, MTPA] chlorides. Next, assignments of as many resonances as possible are made in the ^{1}H-NMR



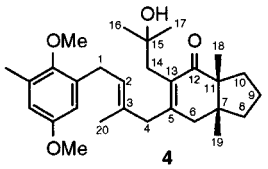
1 R = R' = H
1a R = Me, R' = H
MTPA-**1a** R = Me, R' = MTPA



2 R = R' = H
2a R = Me, R' = H
MTPA-**2a** R = Me, R' = MTPA



3 R = H
MTPA-**3** R = MTPA



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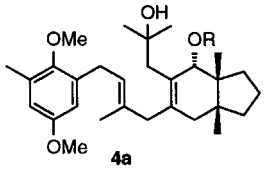
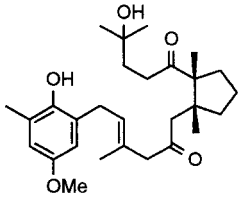
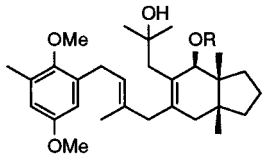


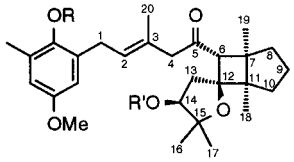
4a
MTPA-**4a** R = MTPA



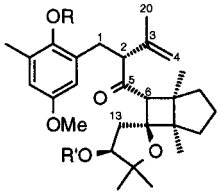
5



4b
MTPA-**4b** R = MTPA



6 R = R' = H
6a R = Me, R' = H
MTPA-**6a** R = Me, R' = MTPA



7 R = R' = H
7a R = Me, R' = H
MTPA-**7a** R = Me, R' = MTPA

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Table 1. Relevant $\Delta\delta$ Values ($\Delta\delta = \delta_S - \delta_R$) Obtained for the MTPA Esters of Compounds **1a**−**7a** and **4b**

H position	1a	2a	3	4a	4b	6a	7a
1-H_a	0.05	0.05	0.06				
1-H_b	0.10	0.09	0.09				
2	0.06	0.09	0.09				
4-H_a	0.07	0.06	0.06	0.15	0.04		
4-H_b	0.05	0.03		−0.08	0.03		
5	−0.02	−0.03	−0.02				
6	−0.17	−0.16	−0.14				0.02
8	−0.22	−0.04					
9	−0.07	−0.03					
10	−0.10		0.03				
12	−0.07		0.07	0.38	0.02		
13-H_a	0.06		0.02				
13-H_b	0.04					0.12	0.13
14-H_a	0.11		0.03	−0.07	0.04	0.07	0.10
14-H_b				0.03	0.03		
16	0.07		−0.10	0.09	0.09	−0.03	−0.08
17	0.05				0.06	−0.15	−0.04
18	−0.13	−0.02	0.38	0.32	−0.39	0.09	0.11
19	−0.02	−0.02	−0.23	0.02	−0.15	0.02	
20	0.08	0.08	0.08	−0.05	0.05		

spectrum for each of the (*R*)- and (*S*)-MTPA esters, followed by evaluation of the difference in chemical shift ($\Delta\delta = \delta_{S-\text{ester}} - \delta_{R-\text{ester}}$) of like sets of protons in the two esters. Finally, confirmation that the assigned protons with positive $\Delta\delta$ values are on the right side, and those with negative values on the left side, of the so-called MTPA plane in the idealized conformation of the esters. This empirical methodology has the advantage over others, such as the Horeau,[6] Mislow,[7] or the original Mosher method, in that it is dependent on many point comparisons (the chemical shifts of many like sets of protons) instead of only one parameter.

Results and Discussion

Compounds with open-chain (**1** and **2**), monocyclic (**3** and **5**), bicyclic (**4**), and tricyclic (**6** and **7**) diterpene moieties were selected for the present study, as representative of the most characteristic subgroups of the *Cystoseira* metabolites.

The first compound examined was **1**, isolated from *Cystoseira adriatica*,[8] which possesses two stereogenic centers, whose configurations had been unknown, at position 5 and 12 of its open-chain diterpenoid moiety. To avoid possible complications, such as cyclization to the corresponding chromane[9] or reaction of the free phenolic hydroxyl with MTPA-Cl, the 1′-phenolic group was methylated (MeI/K_2CO_3) to give **1a**. This was then reacted with MTPA-Cl to afford the diastereoisomeric esters (*R*)-MTPA−**1a** and (*S*)-MTPA−**1a**. Analysis of their 2D COSY spectra resulted in the complete assignment of the ^{1}H-NMR resonances, including those for the methyl groups on sp^2 carbons, which were identified from their allylic couplings. The diagnostic $\Delta\delta$ values for like protons of (*S*)- and (*R*)-MTPA−**1a** are reported in Table 1. The systematic arrangement of positive and negative $\Delta\delta$ values for the protons surrounding the two chiral centers, with the inversion of sign passing through them, allows a confident attribution of the *R* stereochemistry to both position 5 and 12. Therefore, the compound in question is (5*R*,12*R*)-(2*E*,6*E*,10*E*)-1-(2′-hydroxy-5′-methoxy-3′-methylphenyl)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraene-5,12-diol.

Analogously, the methyl ether **2a** obtained from **2**[7] by methylation was converted into the (*R*)- and (*S*)-MTPA esters. Comparison of the $\Delta\delta$ values for (*S*)-MTPA−**2a** and (*R*)-MTPA−**2a** (Table 1) allowed the determination of the stereochemistry at position 5, whereas the configuration at C-11 remains to be ascertained.

The study has been extended to the monocylic zosterdiol A (**3**), possessing, in addition to the oxygen-bearing chiral centers at position 5 and 12 present in **1**, an additional secondary hydroxyl group at position 14.[10] Treatment of **3** with MTPA-Cl afforded the diesters (*S*)-MTPA−**3** and (*R*)-MTPA−**3**, whose ^{1}H-NMR spectra were assigned with the aid of 2D COSY experiments. From the $\Delta\delta$ values of the two diesters, the stereochemistry of the three chiral centers was determined as *R*. It is noteworthy that the configuration of the C-5 carbinol center is the same in the three metabolites **1**, **2**, and **3**, a fact that reinforces the validity of the method.

Cystalgerone (**4**), possessing a bicyclo[4.3.0]nonane ring system,[11] was reduced with $NaBH_4$ to give two epimeric alcohols **4a** and **4b** in 40 and 4% yield, respectively. The structure of these compounds were confirmed by inspection of their ^{1}H-NMR spectra, which differ from that of the parent ketone by the presence of an additional signal (at 3.82 ppm in **4a** and 4.20 ppm in **4b**) due to the oxymethine proton at position 12. A 2D NMR analysis (COSY, HETCOR, long-range HETCOR) of **4a** resulted in the unambiguous assignment of all the resonances, while a NOESY spectrum showed that OH-12 is *cis*-oriented with respect to Me-18 and Me-19 (obviously the opposite *trans*-orientation has to be assumed for **4b**). Conversion of **4a** into the Mosher esters (*S*)-MTPA−**4a** and (*R*)-MTPA−**4a**, followed by analysis of the ^{1}H-NMR data, revealed that the absolute stereochemistry of the alcohol **4a** must be 7*R*,11*R*,12*R*, and this implies the 7*R*,11*R* configuration for cystalgerone **4**. The results obtained for MTPA−**4a** (Table 1) include three irregular $\Delta\delta$ values (+0.15 of 4-H, +0.03 of 14-H, and +0.09 of 16-H), therefore in order to avoid any uncertainty on the exact assignment of absolute configuration, we also applied the MTPA method on the isomer **4b**. This second determination confirms the C-12 configuration, assessing the absolute stereochemistry of epimer **4b** as 7*R*,11*R*,12*S*.

Determination of the absolute configuration of **4** allowed us to assess the stereochemistry of the monocyclic metabolite **5**, originally isolated from *Cystoseira algeriensis*.[12] Treatment of **5** with base resulted in the facile conversion into a compound spectroscopically indistinguishable from **4** and with the same specific optical rotation. Therefore, the 7*R*,11*R* absolute configuration can be confidently assigned to **5**.

Balearone **6**, having a bicyclo[3.2.0]heptane system spiro-fused with a tetrahydrofuran ring, exemplifies the structurally most complicated *Cystoseira* metabolites.[13−15] In this case also, methylation of the free phenolic hydroxyl to afford **6a** preceded coupling with each of the enantiomers of the Mosher acid chloride to yield the esters (*S*)-MTPA−**6a** and (*R*)-MTPA−**6a**. Unambiguous assignment of the proton resonances of these latter could not be obtained from a COSY spectrum and required a HETCOR experiment. Consideration of the chemical shift differences for the relevant protons (Table 1) demonstrates that the larger values are observed for Me-18 ($\Delta\delta = +0.09$) and for Me-17 of MTPA−**6a**. This is surprising in terms of the conventional "ideal" con-

formation of the modified Mosher's method, but can find an explanation in the observation that, in an energy-minimized three-dimensional molecular model, Me-17 and Me-18 reside in the right and left sides of the "MTPA plane", respectively. Therefore, the absolute stereochemistry at C-14 can be confidently assigned as *R* and, from the relative stereochemistry determined through X-ray analysis, the absolute configuration of the remaining centers in **6** must be 6*R*,7*R*,11*R*,12*S*. It is to be noted that the junction of the cyclopentane ring in **6** has the same absolute *cis* geometry as that in **4** and **5** and that the chiral center at position 14 has the same *R* configuration found in **3**.

The study of the irregular meroditerpenoid neobalearone **7**[16] followed the same route as for **6**. Initial methylation yielded the methyl derivative **7a**, which was reacted with MTPA-Cl to give (*S*)-MTPA−**7a** and (*R*)-MTPA−**7a**. The chemical shift differences (Table 1) closely paralleled those of **6a**, indicating an absolute configuration identical to that of balerone, i.e. 6*R*,7*R*,-11*R*,12*S*,14*R*.

In conclusion, the absolute configuration of the stereogenic carbinol centers in seven algal meroditerpenoids (**1**−**7**) from *Cystoseira* species has been determined using the refined Mosher strategy developed by Kakisawa and Kashman.[3] The results, in conjunction with information on the relative stereochemistry available from our earlier studies, allowed the complete assignment of the absolute stereochemistry for all of these compounds but **2**, which embodies a stereogenic center whose configuration remains to be assessed.

Experimental Section

General Experimental Procedures. Metabolites **1**−**7** were available from previous studies or isolated from the corresponding *Cystoseira* spp. as previously described.[7−16] NMR spectra were taken on a Bruker AC-250 spectrometer operating at 250.13 (^{1}H) and 62.9 (^{13}C) MHz using $CDCl_3$ solutions with TMS as internal standard. ^{13}C-DEPT and 2D NMR (COSY, HETCOR, long-range HETCOR, and NOESY) experiments were performed using standard pulse sequences of Bruker microprograms. Long-range HETCOR spectra were acquired using a polarization transfer delay optimized to observe $J = 10$ Hz. Mixing time in NOESY experiment was 0.8 s. (*R*)- and (*S*)-Mosher acid chloride [α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride, MTPA-Cl] were purchased from Aldrich or prepared from the corresponding acids by treatment with $SOCl_2$, paying attention that (*R*)-(+)-MTPA acid gives (*S*)-(+)-MTPA acid chloride and *vice versa*.

General Procedures for the Preparation of MTPA Esters. (*R*)- or (*S*)-MTPA chloride (2-fold millimolar excess over starting alcohol) was added to a solution of starting meroditerpenoid (usually 15−25 mg) in pyridine (200 μL), and the resulting mixture was allowed to stand at room temperature for 4 h. Triethylamine (12.4 μL) was then added, and after 10 min of standing the solvent was removed under vacuum. The residue was chromatographed over a sep-pak cartridge to give the purified Mosher ester.

Methylation of 1 To Give 1a. MeI (2 mL) and K_2CO_3 (1 g) were added to a solution of **1** (200 mg) in acetone (10 mL), and the resulting suspension was stirred under reflux for 15 h. Water was then added and the solution extracted with ether. The ether extract was dried over Na_2SO_4 and evaporated. The residue was subjected to preparative LC (Merck, Kieselgel 60, Et_2O/*n*-hexane, 1:1) to give pure **1a** (150 mg, 75%): ^{1}H-NMR δ 6.54 (bs, 2 H), 5.40 (t, $J = 6.9$ Hz, 1 H), 5.34 (t, $J = 6.2$ Hz, 1 H), 5.14 (d, $J = 8.0$ Hz, 1 H), 5.08 (t, $J = 6.3$ Hz, 1 H), 4.47 (m, 1 H), 3.96 (bt, $J = 6.5$ Hz, 1 H), 3.73 (s, 3 H), 3.67 (s, 3 H), 3.36 (d, $J = 7.1$ Hz, 2 H), 2.26 (s, 3 H), 1.78 (s, 3 H), 1.71 (s, 3 H), 1.68 (s, 3 H), 1.62 (s, 3 H), 1.60 (s, 3 H); ^{13}C-NMR δ 155.5 (s), 150.3 (s), 137.5 (s), 137.1 (s), 134.8 (s), 134.3 (s), 132.5 (s), 131.8 (s), 127.7 (d), 126.8 (d), 125.7 (d), 120.2 (d) 113.7 (d), 112.7 (d), 77.3 (d), 66.0 (d), 60.3 (q), 55.3 (q), 48.1 (t), 39.0 (t), 34.0 (t), 28.7 (t), 25.8 (q), 25.6 (t), 17.9 (q), 16.5 (q), 16.3 (q), 11.5 (q).

(*R*)-MTPA−1a. Preparation was according to the general procedure, with purification using a Florisil sep-pak cartridge, CH_2Cl_2/*n*-hexane (3:2) followed by Et_2O/*n*-hexane (8:92) as eluent: ^{1}H-NMR δ 7.49 (m, mtpa-ArH, 4 H), 7.37 (m, mtpa-ArH, 6 H), 6.54 and 6.46 (AB, $J = 3.1$ Hz, 3′-H and 5′-H, 2 H), 5.89 (m, H-5, 1 H), 5.52 (t, $J = 6.4$ Hz, H-10, 1 H), 5.36 (dd, $J = 8.0$, 6.1 Hz, H-12, 1 H), 5.30 (bt, $J = 7.8$ Hz, H-2, 1 H), 5.19 (d, $J = 9.1$ Hz, H-6, 1 H), 4.91 (t, $J = 7.3$ Hz, H-14, 1 H), 3.71 (s, 4′-OMe, 3 H), 3.64 (s, 1′-OMe, 3 H), 3.50 (bs, mtpa-OMe, 6 H), 3.29 (dd, $J = 15.4$, 7.8 Hz, H_a-2, 1 H), 3.19 (dd, $J = 15.4$, 6.9 Hz, H_b-2, 1 H), 2.43 (H_a-4, 1 H, from COSY), 2.40 (H_a-13, 1 H, from COSY), 2.26 (s, 6′-Me, 3 H), 2.25 (H_b-13, 1 H, from COSY), 2.24 (H_b-4, 1 H, from COSY), 2.12 (H-8, 2 H, from COSY), 2.07 (H-9, 2 H, from COSY), 1.78 (s, H-19, 3 H), 1.70 (s, H-20, 3 H), 1.62 (s, H-16, 3 H), 1.59 (s, H-18, 3 H), 1.53 (s, H-17, 3 H).

(*S*)-MTPA−1a. Preparation was according to the general procedure, with purification using a Florisil sep-pak cartridge, CH_2Cl_2/*n*-hexane (3:2) followed by Et_2O/*n*-hexane (8:92) as eluent: ^{1}H-NMR δ 7.47 (m, mtpa-ArH, 4 H), 7.37 (m, mtpa-ArH, 6 H), 6.54 and 6.48 (AB, $J = 3.1$ Hz, 3′-H and 5′-H, 2 H), 5.87 (m, H-5, 1 H), 5.42 (t, $J = 7.0$ Hz, H-10, 1 H), 5.36 (bt, $J = 7.2$ Hz, H-2, 1 H), 5.29 (dd, $J = 8.3$, 5.7 Hz, H-12, 1 H), 5.02 (d, $J = 9.1$ Hz, H-6, 1 H), 5.02 (H-14, 1 H, from COSY), 3.71 (s, 4′-OMe, 3 H), 3.65 (s, 1′-OMe, 3 H), 3.53 (bs, mtpa-OMe, 3 H), 3.47 (bs, mtpa-OMe, 3 H), 3.34 (dd, $J = 14.5$, 6.6 Hz, H_a-2, 1 H), 3.29 (dd, $J = 14.5$, 5.9 Hz, H_b-2, 1 H), 2.50 (H_a-4, 1 H, from COSY), 2.46 (H_a-13, 1 H, from COSY), 2.29 (H_b-13, 1 H, from COSY), 2.29 (H_b-4, 1 H, from COSY), 2.26 (s, 6′-Me, 3 H), 2.00 (H-9, 2 H, from COSY), 1.90 (H-8, 2 H, from COSY), 1.78 (s, H-20, 3 H), 1.76 (s, H-19, 3 H), 1.69 (s, H-16, 3 H), 1.58 (s, H-17, 3 H), 1.46 (s, H-18, 3 H).

Methylation of 2 To Give 2a. A suspension containing **2** (100 mg), MeI (1 mL), and Cs_2CO_3 (150 mg) in 6 mL of acetone was stirred under reflux for 20 h. Usual workup followed by PLC (silica gel, Et_2O/*n*-hexane, 2:3) afforded **2a** (30 mg): ^{1}H-NMR δ 6.54 and 6.55 (AB, $J = 2.9$ Hz, H-3′, H-5′, 2 H), 5.40 (t, $J = 6.8$ Hz, H-2, 1 H), 5.28 (bt, $J = 7.0$ Hz, H-14, 1 H), 5.15 (bd, $J = 7.5$ Hz, H-6, 1 H), 4.47 (m, H-5, 1 H), 3.73 (s, 4′-OMe, 3 H), 3.67 (s, 1′-OMe, 3 H), 3.37 (bd, $J = 6.8$, H-1, 2 H), 3.12 (d, $J = 7.0$ Hz, H-13, 2 H), 2.56 (m, H-11, 1 H), 2.26 (s, 6′-Me, 3 H), 1.78 (s, H-20, 3 H), 1.74 (s, H-16, 3 H), 1.65 (s, H-19, 3 H), 1.62 (s, H-17, 3 H), 1.05 (d, $J = 6.9$ Hz, H-18, 3 H); ^{13}C-NMR δ 212.8 (s), 155.6 (s), 150.4 (s), 148.7 (s), 137.8 (s), 135.4 (s), 134.8 (s), 132.5 (s), 131.8 (s), 127.6 (d), 127.0 (d), 116.1 (d), 113.8 (d),

112.8 (d), 66.0 (d), 60.4 (q), 55.3 (q), 48.2 (t), 45.6 (d), 41.0 (t), 39.4 (t), 32.5 (t), 28.9 (t), 25.7 (q), 25.2 (t), 18.1 (q), 16.5 (q), 16.4 (q).

(*R*)-MTPA−2a. Preparation was according to the general procedure, with purification using a Florisil sep-pak cartridge, CH_2Cl_2/*n*-hexane (2:3) as eluent: ^{1}H-NMR δ 7.49 (m, mtpa-ArH, 2 H), 7.37 (m, mtpa-ArH, 3 H), 6.54 and 6.47 (AB, J = 2.9 Hz, 3′-H and 5′-H, 2 H), 5.88 (m, H-5, 1 H), 5.28 (bt, J = 7.1 Hz, H-2 and H-14, 2 H), 5.16 (d, J = 9.3 Hz, H-6, 1 H), 3.73 (s, 4′-OMe, 3 H), 3.65 (s, 1′-OMe, 3 H), 3.50 (bs, mtpa-OMe, 3 H), 3.27 (dd, J = 15.5, 7.5 Hz, H_a-2, 1 H), 3.20 (dd, J = 15.5, 6.8 Hz, H_b-2, 1 H), 3.12 (d, J = 7.2 Hz, H-13, 2 H), 2.54 (m, H-11, 1 H), 2.41 (dd, J = 13.8, 7.7 Hz, H_a-4, 1 H), 2.26 (s, 6′-Me, 3 H), 2.24 (dd, J = 13.8, 5.1 Hz, H_b-4, 1 H), 1.98 (bt, J = 7.3 Hz, H-8, 2 H), 1.75 (s, H-19, 3 H), 1.74 (s, H-16, 3 H), 1.69 (s, H-20, 3 H), 1.61 (s, H-17, 3 H), 1.06 (d, J = 6.9 Hz, H-18, 3 H).

(*S*)-MTPA−2a. Preparation was according to the general procedure, with purification using a Florisil sep-pak cartridge, CH_2Cl_2/*n*-hexane (2:3) as eluent: ^{1}H-NMR δ 7.44 (m, mtpa-ArH, 2 H), 7.37 (m, mtpa-ArH, 3 H), 6.55 and 6.48 (AB, J = 3.0 Hz, 3′-H and 5′-H, 2 H), 5.85 (m, H-5, 1 H), 5.37 (t, J = 7.0 Hz, H-2, 1 H), 5.28 (t, J = 7.0 Hz, H-14, 1 H), 5.00 (d, J = 7.9 Hz, H-6, 1 H), 3.72 (s, 4′-OMe, 3 H), 3.65 (s, 1′-OMe, 3 H), 3.47 (bs, mtpa-OMe, 3 H), 3.32 (dd, J = 15.4, 8.0 Hz, H_a-2, 1 H), 3.29 (dd, J = 15.4, 7.3 Hz, H_b-2, 1 H), 3.12 (d, J = 7.2 Hz, H-13, 2 H), 2.51 (m, H-11, 1 H), 2.47 (dd, J = 14.2, 8.0 Hz, H_a-4, 1 H), 2.27 (dd, J = 14.2, 5.1 Hz, H_b-4, 1 H), 2.27 (s, 6′-Me, 3 H), 1.94 (bt, J = 7.6 Hz, H-8) 2 H), 1.77 (s, H-20, 3 H), 1.74 (s, H-16, 3 H), 1.73 (s, H-19, 3 H), 1.61 (s, H-17, 3 H), 1.04 (d, J = 7.0 Hz, H-18, 3 H).

(*R*)-MTPA−3. Preparation was according to the general procedure, with purification using a Florisil sep-pak cartridge, CH_2Cl_2/*n*-hexane (3:2) as eluent: ^{1}H-NMR δ 7.50 (m, mtpa-ArH, 4 H), 7.41 (m, mtpa-ArH, 3 H), 7.37 (m, mtpa-ArH, 3 H), 6.54 and 6.46 (AB, J = 2.9 Hz, 3′-H and 5′-H, 2 H), 5.88 (m, H-5, 1 H), 5.38 (t, J = 5.8 Hz, H-10, 1 H), 5.29 (t, J = 7.2 Hz, H-2, 1 H), 5.16 (d, J = 9.5 Hz, H-6, 1 H), 5.14 (dd, J = 7.0, 3.7 Hz, H-12, 1 H), 4.30 (t, J = 7.4 Hz, H-14, 1 H), 3.72 (s, 4′-OMe, 3 H), 3.64 (s, 1′-OMe, 3 H), 3.54 (bs, mtpa-OMe, 3 H), 3.50 (bs, mtpa-OMe, 3 H), 3.28 (dd, J = 15.4, 7.1 Hz, H_a-2, 1 H), 3.20 (dd, J = 15.4, 6.7 Hz, H_b-2, 1 H), 2.55 (m, H_a-13, 1 H), 2.41 (dd, J = 13.4, 7.4 Hz, H_a-4, 1 H), 2.26 (s, 6′-Me, 3 H), 1.74 (s, H-19, 3 H), 1.69 (s, H-20, 3 H), 1.37 (s, H-18, 3 H), 1.23 (s, H-16 and H-17, 6 H).

(*S*)-MTPA−3. Preparation was according to the general procedure, with purification using a Florisil sep-pak cartridge, CH_2Cl_2/*n*-hexane (3:2) as eluent: ^{1}H-NMR δ 7.48 (m, mtpa-ArH, 4 H), 7.40 (m, mtpa-ArH, 3 H), 7.36 (m, mtpa-ArH, 3 H), 6.55 and 6.48 (AB, J = 3.0 Hz, 3′-H and 5′-H, 2 H), 5.86 (m, H-5, 1 H), 5.41 (t, J = 6.8 Hz, H-10, 1 H), 5.38 (t, J = 7.1 Hz, H-2, 1 H), 5.21 (dd, J = 6.9, 3.9 Hz, H-12, 1 H), 5.02 (d, J = 9.2 Hz, H-6, 1 H), 4.33 (t, J = 7.6 Hz, H-14, 1 H), 3.71 (s, 4′-OMe, 3 H), 3.65 (s, 1′-OMe, 3 H), 3.53 (bs, mtpa-OMe, 3 H), 3.47 (bs, mtpa-OMe, 3 H), 3.34 (dd, J = 15.6, 7.3 Hz, H_a-2, 1 H), 3.29 (dd, J = 15.6, 7.1 Hz, H_b-2, 1 H), 2.57 (m, H_a-13, 1 H), 2.47 (dd, J = 13.8, 7.9 Hz, H_a-4, 1 H), 2.26 (s, 6′-Me, 3 H), 1.77 (s, H-20, 3 H), 1.75 (s, H-18, 3 H), 1.51 (s, H-19, 3 H), 1.23 (s, H-17, 3 H), 1.13 (s, H-16, 3 H).

Reduction of Ketone 4 To Give Alcohols 4a and 4b. A solution of **4** (560 mg) in EtOH (32 mL) was added to an excess of $NaBH_4$ (60 mg) and then allowed to stand for 45 min at room temperature. The solution was then quenched with H_2O and partitioned with Et_2O. The organic phase was dried, evaporated, and subjected to PLC (silica gel, Et_2O/CH_2Cl_2, 13:87) to give in eluting order **4b** (20 mg, 4%) and **4a** (200 mg, 40%).

Cystalgerolo 4a: ^{1}H-NMR δ 6.56 and 6.54 (AB, J = 3.1 Hz, H-5′ and H-3′, 2 H), 5.33 (t, J = 7.2 Hz, H-2, 1 H), 3.82 (s, H-12, 1 H), 3.74 (s, 4′-OMe, 3 H), 3.68 (s, 3′-OMe, 3 H), 3.36 (d, J = 7.2 Hz, H-1, 2 H), 3.12 (d, J = 14.2 Hz, H_a-4, 1 H), 2.95 (d, J = 14.4 Hz, H_a-14, 1 H), 2.52 (d, J = 14.2 Hz, H_b-4, 1 H), 2.11 (d, J = 14.4 Hz, H_b-14, 1 H), 2.27 (s, 6′-Me, 3 H), 1.96 and 1.85 (AB, J = 17.3 Hz, H-6, 2 H), 1.74 (H-9, 2 H, from HETCOR), 1.60 (s, H-20, 3 H), 1.57 and 1.33 (H-8, 2 H, from HETCOR), 1.30 (s, H-17, 3 H), 1.24 (H-10, 2 H, from HETCOR), 1.20 (s, H-16, 3 H), 0.98 (s, H-19, 3 H), 0.73 (s, H-18, 3 H); ^{13}C-NMR δ 155.5 (s, 4′), 150.3 (s, 1′), 135.8 (s, 5), 135.0 (s, 2′), 134.2 (s, 3), 131.7 (s, 6′), 128.9 (s, 13), 124.6 (d, 2), 113.8 (d, 5′), 112.4 (d, 3′), 77.9 (d, 12), 71.4 (s, 15), 60.4 (q, 1′-OMe), 55.3 (s, 4′-OMe), 47.3 (t, 14), 46.7 (s, 11), 45.0 (t, 4), 41.1 (t, 6), 40.8 (s, 7), 36.7 (t, 8), 31.5 (q, 17), 30.1 (t, 10), 28.4 (q, 16), 28.2 (t, 1), 24.8 (q, 19), 22.4 (q, 18), 19.1 (t, 9), 16.4 (q, 6′-Me), 15.7 (q, 20).

(*R*)-MTPA−4a. Preparation was according to the general procedure, with purification using a Florisil sep-pak cartridge, CH_2Cl_2/*n*-hexane (3:2) as eluent: ^{1}H-NMR δ 7.54 (m, mtpa-ArH, 2 H), 7.41 (m, mtpa-ArH, 3 H), 6.55 and 6.51 (AB, J = 2.9 Hz, H-5′ and H-3′, 2 H), 5.27 (t, J = 6.9 Hz, H-2, 1 H), 3.72 (s, 4′-OMe, 3 H), 3.66 (s, 3′-OMe, 3 H), 3.65 (bs, mtpa-OMe, 3 H), 3.34 (d, J = 7.5 Hz, H-1, 2 H), 3.32 (s, H-12, 1 H), 2.88 (d, J = 15 Hz, H_a-14, 1 H), 2.85 (d, J = 15.0 Hz, H_a-4, 1 H), 2.57 (d, J = 15.0 Hz, H_b-14, 1 H), 2.48 (d, J = 15.0 Hz, H_b-4, 1 H), 2.26 (s, 6′-Me, 3 H), 1.69 (s, H-20, 3 H), 1.60 (s, H-17, 3 H), 1.43 (s, H-16, 3 H), 0.77 (s, H-19, 3 H), 0.31 (s, H-18, 3 H).

(*S*)-MTPA−4a. Preparation was according to the general procedure, with purification using a Florisil sep-pak cartridge, CH_2Cl_2/*n*-hexane (3:2) as eluent: ^{1}H-NMR δ 7.53 (m, mtpa-ArH, 2 H), 7.40 (m, mtpa-ArH, 3 H), 6.55 and 6.52 (AB, J = 3.3 Hz, H-5′ and H-3′, 2 H), 5.27 (t, J = 7.1 Hz, H-2, 1 H), 3.72 (s, 4′-OMe, 3 H), 3.70 (bs, H-12, 1 H), 3.67 (s, 1′-OMe, 3 H), 3.53 (bs, mtpa-OMe, 3 H), 3.34 (d, J = 7.1 Hz, H-1, 2 H), 3.00 (d, J = 14.8 Hz, H_a-4, 1 H), 2.81 (d, J = 15.2 Hz, H_a-14, 1 H), 2.60 (d, J = 15.2 Hz, H_b-14, 1 H), 2.40 (d, J = 14.8 Hz, H_b-4, 1 H), 2.26 (s, 6′-Me, 3 H), 1.64 (s, H-20, 3 H), 1.60 (s, H-17, 3 H), 1.52 (s, H-16, 3 H), 0.79 (s, H-19, 3 H), 0.63 (s, H-18, 3 H).

Epicystalgerolo 4b: ^{1}H-NMR δ 6.55 and 6.54 (AB, J = 3.0 Hz, H-5′ and H-3′, 2 H), 5.32 (t, J = 6.9 Hz, H-2, 1 H), 4.20 (s, H-12, 1 H), 3.74 (s, 4′-OMe, 3 H), 3.68 (s, 1′-OMe, 3 H), 3.36 (d, J = 6.9 Hz, H-1, 2 H), 2.87 and 2.69 (AB, J = 14.3 Hz, H-4, 2 H), 2.59 and 2.47 (AB, J = 14.9 Hz, H-14, 2 H), 2.27 (s, 6′-Me, 3 H), 2.04 and 1.80 (AB, J = 17.4 Hz, H-6, 2 H), 1.63 (s, H-20, 3 H), 1.27 (s, H-17, 3 H), 1.17 (s, H-16, 3 H), 0.82 (s, H-19, 3 H), 0.77 (s, H-18, 3 H).

(*R*)-MTPA−4b. Preparation was according to the general procedure, with purification using a Florisil sep-pak cartridge, CH_2Cl_2/*n*-hexane (3:2) as eluent: ^{1}H-NMR δ 7.53 (m, mtpa-ArH, 2 H), 7.40 (m, mtpa-ArH, 3

H), 6.55 and 6.51 (AB, $J = 3.0$ Hz, H-5′ and H-3′, 2 H), 5.30 (t, $J = 7.4$ Hz, H-2, 1 H), 3.86 (bs, H-12, 1 H), 3.72 (s, 4′-OMe, 3 H), 3.66 (s, 1′-OMe, 3 H), 3.52 (bs, mtpa-OMe, 3 H), 3.33 (d, $J = 7.4$ Hz, H-1, 2 H), 3.04 (d, $J = 14.6$ Hz, H_a-4, 1 H), 2.81 (d, $J = 15.3$ Hz, H_a-14, 1 H), 2.42 (d, $J = 15.3$ Hz, H_b-14, 1 H), 2.41 (d, $J = 14.6$ Hz, H_b-4, 1 H), 2.27 (s, 6′-Me, 3 H), 1.67 (s, H-20, 3 H), 1.52 (s, H-17, 3 H), 1.35 (s, H-16, 3 H), 0.77 (s, H-19, 3 H), 0.67 (s, H-18, 3 H).

(*S*)-MTPA−4b. Preparation was according to the general procedure, with purification using a Florisil sep-pak cartridge, CH_2Cl_2/*n*-hexane (3:2) as eluent: ^{1}H-NMR δ 7.53 (m, mtpa-ArH, 2 H), 7.40 (m, mtpa-ArH, 3 H), 6.55 and 6.49 (AB, $J = 3.0$ Hz, H-5′ and H-3′, 2 H), 5.28 (t, $J = 7.3$ Hz, H-2, 1 H), 3.88 (bs, H-12, 1 H), 3.73 (s, 4′-OMe, 3 H), 3.69 (bs, mtpa-OMe, 3 H), 3.66 (s, 1′-OMe, 3 H), 3.32 (d, $J = 7.2$ Hz, H-1, 2 H), 3.08 (d, $J = 14.8$ Hz, H_a-4, 1 H), 2.85 (d, $J = 15.2$ Hz, H_a-14, 1 H), 2.45 (d, $J = 15.2$ Hz, H_b-14, 1 H), 2.44 (d, $J = 14.8$ Hz, H_b-4, 1 H), 2.26 (s, 6′-Me, 3 H), 1.72 (s, H-20, 3 H), 1.58 (s, H-17, 3 H), 1.44 (s, H-16, 3 H), 0.62 (s, H-19, 3 H), 0.28 (s, H-18, 3 H).

Treatment of 5 with Base To Give 4. A solution of **5** (300 mg) in EtOH (3 mL) was mixed with 3 mL of 6 N NaOH and stirred for 5 h at room temperature; usual workup, followed by PLC (Silica gel, Et_2O/*n*-hexane, 35:65), gave **4** (10 mg, 3%), identical in all respect to an authentic sample ($[\alpha]_D$ + 74.5 ($c = 1.2$, EtOH), lit.[11] $[\alpha]_D$ +75).

Methylation of 6 To Give 6a. A sample of **6** (200 mg) was treated as described above for compound **1a**. Usual workup followed by PLC (silica gel, Et_2O/*n*-hexane, 35:65) afforded **6a** (30 mg): ^{1}H-NMR δ 6.56 (bs, H-3′ and H-5′, 2 H), 5.36 (t, $J = 7.1$ Hz, H-2, 1 H), 3.94 (dd, $J = 8.8$, 6.5 Hz, H-14, 1 H), 3.75 (s, 4′-OMe, 3 H), 3.68 (s, 1′-OMe, 3 H); ^{13}C-NMR δ 207.9 (s), 155.5 (s), 150.3 (s), 134.5 (s), 131.8 (s), 129.8 (s), 128.2 (d), 114.0 (d), 112.6 (d), 81.3 (s), 79.9 (s), 78.3 (d), 60.6 (d), 60.5 (q), 55.9 (d), 55.4 (q), 52.6 (s), 46.0 (s), 28.6 (t), 27.5 (q), 24.2 (t), 22.3 (q), 19.0 (q), 17.0 (q), 16.7 (q), 16.4 (q).

(*R*)-MTPA−6a. A sample of **6a** (25 mg) was treated according to the general procedure, with purification using two Florisil sep-pak cartridges (CH_2Cl_2/*n*-hexane, 3:2, followed by Et_2O/*n*-hexane, 8:92) to give (*R*)-MTPA−**6a** (19 mg): ^{1}H-NMR δ 7.52 (m, mtpa-ArH, 2 H), 7.42 (m, mtpa-ArH, 3 H), 6.57 (bs, H-3′ and H-5′, 2 H), 5.38 (t, $J = 7.1$ Hz, H-2, 1 H), 5.19 (dd, $J = 6.9$, 6.8 Hz, H-14, 1 H), 3.76 (s, 4′-OMe, 3 H), 3.68 (s, 1′-OMe, 3 H), 3.54 (bs, mtpa-OMe, 3 H), 3.39 (d, $J = 7.1$ Hz, H-1, 2 H), 3.20 (dd, $J = 13.5$, 6.8 Hz, H_a-13, 1 H), 3.10 (s, H-6, 1 H), 2.95 (s, H-4, 2 H), 2.27 (s, 6′-Me, 3 H), 1.90 (dd, $J = 13.5$, 6.9 Hz, H_b-13, 1 H), 1.73 (s, H-20, 3 H), 1.18 (s, H-16, 3 H), 1.07 (s, H-17, 3 H), 0.90 (s, H-19, 3 H), 0.74 (s, H-18, 3 H); ^{13}C-NMR δ 207.6 (s, 5), 166.0 (s, mtpa-CO), 155.6 (s, 4′), 150.4 (s, 1′), 134.5 (s), 132.0 (s), 131.9 (s), 129.7 (s), 129.6 (d, mtpa), 128.4 (d, 2 and mtpa), 127.5 (d, mtpa), 123.2 (q, mtpa-CF_3, $J_{C-F} = 288.5$ Hz), 114.1 (d, 5′), 112.5 (d, 3′), 84.7 (q, mtpa-C-OMe, $J_{C-F} = 26.8$ Hz), 82.5 (d, 14), 82.2 (s, 12), 80.0 (s, 15), 60.5 (q, 1′-OMe), 60.45 (d, 6), 55.7 (t, 4), 55.4 (q, 4′-OMe, mtpa-OMe), 52.6 (s, 11), 46.2 (s, 7), 40.7 (t, 8), 35.7 (t, 10), 33.4 (t, 13), 28.6 (t, 1), 27.5 (q, 16), 24.2 (t, 9), 23.3 (q, 17), 18.6 (q, 18), 17.0 (q, 19), 16.7 (q, 20), 16.4 (q, 6′-Me).

(*S*)-MTPA−6a. Preparation was according to the general procedure, with purification using a Florisil sep-pak cartridge, CH_2Cl_2/*n*-hexane (3:2) followed by Et_2O/*n*-hexane (8:92) as eluent: ^{1}H-NMR δ 7.52 (m, mtpa-ArH, 2 H), 7.41 (m, mtpa-ArH, 3 H), 6.57 (bs, H-3′ and H-5′, 2 H), 5.38 (t, $J = 7.2$ Hz, H-2, 1 H), 5.26 (dd, $J = 7.3$, 6.9 Hz, H-14, 1 H), 3.76 (s, 4′-OMe, 3 H), 3.68 (s, 1′-OMe, 3 H), 3.54 (bs, mtpa-OMe, 3 H), 3.39 (d, $J = 7.2$ Hz, H-1, 2 H), 3.20 (dd, $J = 13.3$, 6.9 Hz, H_a-13, 1 H), 3.10 (s, H-6, 1 H), 2.95 (s, H-4, 2 H), 2.27 (s, 6′-Me, 3 H), 2.02 (dd, $J = 13.3$, 7.3 Hz, H_b-13, 1 H), 1.73 (s, H-20, 3 H), 1.15 (s, H-16, 3 H), 0.92 (s, H-17 and H-19, 6 H), 0.83 (s, H-18, 3 H); ^{13}C-NMR δ 207.5 (s, 5), 165.8 (s, mtpa-CO), 155.6 (s, 4′), 150.4 (s, 1′), 134.4 (s), 132.2 (s), 131.8 (s), 129.6 (s), 129.6 (d, mtpa-Ar), 128.5 (d, mtpa-Ar), 128.4 (d, 2), 127.4 (d, mtpa-Ar), 123.1 (q, mtpa-CF_3, $J_{C-F} = 288.5$ Hz), 114.2 (d, 5′), 112.5 (d, 3′), 84.4 (q, mtpa-C-OMe, $J_{C-F} = 26.8$ Hz), 82.1 (s, 12), 82.0 (d, 14), 80.2 (s, 15), 60.5 (d, 6), 60.4 (q, 1′-OMe), 55.8 (t, 4), 55.4 (q, 4′-OMe, mtpa-OMe), 52.6 (s, 11), 46.2 (s, 7), 40.9 (t, 8), 35.7 (t, 10), 33.5 (t, 13), 28.7 (t, 1), 27.7 (q, 16), 24.2 (t, 9), 23.1 (q, 17), 18.8 (q, 18), 17.1 (q, 19), 16.8 (q, 20), 16.5 (q, 6′-Me).

Methylation of 7 To Give 7a. A sample of **7** (100 mg) was treated as described above for compound **1a**. Usual workup followed by PLC (silica gel, Et_2O/*n*-hexane, 15:85) afforded **7a** (45 mg): ^{1}H-NMR δ 6.71 and 6.56 (AB, $J = 3.1$ Hz, H-5′ and H-3′, 2 H), 4.95 (s, H_a-4, 1 H), 4.81 (bs, H_b-4, 1 H), 3.75 (s, 1′-OMe, 3 H), 3.69 (s, 4′-OMe, 3 H), 3.39 (dd, $J = 9.1$, 3.2 Hz, H-2, 1 H), 3.05 (dd, $J = 13.0$, 9.6 Hz, H_a-1, 1 H), 2.99 (s, H-6, 1 H), 2.65 (dd, $J = 13.0$, 3.7 Hz, H_b-1, 1 H), 2.57 (t, $J = 5.0$ Hz, 1 H), 2.42 (dd, $J = 12.5$, 6.3 Hz, H_a-13, 1 H), 2.23 (s, 6′-Me, 3 H), 1.72 (s, H-20, 3 H), 0.95 (s, H-16, 3 H), 0.89 (s, H-17, 3 H), 0.86 (s, H-19, 3 H), 0.84 (s, H-18, 3 H); ^{13}C-NMR δ 207.0 (s), 155.0 (s), 151.1 (s), 141.8 (s), 134.6 (s), 132.1 (s), 114.8 (t), 114.6 (d), 81.9 (s), 79.5 (s), 77.3 (d), 64.5 (d), 62.1 (d), 60.3 (q), 55.6 (q), 52.5 (s), 44.6 (s), 40.9 (t), 36.0 (t), 34.6 (t), 30.7 (t), 27.1 (q), 24.3 (t), 21.9 (q), 20.7 (q), 18.9 (q), 17.0 (q), 16.3 (q).

(*R*)-MTPA−7a. A sample of **7a** (15 mg) was treated according to general procedure, with purification using a Florisil sep-pak cartridge (CH_2Cl_2/*n*-hexane, 2:3) to give (*R*)-MTPA−**7a** (12 mg): ^{1}H-NMR δ 7.49 (m, mtpa-ArH, 2 H), 7.40 (m, mtpa-ArH, 3 H), 6.55 and 6.51 (AB, $J = 2.2$ Hz, H-5′ and H-3′, 2 H), 4.93 (bs, H_a-4, 1 H), 4.81 (bs, H_b-4, 1 H), 4.67 (t, $J = 6.2$ Hz, H-14, 1 H), 3.70 (s, 1′-OMe, 3 H), 3.66 (s, 4′-OMe, 3 H), 3.52 (s, mtpa-OMe, 3 H), 3.48 (t, $J = 7.0$ Hz, H-2, 1 H), 3.11 (s, H-6, 1 H), 3.06 (dd, $J = 13.3$, 7.0 Hz, H_a-1, 1 H), 2.75 (dd, $J = 14.1$, 6.5 Hz, H_a-13, 1 H), 2.66 (dd, $J = 13.5$, 6.5 Hz, H_b-1, 1 H), 2.22 (s, 6′-Me, 3 H), 1.84 (dd, $J = 14.2$, 6.0, H_b-13, 1 H), 1.65 (s, H-20, 3 H), 1.02 (s, H-16, 3 H), 0.94 (s, H-17, 3 H), 0.87 (s, H-19, 3 H), 0.68 (s, H-18, 3 H).

(*S*)-MTPA−7a. Preparation was according to the general procedure, with purification using a Florisil sep-pak cartridge, CH_2Cl_2/*n*-hexane (2:3) as eluent to afford 11 mg of **7a**: ^{1}H-NMR δ 7.49 (m, mtpa-ArH, 2 H), 7.40 (m, mtpa-ArH, 3 H), 6.55 and 6.54 (AB, $J = 2.0$ Hz, H-3′ and H-5′, 2 H), 4.93 (s, H_a-4, 1 H), 4.81 (s, H_b-4, 1 H),4.77 (t, $J = 6.5$, H-14, 1 H), 3.71 (s, 1′-OMe, 3 H), 3.67 (s, 4′-OMe, 3 H), 3.51 (s, mtpa-OMe, 3 H), 3.48 (t, $J = 7.0$ Hz, H-2, 1 H), 3.13 (s, H-6, 1 H), 3.06 (dd, $J = 13.5$, 7.0 Hz, H_a-1, 1 H), 2.75 (dd, $J = 14.0$, 6.5 Hz, H_a-13, 1 H), 2.66 (dd, $J = 13.5$, 7.0 Hz, H_b-1, 1 H), 2.23 (s, 6′-Me, 3

H), 1.97 (dd, J = 14.0, 6.2, H_b-13, 1 H), 1.65 (s, H-20, 3 H), 0.94 (s, H-16, 3 H), 0.90 (s, H-17, 3 H), 0.87 (s, H-19, 3 H), 0.79 (s, H-18, 3 H).

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