Isolation, Structural Elucidation, and Synthesis of Curcutetraol

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The new natural products (+)-curcutetraol and (–)-curcutriolamide were isolated from the bacterium CNH-741 and the fungus CNC-979, isolated from marine sediment. (+)-Curcutetraol is a polar compound and contains a tertiary benzylic alcohol moiety at the single stereogenic center, which was retained without racemization by avoiding chromatography on silica. The absolute configuration of (+)-curcutetraol was determined by comparison of its experimental CD spectrum with the spectra predicted by quantum-chemical CD calculations. Phenolic bisabolane sesquiterpenoids from marine sources were previously known only from gorgonians and sponges. A short total synthesis of racemic curcutetraol has been developed.

Introduction

Microorganisms isolated from the marine environment have been the source of an impressive variety of biologically active natural products.[1] In particular, the possibility of fermentation of microorganisms promises to provide large amounts of any particular secondary metabolite for further studies. Consequently, there is also pronounced interest in the discovery of microbial natural products that are biogenetically related to metabolites isolated earlier from difficult-to-grow marine invertebrates. In the course of our investigations on the constituents of microorganisms collected from marine sediments, we have found two new sesquiterpenes closely related to natural products isolated earlier from gorgonians and sponges (Figure 1).

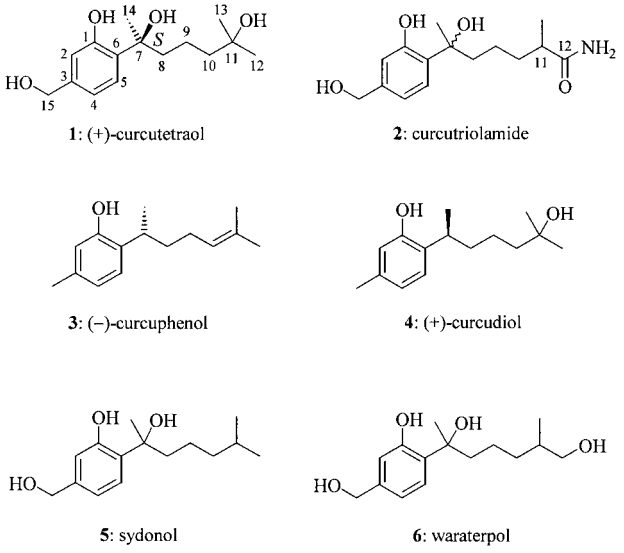

Figure 1. Bisabolane-type sesquiterpenoids sharing a substituted *m*-cresol partial structure

Results and Discussion

The EtOAc extract obtained from an overall 20 L fermentation of a co-culture of the bacterial strain CNH-741 and the fungus CNC-979 (collected from marine sediment at a depth of one meter in the Bahamas) was subjected to repeated chromatography on RP-18 and RP-2 stationary phases rather than silica gel. The new natural products **1** and **2** were isolated in 14.8 and 2.4 mg quantities, respectively. The NMR spectroscopic data of compounds **1** and **2** are summarized in Table 1. HREIMS analysis of the major compound **1** gave the molecular formula $C_{15}H_{24}O_4$. Connectivity information derived from HSQC, COSY, and HMBC experiments unambiguously determined its constitution, with two tertiary, one phenolic, and one primary alcohol moieties.

The ^{13}C NMR spectrum of the minor compound **2** shows, in part, doubled or broadened signals, which indicates the presence of two diastereomers and, thereby, of at least two stereogenic centers. As the major difference with **1**, a new methyl doublet at $\delta_H = 1.05$ ppm is observed in the ^1H NMR spectrum of **2**, which couples to a methine

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Table 1. ^{13}C and ^{1}H NMR spectroscopic data of (+)-curcutetraol (**1**) and (−)-curcutriolamide (**2**) in CD_3OD; assignments were made on the basis of HMBC, HSQC, COSY, and DEPT experiments; coupling constants are given in Hz; nr: not resolved.

#	(+)-Curcutetraol (**1**)			(−)-Curcutriolamide (**2**)		
	δ(^{13}C)	δ(^{1}H) (mult., *J*)	HMBC (#)	δ(^{13}C)	δ(^{1}H) (mult., *J*)	HMBC (#)
1	157.0	–	–	156.9[a]	–	–
2	116.1	6.74 (d, 1.6)	1, 4, 6, 15	116.0[b]	6.73 (s)	1, 4, 6, 15
3	142.8	–	–	142.6	–	–
4	118.8	6.77 (dd, 7.7, 1.6)	2, 15, 6	118.6[a]	6.76 (d, 7.7)	2, 6, 15
5	127.6	7.10 (d, 7.7)	1, 2,[c] 3, 7	127.4[a]	7.08 (d, 7.7)	1, 2[a], 3, 7
6	131.3	–	–	131.0[b]	–	–
7	78.0	–	–	77.8[a]	–	–
8	44.6	1.79, 1.91 (nr)	6, 7, 9, 10, 14	44.6	1.79, 1.91 (nr)	7, 9
9	20.1	1.32 (nr)	8, 10	22.9[b]	1.30 (nr)	8, 10
10	45.1	1.39 (nr)	8,9, 11, 12, 13	35.5[b]	1.30 (nr)	9, 11
11	71.4	–	–	41.3	2.27 (nr)	9,[c] 10, 12, 13[c]
12	29.1	1.09 (s)	10, 11	182.5	–	–
13	29.1	1.10 (s)	10, 11	18.1[a]	1.05 (d, 6.7)	10, 11, 12
14	28.3	1.58 (s)	6, 7, 8	29.1	1.56 (s)	6, 7, 8, 9[c]
15	64.8	4.50 (s)	2, 3, 4	64.7[a]	4.50 (s)	2, 3, 4

[a] Broadened. [b] Split. [c] Weak intensity.

proton. Additionally, a carbonyl carbon signal is observed at δ_C = 182.5 ppm. The IR band at 1648 cm^{-1} suggested the presence of an amide group. HRMS analysis was possible only in the negative FAB mode and revealed the molecular formula $C_{15}H_{23}NO_4$. Upon treatment with Ac_2O/pyridine, three acetyl moieties were incorporated [HRFAB(+)MS], thus confirming the presence of three free hydroxy groups in **2**.

The two new natural products **1** and **2** belong to the extended group of bisabolane-type sesquiterpenoids. The underlying aromatic hydrocarbon α-curcumene, which had earlier been discovered in plants,[2] was the first bisabolane-type sesquiterpenoid isolated from marine organisms, the gorgonians *Muricia elongata* and *Plexaurella nutans*.[3] The first phenolic bisabolane sesquiterpenoids from marine organisms were reported by McEnroe and Fenical, who described (−)-curcuphenol (**3**), the corresponding (−)-curcuhydroquinone, and the oxidized (−)-curcuquinone from the gorgonian coral *Pseudopterogorgia rigida*.[4] Later, several groups isolated (+)-curcudiol (**4**) from the marine sponges *Didiscus* sp.,[5] *Epipolasis* sp.,[6] and *Arenochalina* sp.[7] Overall, sponges have been the most frequent sources of phenolic bisabolane sesquiterpenoids from marine organisms.[8] Curcutetraol (**1**), with its four hydroxyl groups, is the most polar member of the family, and curcutriolamide (**2**) is the first amide in the series. Incorporation of nitrogen into marine bisabolane sesquiterpenoids has only been observed for nonaromatized compounds.[7,9,10] To date, none of the bisabolane sesquiterpenoids isolated from the marine environment have been found to possess a tertiary alcohol moiety in the *o*-position of a phenol. However, fungi isolated from land sources have provided a few structural analogs of cuructetraol (**1**). Among them, sydonol (**5**), from *Aspergillus* sp.[11] and waraterpol (**6**), from *Penicillium* sp.,[12] are the most similar to compounds **1** and **2**. In both cases, the absolute configuration of the tertiary, benzylic alcohol moiety has not yet been elucidated and remains a challenging task.

A carbenium intermediate formed upon protonation and subsequent dehydration of **1** should be stabilized, thus exposing the 7-position to facile exchange with nucleophiles. Indeed, when a pure sample was passed through a normal-phase chromatography column with methanol-containing solvent mixtures as the eluent, incorporation of a methoxy group at the tertiary benzylic position took place. Earlier, a 2,2,6,6-tetrasubstituted tetrahydropyran has been reported to be formed upon treatment of 15-deoxycurcutetraol with dilute aqueous H_2SO_4.[13] Upon using solely reversed stationary phases, and strictly excluding acid, we were able to isolate optically active (+)-curcutetraol (**1**). HPLC employing the chiral stationary phases Chiralpak AD-H and Chiralcel OJ was monitored by a CD (circular dichroism) detector and the CD trace was positive over the entire peak. This indicates high enantiomeric purity of the natural product **1**.[14]

Independently, a series of ^{1}H NMR experiments in the presence of the shift reagent $Pr(hfc)_3$ was performed. $Pr(hfc)_3$ has proven to be useful with regard to the determination of the enantiomeric excess of the tertiary alcohol tramadol,[15] and has been reported to be superior to $Eu(hfc)_3$.[16] Figure 2 shows the upfield shifts of the signals corresponding to the aromatic protons 2-H, 4-H, and 5-H, and to the hydroxymethyl protons 15-H. The shift experiment was performed at 200 MHz because, under fast-exchange conditions, line broadening is proportional to the square of the magnetic field strength.[16]

The presence of only three signals for the aromatic protons at all tested concentrations of the shift reagent indicated that only one kind of complex is formed. None of the aromatic signals evolved into more than one peak. The signal of the hydroxymethyl group, which appears to take part directly in complex formation, rapidly moved upfield and could not be identified any more at higher concentrations of $Pr(hfc)_3$. We thus concluded that (+)-curcutetraol (**1**) had been isolated in high enantiomeric purity. This was corroborated by the high intensities of the two CD peaks of

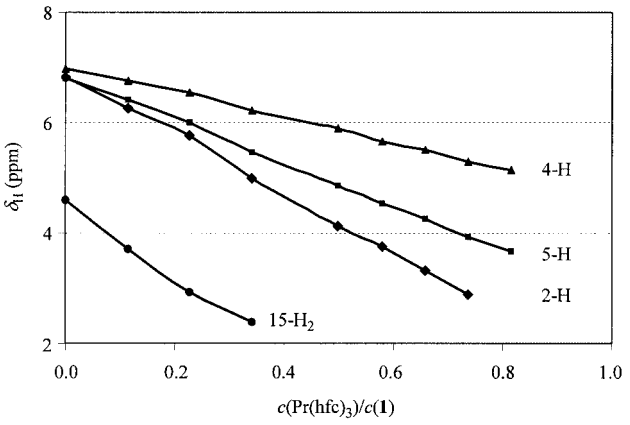


Figure 2. High-field shifts of the aromatic protons 2-H, 4-H, and 5-H on addition of the chiral NMR shift reagent Pr(hfc)$_3$ to a solution of (+)-curcutetraol (**1**) in $CDCl_3$ (200 MHz)

(+)-curcutetraol (**1**) at 281 nm ($\Delta\varepsilon$ = +3.5) and 229 nm ($\Delta\varepsilon$ = +2.6) in acetonitrile.

The single stereogenic center of (+)-curcutetraol (**1**) is situated at a tertiary, benzylic position. Extensive work on Mosher and related esters only covers the stereochemical

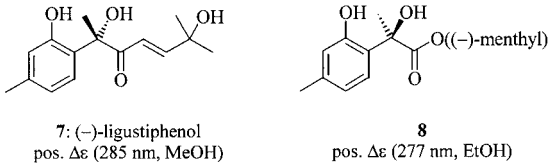


Figure 3. Cotton effects and assignments of the absolute configurations of the bisabolane sesquiterpenoid (−)-ligustiphenol (**7**) and of the atrolactic ester **8**

analysis of secondary alcohols.[17] Comparison of the specific optical rotation of **1** with those of structurally similar, but not closely analogous, compounds[18,19] can hardly be trusted, and more-significant CD data suitable for comparison have only been described for compounds possessing a carbonyl oxygen at C-8, which facilites the formation of additional hydrogen bonds. For the plant sesquiterpenoid (−)-ligustiphenol (**7**, $\Delta\varepsilon$ = +3.2, λ = 285 nm), a 7*S* configuration has been deduced by comparing its CD bands with those of α-hydroxy-α-phenylketones (Figure 3).[19,20] However, the opposite (*R*)-configuration has been assigned to several atrolactic esters, such as **8**, which also show positive CD bands at about 280 nm (ethanol) and are hydroxylated

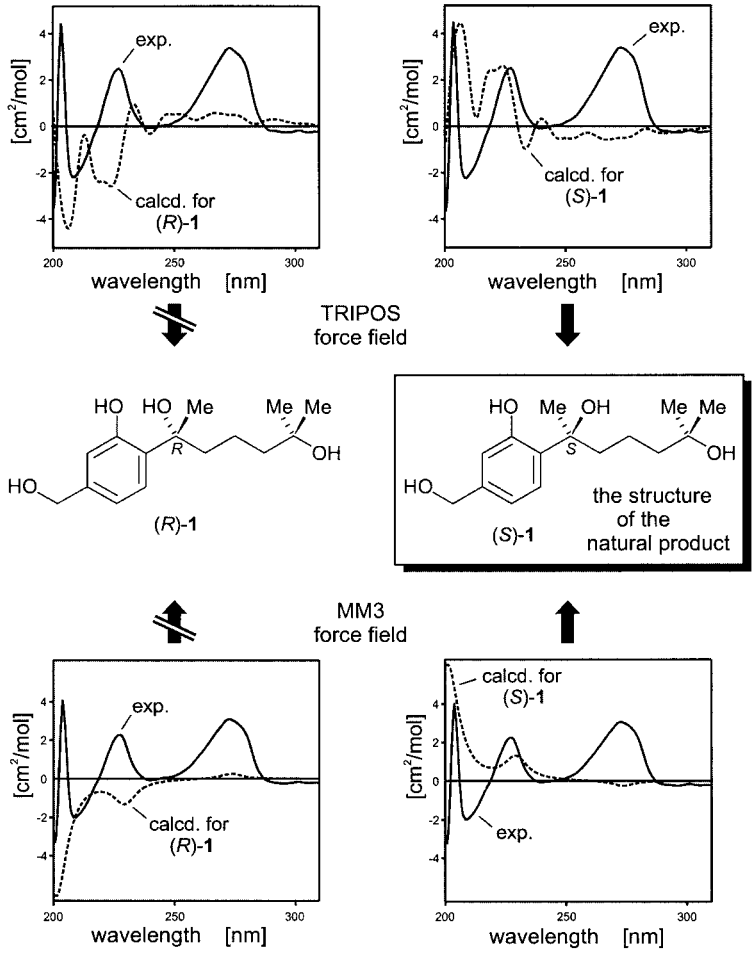


Figure 4. Assignment of the absolute configuration of curcutetraol (**1**) by comparison of the experimental CD spectrum (in MeCN) with the spectra calculated for (*R*)-**1** (left) and (*S*)-**1** (right) following the MD-CNDO/2S approach, using the TRIPOS (top) and the MM3 force fields (bottom), with subsequent calculation of the CD spectra using the CNDO/2S method

in the phenyl *o*-position, too.[21] Compounds **7** and **8** are not fully suitable for comparison. However, they are among the only tertiary benzylic alcohols with a phenolic hydroxy group in the *o*-position for which CD data can be found in the literature.

Therefore, the absolute configuration of curcutetraol (**1**) was determined by quantum-chemical circular dichroism (CD) investigations.[22−25] Due to the flexibility of **1** our first approach was based on molecular dynamics (MD) simulations,[23] arbitrarily starting with the (*R*)-enantiomer and using the TRIPOS[26] and the MM3[27] force fields at virtual temperatures of 500 and 400 K, respectively. In both cases 1000 geometries were extracted from the trajectories of motion. For all of these geometries the single CD spectra were calculated using the semiempirical CNDO/2S[28] method. These spectra were then summed to give the overall theoretical CD curves, which, after "UV correction",[22] showed a reversed image behavior in comparison to the measured CD spectrum for both force fields (Figure 4, left), while the spectrum calculated for the (*S*)-enantiomer was in good accordance with the experimental one (Figure 4, right).[29]

To verify the (*S*)-configuration of the stereocenter of **1**, a second computational CD study was launched, now based on a conformational analysis. In the course of this approach, twelve conformers were found within an energetic cut-off of 3 kcal/mol above the global minimum, using the semiempirical AM1[30] approach. For each conformer the respective CD spectrum was calculated, now with the OM2[31] method, followed by their addition according to Boltzmann statistics. After "UV correction",[22] the overall theoretical CD curve thus obtained for the (*R*)-enantiomer was again opposite to the experimental spectrum (Figure 5, left), while the overall CD curve calculated for the (*S*)-enantiomer again gave a good agreement with the measured one (Figure 5, right). Consequently, the absolute stereostructure of **1** was assigned to be *S* as proven by two different theoretical approaches.

The new, nitrogen-containing natural product (−)-curcutriolamide (**2**), which was isolated as a mixture of diastereomers, possesses two stereogenic centers at C-7 and C-11. The CD spectrum of **2** shows a flat line above 230 nm indicating the presence of both epimers at the benzylic position C-7. (−)-Curcutriolamide (**2**) shows optical activity

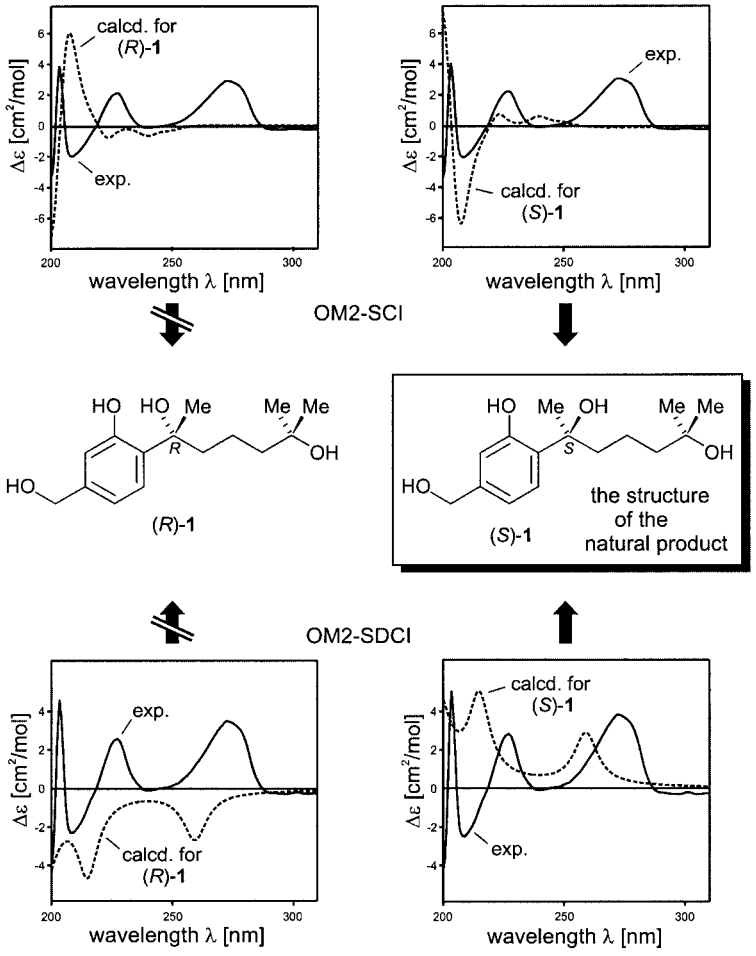
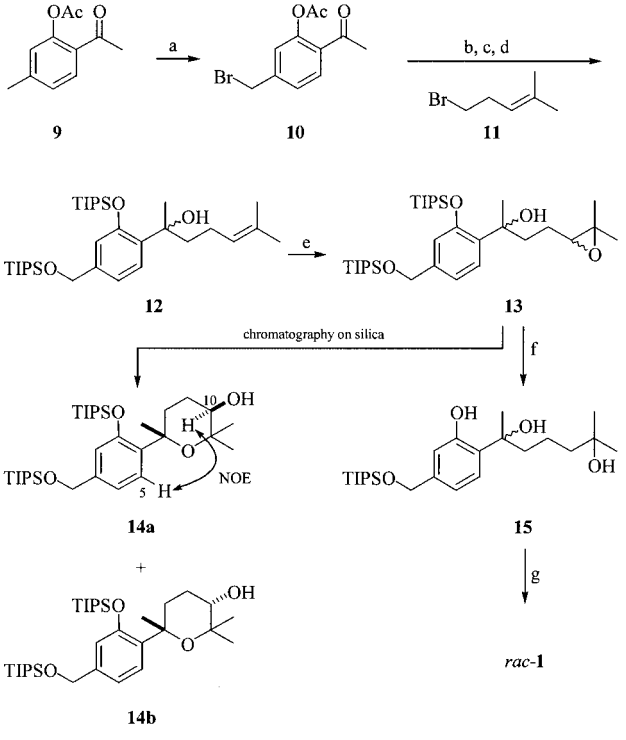


Figure 5. Confirmation of the absolute configuration of the stereocenter of **1** as *S* by comparison of the CD spectrum measured in MeCN with the CD curves computed for (*R*)-**1** (left) and (*S*)-**1** (right) following the conformational-analysis-OM2 approach, considering SCI (top) and SDCI calculations (bottom)

and there should be a preference with regard to one of the two possible configurations at C-11. Curcutriolamide (**2**) may form a seven-membered ring intermediate by intramolecular nucleophilic attack of the amide oxygen or nitrogen at C-7, leading to the formation of two diastereomers of **2**. A similar reaction has been observed for waraterpol (**6**).[12] Due to scarce amounts of available material, we were not able to derivatize the primary amide in order to determine the configuration of the remaining stereocenter C-11.

We also developed a short total synthesis of racemic curcutetraol (*rac*-**1**), which secures the ready availability of the natural product (Scheme 1). The sequence starts with *o*-hydroxy-*p*-methylacetophenone, which has to be oxygenated in the benzylic position. While direct bromination of the free phenol occurs at the aromatic ring, the acetylated phenol **9** is brominated in the benzylic position upon treatment with NBS, to afford **10**. This was followed by saponification of the ester and the benzylic bromide with NaOH. For the subsequent Grignard reaction employing homoprenyl bromide (**11**), TIPS protecting groups had to be introduced. The tertiary alcohol **12** already possesses the complete sesquiterpenoid skeleton. Epoxidation of **12** with buffered *m*-CPBA provided the sensitive compound **13**, which had to be chromatographed on a reversed phase stationary phase (RP-18). If **13** is chromatographed on silica, the two diastereomeric tetrahydropyrans **14a** and **14b** are formed in a ratio of 3:2 with regard to the configuration at position 10. An NOE correlation between the protons 5-H and 10-H, which can only be present in diastereomer **14a**, allowed the unambiguous assignment (Scheme 1). Of course, the very low diastereoselectivity of the previous epoxidation does not hamper the synthesis because the stereogenic center at C-10 is removed on regioselective reduction of the epoxide **13** with $LiAlH_4$. Simultaneously, one of the two TIPS protecting groups is lost. Generally, aryl silyl ethers can cleaved with various nucleophiles, while alkyl silyl ethers are stable under those conditions.[32] Therefore, we assigned the regioisomer **15** to the reduction product. The sequence was completed by cleavage of the remaining aliphatic silyl ether with TBAF to provide *rac*-curcutetraol (*rac*-**1**) in seven steps starting from **9**.



Scheme 1. Synthesis of *rac*-curcutetraol (**1**): (a) NBS, AIBN, CCl_4, reflux, 8 h, 63%; (b) 2 M NaOH, room temp., 12 h, 54%; (c) TIPSCl, imidazole, DMF, room temp., 12 h, 87%; (d) **11**, Mg, Et_2O, room temp. to 50 °C, 2 h, 74%; (e) *m*-CPBA, Na_2HPO_4, THF, room temp., 12 h, 87%; (f) $LiAlH_4$, THF, 0 °C to room temp., 30 min, 21%; (g) TBAF, THF, room temp., 3 h, 56%

Experimental Section

General: Optical rotations were measured on a Perkin−Elmer 241 Polarimeter. IR and UV spectra were recorded on a Perkin−Elmer Spectrum 1000 and a Perkin−Elmer Lambda 16 UV/Vis spectrometer, respectively. CD spectra were obtained on a Jobin Yvon CD6 circular dichroism spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 600 (600.19 and 150.92 MHz, respectively) or a Varian VRX 400S (399.9 MHz and 100.6 MHz, respectively) spectrometer, with the solvent (CD_3OD: δ_C = 49.0 ppm; δ_H = 3.31 ppm) as the internal standard. Mass spectra were recorded on Finnigan MAT95Q and Varian MAT-311 spectrometers. HPLC isolations were performed using Varian Prep Star 218 or Varian Pro Star 320 UV/Vis detectors and an ELSD Sedex 75 light-scattering detector. As columns, Merck LiChroprep RP-18, LiChroprep RP-2 (each 25−40 μm, 250 × 210), and LiChroprep Si-60 (25−40 μm, 250 × 10 mm) were used. The position numbers of carbon atoms are given according to Figure 1.

Fermentation and Isolation: The bacterial strain CNH-741 and the fungus CNC-979 were isolated from a sediment sample (collected at a depth of one meter, Bahamas) using serial dilution and plating techniques on medium A1 (1.6% agar, 1% starch, 0.4% yeast extract, 0.2% peptone, 100% seawater). A 20 L cultivation was extracted with EtOAc, and the solvent was concentrated to produce 3.7 g of crude extract, which was subjected to RP-18 flash chromatography (water/MeOH/CH_3CN) to produce distinct fractions. The fraction eluting with water/MeOH (4:6) was further purified by RP-18 HPLC (gradient; water/CH_3CN, 7:3 to 1:1) and RP-2 HPLC (isocratic; water/CH_3CN, 6:4) to yield 14.8 mg of (+)-curcutetraol (**1**) and 2.4 mg of (−)-curcutriolamide (**2**).

(+)-Curcutetraol (1): Brownish oil. $[\alpha]_D^{20}$ = +5.24 (*c* = 7.4 mg/mL, MeOH). ^1H NMR (600.19 MHz, CD_3OD): δ = 1.09 (s, 3 H), 1.10 (s, 3 H), 1.32 (br., 2 H), 1.39 (br., 2 H), 1.58 (s, 3 H), 1.79 (m, *J* = 11.3, 4.5, 1.2 Hz, 1 H), 1.91 (m, *J* = 11.3, 4.5, 1.2 Hz, 1 H), 4.50 (s, 2 H), 6.74 (d, *J* = 1.6 Hz, 1 H), 6.77 (dd, *J* = 7.7, 1.6 Hz, 1 H), 7.10 (d, *J* = 7.7 Hz, 1 H) ppm. ^{13}C NMR (150.9 MHz, CD_3OD): δ = 20.1 (CH_2), 29.1 (3 CH_3), 44.6 (CH_2), 45.1 (CH_2), 64.8 (CH_2), 71.4 (C_q), 78.0 (C_q), 116.1 (CH), 118.8 (CH), 127.6 (CH), 131.3 (C_q), 142.8 (C_q), 157.0 (C_q) ppm. IR (KBr): $\tilde{\nu}$ = 3306, 2921, 1630, 1578, 1429, 1296, 1261, 1156, 1032, 942, 877, 816, 754 cm^{-1}. UV (MeOH): λ_{max} (ε) = 219 nm (13534), 278 (7490). CD (CH_3CN): λ ($\Delta\varepsilon$) = 211 (−0.43, tr.), 229 (0.29, pk.), 249 (0.00, tr.), 281 (0.50, pk.). EIMS: *m*/*z* (%) = 268 (3) $[M]^+$, 250 (8) $[M - H_2O]^+$, 232 (51) $[M - 2H_2O]^+$, 217 (36) $[M - 2H_2O - CH_3]^+$, 189 (100), 167 (67). HREIMS, calcd. for $[M^+]$ ($C_{15}H_{24}O_4$): 268.1675; found 268.1661.

(−)-Curcutriolamide (2): Brownish oil. $[\alpha]_D^{20} = -3.8$ ($c = 0.3$ mg/mL; MeOH). ^{1}H NMR (600.19 MHz, CD_3OD): $\delta = 1.05$ (d, $J = 6.7$ Hz, 3 H), 1.30 (m, 4 H), 1.56 (s, 3 H), 1.79 (m, 1 H), 1.94 (m, 1 H), 2.27 (m, 1 H), 4.50 (s, 2 H), 6.73 (s, 1 H), 6.76 (d, $J = 7.7$ Hz, 1 H), 7.08 (d, $J = 7.7$ Hz, 1 H) ppm. ^{13}C NMR (150.9 MHz, CD_3OD): $\delta = 18.1$ (br., CH_3), 22.9/22.8 (CH_2), 29.1 (CH_3), 35.5 (br., CH_2), 41.3 (CH), 44.6 (CH_2), 64.7 (br., CH_2), 77.8 (br., C_q), 116.0/116.1 (CH), 118.6 (br., CH), 127.4 (br., CH), 131.0/131.1 (C_q), 142.6 (C_q), 156.9 (br., C_q), 182.5 (C_q) ppm. IR (KBr): $\tilde{\nu}$ = 3369, 2920, 2853, 1648, 1427, 1032, 870, 712 cm^{-1}. UV (MeOH): λ_{max} (ε) = 203 nm (138523), 282 (18014). HRFAB(−)MS calcd. for $[M - H]^-$ ($C_{15}H_{22}NO_4$): 280.1549; found 280.1558.

7-*O*-Methylcurcutetraol: This compound was obtained as a brownish oil by chromatography of **1** on silica gel ($MeOH/CHCl_3$, 9:1); yield: 1.5 mg. ^{1}H NMR (600.19 MHz, CD_3OD): $\delta = 1.09$ (s, 3 H), 1.10 (s, 3 H), 1.28 (br., 2 H), 1.38 (br., 2 H), 1.58 (s, 3 H), 1.85 (m, 2 H), 3.21 (s, 3 H), 4.50 (s, 2 H), 6.78 (d, $J = 1.6$ Hz, 1 H), 6.82 (dd, $J = 8.2$, 1.6 Hz, 1 H), 7.10 (d, $J = 8.2$ Hz, 1 H) ppm. ^{13}C NMR (150.9 MHz, CD_3OD): $\delta = 19.9$ (CH_2), 22.8 (CH_3), 29.1 (2 CH_3), 41.4 (CH_2), 45.0 (CH_2), 50.5 (CH_3), 64.7 (CH_2), 71.3 (C_q), 83.5 (C_q), 116.0 (CH), 119.0 (CH), 128.3 (CH), 128.8 (C_q), 143.7 (C_q), 156.9 (C_q) ppm. IR (KBr): $\tilde{\nu}$ = 3400, 2919, 1659, 1433, 876 cm^{-1}. HRFAB(−)MS calcd. for $[M - H]^-$ ($C_{16}H_{26}O_4$): 282.1831; found 282.1812.

1-[2-Acetoxy-4-(bromomethyl)phenyl]ethan-1-one (10): A solution of NBS (1.11 g, 6.25 mmol), AIBN (40 mg, 0.24 mmol), and **9**[33] (1.00 g, 5.20 mmol) in CCl_4 (30 mL) was refluxed for 8 h. The precipitate was filtered off and the filtrate washed with 1 M HCl, water, and aqueous $NaHCO_3$ solution. The organic layer was dried, concentrated, and the residue purified by chromatography (silica; isohexane/EtOAc, 3:1) to give the product as a colorless oil (0.89 g, 3.30 mmol, 63%). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 2.35$ (s, 3 H, OAc), 2.55 (s, 3 H, C6-Ac), 4.45 (s, 2 H, CH_2), 7.15 (d, $^4J = 1.8$ Hz, 1 H, 2-H), 7.33 (dd, $^3J = 8.1$ Hz, 1 H, 4-H), 7.79 (d, $^3J = 8.1$ Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 21.5$ (OAc), 29.7 (C6-*Ac*), 31.6 (CH_2), 124.8 (C2), 126.9 (C4), 130.8 (C6), 131.2 (C5), 143.8 (C3) 149.6 (C1), 169.7 (OAc), 197.2 (C6-*Ac*) ppm. MS (FAB+, NBA): *m/z* (%) = 271/273 (20/21) $[M + H]^+$, 231/229 (29/33), 154/155 (100/24). IR (KBr): $\tilde{\nu}$ = 1769, 1682, 1651, 1615, 1567, 1368, 1284, 1252, 1196 cm^{-1}. UV ($CHCl_3$): λ_{max} (log ε) = 253 nm (4.15), 290 (3.22). HRFABMS ($C_{11}H_{12}BrO_3$): calcd. 270.9970; found 270.9949.

1-[2-Hydroxy-4-(hydroxymethyl)phenyl]ethan-1-one: A solution of **10** (0.45 g, 270 mmol) in 2 N NaOH (5 mL) was stirred at room temp. for 12 h. The reaction mixture was then adjusted to pH 2 by addition of 2 M HCl. The aqueous phase was extracted with chloroform and the unified organic phases were dried ($MgSO_4$). Chromatography (silica; isohexane/ethyl acetate, 2:1) provided the product as an oil (0.15 g, 0.90 mmol, 54%). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.87$ (br. s, 1 H, CH_2OH), 2.62 (s, 3 H, CH_3), 4.70 (s, 2 H, CH_2), 6.89 (d, $^3J = 8.3$ Hz, 1 H, 4-H), 6.91 (s, 1 H, 2-H), 7.71 (d, $^3J = 8.3$ Hz, 1 H, 5-H), 12.30 (s, 1 H, C1-OH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 26.6$ (CH_3), 64.4 (CH_2), 115.7 (C2), 116.8 (C4), 118.8 (C6), 130.9 (C5), 150.3 (C3), 162.7 (C1), 204.1 (C=O) ppm. MS (EI, 70 eV): *m/z* (%) = 166 (59) $[M]^+$, 151 (100), 105 (17), 77 (11), 67 (7), 65 (6), 43 (16). IR (KBr): $\tilde{\nu}$ = 3480, 1634, 1574, 1460, 1417, 1368, 1328, 1299, 1253, 1220 cm^{-1}. UV ($CHCl_3$): λ_{max} (log ε) = 259 nm (4.11), 327 (3.62). HREIMS ($C_9H_{10}O_3$): calcd. 166.0630; found 166.0629.

1-[2-(Triisopropylsilanyloxy)-4-(triisopropylsilanyloxymethyl)phenyl]ethan-1-one: A solution of 1-[2-hydroxy-4-(hydroxymethyl)phenyl]ethan-1-one (0.19 g, 1.08 mmol), imidazole (0.37 g, 5.5 mmol), and TIPSCl (0.46 g, 2.40 mmol, 0.50 mL) in dry DMF (4 mL) was stirred at room temp. for 12 h. The organic layer was then washed with 2 M HCl (5 mL), diluted with water, and extracted with Et_2O. The ether phase was dried ($MgSO_4$), concentrated, and the crude product was purified by chromatography (silica; isohexane/EtOAc, 20:1) to yield a colorless oil (0.45 g, 0.94 mmol, 87%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.12 {m, 39 H, 12 CH_3 and $CH_2OSi[CH(CH_3)_2]_3$}, 1.38 {m, 3 H, C1-OSi[$CH(CH_3)_2]_3$}, 2.62 (s, 3 H, Ac), 4.76 (s, 2 H, CH_2), 6.82 (dd, $^3J = 7.9$, $^4J = 0.9$ Hz, 1 H, 4-H), 7.01 (d, $^4J = 0.9$ Hz, 1 H, 2-H), 7.59 (d, $^3J = 7.9$ Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.0 {3 C, $CH_2OSi[CH(CH_3)_2]_3$}, 13.4 {3 C, C1-OSi[$CH(CH_3)_2]_3$}, 17.9 {12 C, 2 OSi[$CH(CH_3)_2]_3$}, 31.3 (Ac), 64.4 (CH_2), 116.4 (C4) 117.8 (C2), 129.1 (C6), 130.0 (C5), 147.5 (C3), 155.8 (C1), 200.4 (C=O) ppm. MS (EI, 70 eV): *m/z* (%) = 479 (20) $[M + H]^+$, 438 (14), 437 (37), 436 (100), 263 (13), 262 (41), 115 (19), 87 (18), 73 (22), 59 (29). IR (KBr): $\tilde{\nu}$ = 2945, 2868, 2892, 1610, 1423, 883 cm^{-1}. UV ($CHCl_3$): λ_{max} (log ε) = 255 nm (4.01), 306 (3.57). HRFABMS ($C_{27}H_{51}O_3Si_2$): calcd. 479.3377; found 479.3380.

6-Methyl-2-[2-(triisopropylsilanyloxy)-4-(triisopropylsilanyloxymethyl)phenyl]hept-5-en-2-ol (12): Under dry conditions, 5-bromo-2-methylpent-2-ene (**11**; 0.17 g, 1.05 mmol) was added to a suspension of Mg slices (26 mg, 1.05 mmol) in Et_2O (10 mL). A solution of 1-[2-triisopropylsilanyloxy-4-(triisopropylsilanyloxymethyl)-phenyl]ethan-1-one (0.40 g, 0.84 mmol) in Et_2O (4 mL) was added and the reaction mixture was refluxed for 2 h. Ice water and saturated NH_4Cl solution (1 mL) were then added. The water phase was extracted twice with Et_2O and the combined organic layers were washed with aqueous $NaHSO_3$ and $NaHCO_3$ (10%) solutions, and then with water. The dried ($MgSO_4$) ether phase was concentrated and the product purified by chromatography (silica; isohexane/EtOAc, 20:1) to yield a colorless oil (0.35 g, 0.62 mmol, 74%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.06−1.15 {m, 39 H, 12 CH_3 and $CH_2OSi[CH(CH_3)_2]_3$}, 1.41 {m, 3 H, C1-OSi[$CH(CH_3)_2]_3$}, 1.50 (br, s, 3 H, 11-CH_3), 1.57 (br. s, 3 H, 7-CH_3), 1.63 (br. s, 3 H, 11-CH_3), 1.83 −2.00 (m, 2 H, 8-H_2), 1.90−1.99 (m, 2 H, 9-H_2), 4.49 (br. s, 1 H, OH), 4.76 (s, 2 H, CH_2OSi), 5.04 (m, 1 H, 10-H), 6.78 (dd, $^3J = 8.0$, $^4J = 1.5$ Hz, 1 H, 4-H), 6.92 (d, $^4J = 1.5$ Hz, 1 H, 2-H), 7.19 (d, $^3J = 7.9$ Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 11.9 {3 C, $CH_2OSi[CH(CH_3)_2]_3$}, 13.4 {3 C, $C_{ar}OSi[CH(CH_3)_2]_3$}, 17.4 (11-CH_3), 18.4 {12 C, 2 OSi[$CH(CH_3)_2]_3$}, 23.8 (C-9), 26.1 (11-CH_3), 27.6 (7-CH_3), 42.6 (C8), 64.9 (CH_2OSi), 75.6 (C7), 116.4 (C2), 118.3 (C4), 125.0 (C10), 127.2 (C5), 131.6 (C11), 134.3 (C6), 141.9 (C3), 153.7 (C1) ppm. MS (EI, 70 eV): *m/z* (%) = 562 (0.33) $[M]^+$, 480 (39), 436 (32), 372 (26), 157 (43), 145 (36), 115 (90), 87 (74). IR (KBr): $\tilde{\nu}$ = 2945, 2868, 683, 659 cm^{-1}. UV ($CHCl_3$): λ_{max} (log ε) = 259 nm (3.35), 272 (3.31), 280 (3.28). HREIMS ($C_{30}H_{53}O_2Si_2$): calcd. 501.3584; found 501.3548.

4-Dimethyloxiranyl-2-[2-(triisopropylsilanyloxy)-4-(triisopropylsilanyloxymethyl)phenyl]butan-2-ol (13): At 0 °C, Na_2HPO_4 (32.0 mg, 0.22 mmol) was added to a solution of **12** (0.05 g, 0.09 mmol) in THF (4 mL). After 5 min, *m*-CPBA (39.0 mg, 0.22 mmol) was added and the reaction mixture was stirred for 12 h, before being washed with saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ solutions (5 mL each). The mixture was then extracted with dichloromethane and the combined organic phases were dried with $MgSO_4$. After concentration, the product was purified by flash chromatography (RP-18; MeOH/water, 20:1) to afford a colorless oil (45.0 mg, 0.08 mmol, 87%). ^{1}H NMR (CD_3OD, 400 MHz): δ = 1.06−1.24 (m, 39 H, 12 CH_3 and $CH_2OSi[CH$-

$(CH_3)_2]_3$), 1.14 (s, 3 H, 11-CH_3), 1.17 (s, 3 H, 11-CH_3), 1.41 {m, 3 H, $C_{ar}OSi[CH(CH_3)_2]_3$}, 1.63 (s, 3 H, 7-CH_3), 2.10−2.33 (m, 2 H, 8-H_2), 1.74−2.20 (m, 2 H, 9-H_2), 2.65 (dd, ^3J = 5.9 Hz, 1 H, 10-H), 4.77 (s, 2 H, CH_2OSi), 6.79 (dd, ^3J = 8.1, ^4J = 1.5 Hz, 1 H, 4-H), 6.97 (d, ^4J = 1.5 Hz, 1 H, 2-H), 7.47 (d, ^3J = 8.1 Hz, 1 H, 5-H) ppm. ^{13}C NMR (CD_3OD, 100 MHz): δ = 11.9 {3 C, $CH_2OSi[CH(CH_3)_2]_3$}, 13.4 {3 C, $C_{ar}OSi[CH(CH_3)_2]_3$}, 17.2 {12 C, 2 $OSi[CH(CH_3)_2]_3$}, 17.4 (11-CH_3), 23.6 (11-CH_3), 26.1 (C9), 27.2 (7-CH_3), 37.2 (C8), 58.8 (C11), 64.4 (CH_2OH), 64.9 (C10), 73.8 (C7), 115.5 (C2), 117.6 (C4), 126.8 (C5), 134.2 (C6), 141.4 (C3), 152.4 (C1) ppm. MS (EI, 70 eV): *m*/*z* (%) = 577 (16) $[M - H]^+$, 564 (26), 563 (60), 435 (31), 433 (62), 387 (78), 361 (100), 346 (39), 345 (80), 301 (36), 161 (22). HREIMS ($C_{33}H_{61}O_4Si_2$): calcd. 577.4108; found 577.4108.

2,2,6-Trimethyl-6-[2-(triisopropylsilanyloxy)-4-(triisopropylsilanyloxymethyl)phenyl]-tetrahydropyran-3-ol (14a and 14b): Chromatography of the epoxide **13** on silica (isohexane/ethyl acetate, 4:1) quantitatively affords a mixture the diastereomers **14a** and **14b** in a ratio of 3:2. Small samples were purified for characterization.
14a: R_f = 0.40. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.08−1.15 [m, 39 H, 12 CH_3 (TIPS) and 3 CHSi], 1.17 (s, 3 H, 11-CH_3), 1.32 (s, 3 H, 11-CH_3), 1.40 (m, 3 H, 3 CHSi), 1.57 (s, 3 H, 7-CH_3), 1.66−1.88 (m, 2 H, 9-H_2), 2.13−2.43 (m, 2 H, 8-H_2), 3.78 (dd, ^3J = 6.6, 7.8 Hz, 1 H, 10-H), 4.76 (s, 2 H, CH_2OSi), 6.77 (dd, ^3J = 8.1, ^4J = 0.7 Hz, 1 H, 4-H), 6.90 (d, ^4J = 0.7 Hz, 1 H, 2-H), 7.47 (d, ^3J = 8.1 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.1 (3 C, CHSi), 13.5 (3 C, CHSi), 18.0 [6 C, CH_3 (TIPS)], 18.2 [6 C, CH_3 (TIPS)+, 24.3 (11-CH_3), 26.6 (C9), 27.4 (11-CH_3), 27.9 (7-CH_3), 38.6 (C8), 64.6 (CH_2OSi), 71.0 (C11), 84.0 (C10), 84.7 (C7), 115.6 (C2), 117.4 (C4), 125.6 (C5), 135.4 (C6), 141.2 (C3), 152.2 (C1) ppm. IR (KBr): $\tilde{\nu}$ = 2945, 1418, 1174, 1066, 883 cm^{-1}.
14b: R_f = 0.36. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.08−1.15 [m, 39 H, 12 CH_3 (TIPS) and 3 CHSi], 1.17 (s, 3 H, 11-CH_3), 1.31 (s, 3 H, 11-CH_3), 1.40 (m, 3 H, 3 CHSi), 1.52 (s, 3 H, 7-CH_3), 1.70−2.19 (m, 2 H, 9-H), 2.13−2.41 (m, 2 H, 8-H), 3.93 (dd, ^3J = 7.5, ^3J = 7.8 Hz, 1 H, 10-H), 4.76 (s, 2 H, CH_2OSi), 6.77 (dd, ^3J = 8.1, ^4J = 1.5 Hz, 1 H, 4-H), 6.90 (d, ^4J = 1.5 Hz, 1 H, 2-H), 7.56 (d, ^3J = 8.1 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.1 (3 C, CHSi), 13.6 (3 C, CHSi), 18.1 [6 C, CH_3 (TIPS)], 18.2 [6 C, CH_3 (TIPS)], 24.6 (11-CH_3), 26.3 (C9), 26.8 (11-CH_3), 27.3 (7-CH_3), 38.0 (C8), 64.6 (CH_2OSi), 71.7 (C11), 83.8 (C10), 84.7 (C7), 115.4 (C2), 117.4 (C4), 125.6 (C5), 135.9 (C6), 141.2 (C3), 151.8 (C1) ppm. IR (KBr): $\tilde{\nu}$ = 2944, 2866, 1463, 1162, 1100, 1068, 883 cm^{-1}. MS (EI, 70 eV, mixture of both diastereomers): *m*/*z* (%) = 577 (40) $[M]^+$, 563 (20), 517 (65), 387 (50), 361 (100). HREIMS ($C_{33}H_{62}O_4Si_2$): calcd. 578.4187; found 578.4165.

2-[2-Hydroxy-4-(triisopropylsilanyloxymethyl)phenyl]methylheptane-2,6-diol (15): At 0 °C, a solution of the epoxide **13** (0.16 g, 0.28 mmol) in dry THF (5 mL) was slowly added to a suspension of $LiAlH_4$ in dry THF (4 mL). The reaction mixture was allowed to warm up to 20 °C, was stirred for 60 min, and then cooled again to 0 °C, before being quenched with water (1 mL). The mixture was poured onto ice and extracted three times with DCM. The combined organic layers were dried with $MgSO_4$ and concentrated. The residue was purified by flash chromatography (RP-18; MeOH/water, 8:1) to provide a colorless oil (25.0 mg, 0.06 mmol, 21%). ^{1}H NMR (CD_3OD, 400 MHz): δ = 1.06−1.15 (m, 24 H, 6 CH_3 and 2 CH_3), 1.16−1.21 {m, 3 H, $CH_2OSi[CH(CH_3)_2]_3$}, 1.26−1.47 (m, 4 H, 9-H_2, 10-H_2), 1.58 (s, 3 H, 7-CH_3), 1.75−2.00 (m, 2 H, 8-H_2), 4.74 (s, 2 H, CH_2OTIPS), 6.75 (d, ^3J = 8.8 Hz, 1 H, 4-H), 6.77 (s, 1 H, 2-H), 7.07 (d, ^3J = 8.8 Hz, 1 H, 5-H) ppm. ^{13}C NMR (CD_3OD, 100 MHz): δ = 11.9 {3 C, $OSi[CH(CH_3)_2]_3$}, 17.1 {6 C, $OSi[CH(CH_3)_2]_3$}, 18.7 (C9), 27.7 (7-CH_3), 27.8 (2C, 2 CH_3), 43.1 (C8), 43.7 (C10), 64.6 (CH_2OTIPS), 70.0 (C11), 76.7 (C7), 113.9 (C2), 116.4 (C4), 126.0 (C5), 129.4 (C6), 141.6 (C3), 155.5 (C1) ppm. MS (EI, 70 eV): *m*/*z* (%) = 424 (1) $[M]^+$, 363 (29), 345(29), 323 (32), 289 (24) 281 (62), 267 (19), 217 (22), 215 (64), 173 (12), 159 (100). IR (KBr): $\tilde{\nu}$ = 3369, 2944, 2866, 1150, 1100, 961, 953, 672 cm^{-1}. HREIMS ($C_{24}H_{44}O_4Si$): calcd. 424.3009; found 424.2979.

***rac*-Curcutetraol (1):** TBAF was added to a solution of **15** (35 mg, 0.08 mmol) in dry THF (2 mL). After 3 h at room temp., the reaction mixture was concentrated and purified by flash chromatography (RP-18; MeOH/water, 1:1). The racemate of the natural product **1** was obtained as a colorless oil (12.0 mg, 0.05 mmol, 56%). With the exception of the absence of optical activity, the spectroscopic data were identical to those reported for the isolated natural product. HREIMS ($C_{15}H_{24}O_4$): calcd. 268.1675; found 268.1681.

Computational Methods: The MD simulations of **1** were performed using the TRIPOS[26] (virtual temperature 500 K) and the MM3[27] force fields (virtual temperature 400 K) as implemented in the molecular modeling package SYBYL 6.7,[26] with an overall simulation time of 500 ps and an extraction of single geometries every 0.5 ps.
The conformational analysis was conducted on a Silicon Graphics OCTANE R10000 workstation by means of the semiempirical AM1[30] approach, as implemented in the program package VAMP 6.5,[34] starting from preoptimized structures generated by the TRIPOS force field.
The wavefunctions required for the computation of the rotational strengths for the electronic transitions from the ground state to excited states were obtained by CNDO/2S[28] calculations followed by single configuration interaction (SCI) calculations including 625 singly occupied configurations and the ground state determinant in the case of the MD-based CD computations, and by OM2[31] calculations followed by SCI and SDCI calculations including 900 singly and 256 doubly occupied configurations, respectively, and the ground state determinant in the case of the conformational-analysis-based ones. These computations were carried out with Linux Pentium III workstations using the BDZDO/MCDSPD[35] program package, and with Linux AMD MP 2400+ workstations with the MNDO99[36] software package. In the case of the MD-based calculations, the single CD spectra were summed up arithmetically, while in the case of the conformational analysis they were additionally weighted by following Boltzmann statistics, i.e., according to the respective heats of formation. The rotational strengths were transformed into $\Delta\varepsilon$ values and, for a better visualization, superimposed with a Gaussian band-shape function.

Supporting Information (see also footnote on the first page of this article): Spectroscopic and spectrometric data of the natural products (+)-curcutetraol (**1**) and (−)-curcutriolamide (**2**).

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