Chagosensine, a New Chlorinated Macrolide from the Red Sea Sponge *Leucetta chagosensis*

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Keywords: Chagosensine / Sixteen-membered chlorinated macrolide / Red Sea sponge *Leucetta chagosensis* / Natural products

Chagosensine, a sixteen-membered chlorinated macrolide, was isolated from the Red Sea calcareous sponge *Leucetta chagosensis*. Its structure was elucidated mainly on the basis of NMR spectroscopic data. The relative and absolute configurations were determined by analysis of ^{1}H and ^{13}C NMR, NOESY, and CD data, by the modified Mosher's method, and by using degradation products.

Introduction

Leucetta chagosensis is a widespread calcareous sponge, occurring in shaded habitats of Indo-Pacific coral reefs,[1,2] and also in Red Sea coral reefs.[3] Sponges of the genus *Leucetta* have been sources of interesting imidazole alkaloids, including 2-amino imidazoles and substituted imidazolyl-2,4-dioxoimidazolidinylamines.[4] Nine new 2-amino imidazole alkaloids belonging to four different groups[5] and 9-(*N*-methylimine)-(2*E*,9*E*)-pyronamidine, a new imidazole alkaloid from the Northern Mariana Islands sponge *Leucetta chagosensis* have been isolated.[6] Antifungal imidazole alkaloids were also isolated from the Egyptian Red Sea sponge *Leucetta chagosensis*.[7]

According to Copp et al.[8] the extract of the *Leucetta* sp. sponge exhibited potent ability to inhibit the epidermal growth factor receptor signaling pathway. A new mechanism for the action of naamidine A and inhibition of tumor cells was shown. Other members of the genus *Leucetta* contain bioactive alkaloids, namely cytotoxic imidazoles from a Micronesian specimen,[9] a leukotriene B4 receptor antagonist from a Palauan specimen of *L. microraphis*,[10] antimicrobial lipids from a Micronesian *L. microraphis*,[11] and *L. leptorhapsisis* with cytotoxic activity from Ross Island, Antarctica.[12]

Halogenated macrolides, and their precursor halogenated fatty acids, are widespread in marine invertebrates, particularly in sponges[13] and soft corals.[14] Similar cytotoxic chlorinated macrolides named as haterumalides NA, NB, NC, and NE have been isolated from Okinawan sponge *Ircinia* sp.,[15] and Okinawan ascidian *Lissoclinum* sp.[16] Haterumalide A and NA have also been isolated from the soil bacteria *Serratia plymuthica* and *S. marcesens*.[17,18]

In the course of our investigation of the chemical composition of marine invertebrates and algae[14,19–22] we have examined marine sponge *Leucetta chagosensis* from the Red Sea, collected in the Gulf of Aqaba (Eilat, Israel). Chagosensine (**1**), a novel chloro-substituted macrolide, has been isolated from the sponge extract by the method of Bligh and Dyer.[23] Here we report on the structure elucidation of this new chlorinated macrolide, based mainly on its spectral characteristics.

Results and Discussion

A bright yellow sponge *Leucetta chagosensis* (Dendy 1913) was collected in the Red Sea, Aqaba Gulf (Israel). The sponge was extracted with $CHCl_3$/methanol, and the extract was subjected to repeated chromatography on Sephadex LH-20 with $CHCl_3$/methanol, followed by RP-HPLC on ODS with CH_3CN/H_2O (75:25) to give chagosensine (**1**) (Figure 1).

The molecular formula, $C_{24}H_{33}{}^{35}ClO_{10}$, was determined by HRFABMS $[M + H]^+$ at m/z = 517.2153. ^{1}H and ^{13}C NMR studies of chagosensine revealed the presence of an ester carbonyl, three olefins, 16 methines (nine of them bearing oxygen atoms), three methylenes, and two methyl groups. Multiplicities of the ^{13}C signals were determined by DEPT experiments. Considering that **1** has eight unsaturations, it was suggested that the molecule contained three rings (two ethers and one lactone). The ultraviolet spectrum of **1** in methanol, λ = 230 nm (log ε = 4.16), was similar

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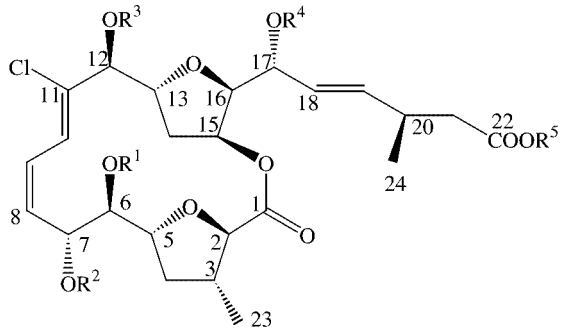
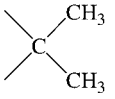
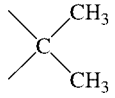
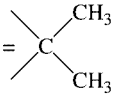


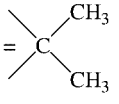
1: $R^1 = R^2 = R^3 = R^4 = R^5 = H$

2: $R^1 = R^2 = R^3 = R^4 = H, R^5 = CH_3$

3: $R^1 R^2 =$  $R^3 = R^4 = H, R^5 = CH_3$

4: $R^1 R^2 =$  $R^3 = R^4 = R^5 = CH_3$

5a: $R^1 R^2 =$  $R^3 = R^4 = (S)$-MTPA $R^5 = CH_3$

5b: $R^1 R^2 =$  $R^3 = R^4 = (R)$-MTPA $R^5 = CH_3$

6: $R^1 = R^2 = H, R^3 = R^4 = R^5 = CH_3$

7: $R^1 = R^2 = p$-MeOCinn, $R^3 = R^4 = R^5 = CH_3$

Figure 1. Chagosensine (**1**), a new chlorinated macrolide from the Red Sea sponge *Leucetta chagosensis* and its derivatives **2**−**7**

to those of 7-chloroocta-4,6-dienoic acids,[24] indicating that the absorption was due to a diene chromophore. Analysis of the IR spectrum ($\tilde{\nu}$ = 3650, 2900, 1735, and 1680 cm^{-1}) indicated the presence of ester and carboxylic acid groups.

Two-dimensional NMR techniques, in particular conventional COSY, were very efficient for presenting the proposed partial structures: C-2−C-10 (A), and C-12−C-22 (B) (bold line, Figure 2). The assignments of the carbons bearing hydrogens were established by ^1H-^{13}C COSY via

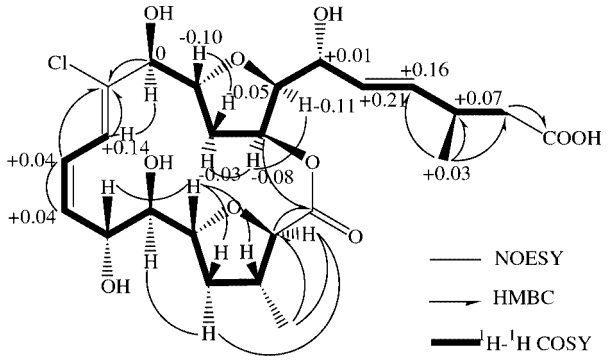
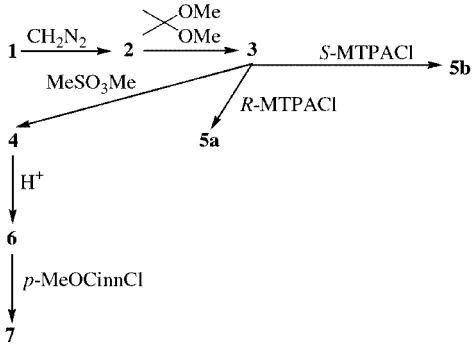


Figure 2. The NOESY, HMBC and COSY correlations of chagosensine

one-bond coupling. The two segments were separated by only one quaternary carbon (δ = 136.2 ppm). Since information on C−H long-range couplings were vital to connect those segments through the quaternary carbon (C-11), the HMBC technique was then applied. The HMBC spectrum clearly established the connectivities of both segments (A−B) through the quaternary carbon to construct the whole molecule. Both the above mentioned partial structures contained all the elements except for a chlorine. Thus, the chlorine substituent was placed at C-11.

The HMBC correlations between 15-H and C-1 (see Figure 2) suggested a macrocyclic lactone. Further, the HMBC cross-peak from 2-H to C-5 suggested that C-2 and C-5 are linked through an oxygen to form a tetrahydrofuran ring. The presence of an ether bridge between C-13 and C-16 was confirmed by the HMBC correlation between 16-H and C-13. Further HMBC correlations between 16-H and other carbons (C-15, C-17, and C-18) are also shown in Figure 2.

The NOESY spectrum of chagosensine was recorded and the relative stereochemistries of the oxymethine protons of the first tetrahydrofuran ring (2-H/5-H) was suggested to be *anti* and the methyl group on C-3 (C-23) was inferred to be *syn* to 2-H, since NOESY cross-peaks were clearly observed for 2-H/23-H_3, 2-H/4-H, 4-H/6-H, and 3-H/5-H with no correlation being observed for 2-H/5-H. The NOESY spectrum of **1** also revealed substantial cross-peaks for 5-H/7-H, 8-H/9-H, and 10-H/12-H. From these cross-peaks we tentatively considered the relative configurations of the C-2−C-12 moiety of **1** as 2*R**, 3*R**, 5*R**, 6*R**, and 7*R**, with the *Z*,*Z* configuration for the C-8−C-10 diene moiety; the cross-peak observed for 7-H, 8-H, and 9-H implied that these hydrogens were likely to be oriented to the outside of the macrocycle and 10-H to the inside. In addition, the 6,7-*O*-isopropylidene derivative (**3**) was prepared (Scheme 1) from methyl ester **2** by treatment with dimethoxypropane in the presence of pyridinium *p*-toluenesulfonate.



Scheme 1. Reaction schema for the preparation of the chagosensine derivatives **2**−**7**

The relative stereochemistry of the second tetrahydrofuran ring moiety was deduced from the NOESY correlations (13-H/14-Ha, 14-Hb/15-H, 15-H/16-H) and the ^1H-^1H coupling constants (see Table 1) for the tetrahydrofuran ring protons, which are analogous to the protons of the similarly substituted tetrahydrofuran rings in haterumalides.[15−18] These correlations suggested that the

Table 1. ^{1}H NMR of chagosensine (**1**) and its derivatives **2**−**7**

	1	**2**	**3**
2	4.38 (d, *J* = 8.8 Hz, 1 H)	4.38 (d, *J* = 8.8 Hz, 1 H)	4.42 (d, *J* = 8.8 Hz, 1 H)
3	2.38 (m, 1 H)	2.38 (m, 1 H)	2.41 (m, 1 H)
4a	2.14 (dt, 1 H, *J* = 11.8; 6.5)	2.14 (dt, 1 H, *J* = 11.8; 6.5)	2.19 (dt, 1 H, *J* = 11.8; 6.5)
4b	1.96 (m, 1 H)	1.96 (m, 1 H)	2.02 (m, 1 H)
5	4.19 (ddd, 1 H, *J* = 2.0; 4.5; 6.5)	4.19 (ddd, 1 H, *J* = 2.0; 4.5; 6.5)	4.31 (ddd, 1 H, *J* = 2.0; 4.5; 9.5)
6	4.03 (dd, 1 H, *J* = 4.5; 10.0)	4.03 (dd, 1 H, *J* = 4.5; 10.0)	4.06 (dd, 1 H, *J* = 9.5; 7.8)
7	4.31 (dd, 1 H, *J* = 10.0; 8.1)	4.31 (dd, 1 H, *J* = 10.0; 8.1)	3.91 (dd, 1 H, *J* = 7.8; 9.6)
8	5.93 (dd, 1 H, *J* = 8.1; 10.9)	5.93 (dd, 1 H, *J* = 8.1; 10.9)	5.89 (dd, 1 H, *J* = 9.6; 10.9)
9	6.17 (dd, 1 H, *J* = 10.9; 7.7)	6.17 (dd, 1 H, *J* = 10.9; 7.7)	6.26 (dd, 1 H, *J* = 10.9; 7.7)
10	6.42 (d, *J* = 7.7 Hz, 1 H)	6.42 (d, *J* = 7.7 Hz, 1 H)	6.45 (d, *J* = 7.7 Hz, 1 H)
12	4.42 (d, *J* = 3.5 Hz, 1 H)	4.42 (d, *J* = 3.5 Hz, 1 H)	4.42 (d, *J* = 3.5 Hz, 1 H)
13	4.15 (ddd, 1 H, *J* = 3.5; 7.8; 2.7)	4.15 (ddd, 1 H, *J* = 3.5; 7.8; 2.7)	4.15 (ddd, 1 H, *J* = 3.5; 7.8; 2.7)
14a	2.14 (dt, 1 H, *J* = 12.3; 2.7)	2.14 (dt, 1 H, *J* = 12.3; 2.7)	2.14 (dt, 1 H, *J* = 12.3; 2.7)
14b	1.58 (m, 1 H)	1.58 (m, 1 H)	1.58 (m, 1 H)
15	5.08 (ddd, *J* = 2.9, 8.1, 5.9 Hz, 1 H)	5.08 (ddd, *J* = 2.9, 8.1, 5.9 Hz, 1 H)	5.08 (ddd, *J* = 2.9, 8.1, 5.9 Hz, 1 H)
16	4.20 (dd, 1 H, *J* = 5.9; 7.7)	4.20 (dd, 1 H, *J* = 5.9; 7.7)	4.20 (dd, 1 H, *J* = 5.9; 7.7)
17	4.52 (dd, 1 H, *J* = 7.7; 6.1)	4.52 (dd, 1 H, *J* = 7.7; 6.1)	4.52 (dd, 1 H, *J* = 7.7; 6.1)
18	5.71 (dd, 1 H, *J* = 6.1; 15.0)	5.52 (dd, 1 H, *J* = 6.1; 15.0)	5.71 (dd, 1 H, *J* = 6.1; 15.0)
19	5.94 (dd, 1 H, *J* = 15.0; 7.8)	5.71 (dd, 1 H, *J* = 15.0; 7.8)	5.94 (dd, 1 H, *J* = 15.0; 7.8)
20	2.85 (m, 1 H)	2.75 (m, 1 H)	2.85 (m, 1 H)
21a	2.40 (dd, 1 H, *J* = 5; = 16)	2.33 (dd, 1 H, *J* = 5; = 16)	2.40 (dd, 1 H, *J* = 5; = 16)
21b	2.20 (dd, 1 H, *J* = 10, 16)	2.45 (dd, 1 H, *J* = 10, 16)	2.20 (dd, 1 H, *J* = 10, 16)
23	1.05 (d, *J* = 6.6 Hz, 3 H)	0.98 (d, *J* = 6.6 Hz, 3 H)	1.05 (d, *J* = 6.6 Hz, 3 H)
24	1.08 (d, *J* = 6.5 Hz, 3 H)	1.08 (d, *J* = 6.5 Hz, 3 H)	1.08 (d, *J* = 6.5 Hz, 3 H)
COOMe	–	3.67 (s, 3 H)	3.67 (s, 3 H)
Me−C	–	–	1.48 (s, 3 H)
Me−C	–	–	1.38 (s, 3 H)

	4	**5a**	**5b**
2	4.38 (d, *J* = 8.8 Hz, 1 H)	4.38 (d, *J* = 8.8 Hz, 1 H)	4.38 (d, *J* = 8.8 Hz, 1 H)
3	2.38 (m, 1 H)	2.38 (m, 1 H)	2.38 (m, 1 H)
4a	2.14 (dt, 1 H, *J* = 11.8; 6.5)	2.14 (dt, 1 H, *J* = 11.8; 6.5)	2.14 (dt, 1 H, *J* = 11.8; 6.5)
4b	1.96 (m, 1 H)	1.96 (m, 1 H)	1.96 (m, 1 H)
5	4.19 (ddd, 1 H, *J* = 2.0; 4.5; 6.5)	4.19 (ddd, 1 H, *J* = 2.0; 4.5; 6.5)	4.19 (ddd, 1 H, *J* = 2.0; 4.5; 6.5)
6	4.03 (dd, 1 H, *J* = 4.5; 10.0)	4.03 (dd, 1 H, *J* = 4.5; 10.0)	4.03 (dd, 1 H, *J* = 4.5; 10.0)
7	4.31 (dd, 1 H, *J* = 10.0; 8.1)	4.31 (dd, 1 H, *J* = 10.0; 8.1)	4.31 (dd, 1 H, *J* = 10.0; 8.1)
8	5.93 (dd, 1 H, *J* = 8.1; 10.9)	5.93 (dd, 1 H, *J* = 8.1; 10.9)	5.89 (dd, 1 H, *J* = 8.1; 10.9)
9	6.31 (dd, 1 H, *J* = 10.9; 7.7)	6.17 (dd, 1 H, *J* = 10.9; 7.7)	6.13 (dd, 1 H, *J* = 10.9; 7.7)
10	6.62 (d, *J* = 7.7 Hz, 1 H)	6.42 (d, *J* = 7.7 Hz, 1 H)	6.28 (d, *J* = 7.7 Hz, 1 H)
12	4.36 (d, *J* = 3.5 Hz, 1 H)	4.14 (d, *J* = 3.5 Hz, 1 H)	4.14 (d, *J* = 3.5 Hz, 1 H)
13	4.31 (ddd, 1 H, *J* = 3.5; 7.8; 2.7)	4.05 (ddd, 1 H, *J* = 3.5; 7.8; 2.7)	4.15 (ddd, 1 H, *J* = 3.5; 7.8; 2.7)
14a	2.24 (dt, 1 H, *J* = 12.3; 2.7)	2.11 (dt, 1 H, *J* = 12.3; 2.7)	2.14 (dt, 1 H, *J* = 12.3; 2.7)
14b	1.70 (m, 1 H)	1.54 (m, 1 H)	1.59 (m, 1 H)
15	5.19 (ddd, *J* = 2.9, 8.1, 5.9 Hz, 1 H)	5.00 (ddd, *J* = 2.9, 8.1, 5.9 Hz, 1 H)	5.08 (ddd, *J* = 2.9, 8.1, 5.9 Hz, 1 H)
16	4.36 (dd, 1 H, *J* = 5.9; 7.7)	4.17 (dd, 1 H, *J* = 5.9; 7.7)	4.28 (dd, 1 H, *J* = 5.9; 7.7)
17	4.93 (dd, 1 H, *J* = 7.7; 6.1)	4.52 (dd, 1 H, *J* = 7.7; 6.1)	4.51 (dd, 1 H, *J* = 7.7; 6.1)
18	6.07 (dd, 1 H, *J* = 6.1; 15.0)	5.64 (dd, 1 H, *J* = 6.1; 15.0)	5.43 (dd, 1 H, *J* = 6.1; 15.0)
19	5.32 (dd, 1 H, *J* = 15.0; 7.8)	5.94 (dd, 1 H, *J* = 15.0; 7.8)	5.78 (dd, 1 H, *J* = 15.0; 7.8)
20	3.08 (m, 1 H)	2.92 (m, 1 H)	2.85 (m, 1 H)
21a	2.47 (dd, 1 H, *J* = 5; = 16)	2.43 (dd, 1 H, *J* = 5; = 16)	2.43 (dd, 1 H, *J* = 5; = 16)
21b	2.06 (dd, 1 H, *J* = 10, 16)	2.14 (dd, 1 H, *J* = 10, 16)	2.14 (dd, 1 H, *J* = 10, 16)
23	1.05 (d, *J* = 6.6 Hz, 3 H)	1.05 (d, *J* = 6.6 Hz, 3 H)	1.05 (d, *J* = 6.6 Hz, 3 H)
24	1.01 (d, *J* = 6.5 Hz, 3 H)	1.08 (d, *J* = 6.5 Hz, 3 H)	1.11 (d, *J* = 6.5 Hz, 3 H)
COOMe	3.67 (s, 3 H)	3.67 (s, 3 H)	3.67 (s, 3 H)
Me−C	1.48 (s, 3 H)	1.48 (s, 3 H)	1.48 (s, 3 H)
Me−C	1.38 (s, 3 H)	1.38 (s, 3 H)	1.38 (s, 3 H)
12-OMe	3.39 (s, 3 H)	3.55 (s, 3 H)	3.55 (s, 3 H)
17-OMe	3.26 (s, 3 H)	3.55 (s, 3 H)	3.55 (s, 3 H)
2′, 2′′,3′,3′′,6′,6′′	–	7.43 (br. s, 6 H)	7.43 (br. s, 6 H)
3′, 3′′, 5′, 5′′	–	7.17 (br. s, 4 H)	7.17 (br. s, 4 H)

	6	**7**
2	4.38 (d, *J* = 8.8 Hz, 1 H)	4.50 (d, *J* = 8.8 Hz, 1 H)
3	2.38 (m, 1 H)	2.49 (m, 1 H)
4a	2.14 (dt, 1 H, *J* = 11.8; 6.5)	2.34 (dt, 1 H, *J* = 11.8; 6.5)
4b	1.96 (m, 1 H)	2.16 (m, 1 H)
5	4.19 (ddd, 1 H, *J* = 2.0; 4.5; 6.5)	4.37 (ddd, 1 H, *J* = 2.0; 4.5; 6.5)
6	4.03 (dd, 1 H, *J* = 4.5; 10.0)	5.47 (dd, 1 H, *J* = 4.5; 10.0)
7	4.31 (dd, 1 H, *J* = 10.0; 8.1)	5.28 (dd, 1 H, *J* = 10.0; 8.1)
8	5.93 (dd, 1 H, *J* = 8.1; 10.9)	5.83 (dd, 1 H, *J* = 8.1; 10.9)
9	6.19 (dd, 1 H, *J* = 10.9; 7.7)	6.26 (dd, 1 H, *J* = 10.9; 7.7)
10	6.67 (d, *J* = 7.7 Hz, 1 H)	6.34 (d, *J* = 7.7 Hz, 1 H)
12	4.36 (d, *J* = 3.5 Hz, 1 H)	4.45 (d, *J* = 3.5 Hz, 1 H)
13	4.31 (ddd, 1 H, *J* = 3.5; 7.8; 2.7)	4.01 (ddd, 1 H, *J* = 3.5; 7.8; 2.7)
14a	2.25 (dt, 1 H, *J* = 12.3; 2.7)	2.07 (dt, 1 H, *J* = 12.3; 2.7)
14b	1.70 (m, 1 H)	1.71 (m, 1 H)
15	5.19 (ddd, *J* = 2.9, 8.1, 5.9 Hz, 1 H)	5.02 (ddd, *J* = 2.9, 8.1, 5.9 Hz, 1 H)
16	4.36 (dd, 1 H, *J* = 5.9; 7.7)	4.07 (dd, 1 H, *J* = 5.9; 7.7)
17	4.93 (dd, 1 H, *J* = 7.7; 6.1)	4.17(dd, 1 H, *J* = 7.7; 6.1)
18	5.71 (dd, 1 H, *J* = 6.1; 15.0)	5.43(dd, 1 H, *J* = 6.1; 15.0)
19	6.34 (dd, 1 H, *J* = 15.0; 7.8)	5.75 (dd, 1 H, *J* = 15.0; 7.8)
20	3.06 (m, 1 H)	2.69 (m, 1 H)
21a	2.47 (dd, 1 H, *J* = 5; = 16)	2.34 (dd, 1 H, *J* = 5; = 16)
21b	2.06 (dd, 1 H, *J* = 10, 16)	2.32 (dd, 1 H, *J* = 10, 16)
23	1.05 (d, *J* = 6.6 Hz, 3 H)	1.05 (d, *J* = 6.6 Hz, 3 H)
24	1.14 (d, *J* = 6.5 Hz, 3 H)	1.02 (d, *J* = 6.5 Hz, 3 H)
COOMe	3.67 (s, 3 H)	3.67 (s, 3 H)
12-OMe	3.39 (s, 3 H)	3.39 (s, 3 H)
17-OMe	3.26 (s, 3 H)	3.26 (s, 3 H)
2′, 2′′, 6′, 6′′	–	7.93 (br. s, 4 H)
3′, 3′′, 5′, 5′′	–	7.61 (br. s, 4 H)
MeO-Cinn	–	3.64

relative stereochemistries at C-13, C-15, and C-16 were 13*R**, 15*S**, and 16*S**.

All the NOESY correlations 3-H/5-H, 4-H/6-H, 5-H/7-H and 8-H/9-H, 10-H/12-H, 13-H/14-Ha, 14-Hb/15-H, and 15-H/16-H suggested a plausible conformation for the macro ring in **1**.

Absolute Configurations at C-2, C-3, and C-5

To investigate the absolute stereochemistry at C-2, C-3, and C-5, oxidative degradation (Figure 3) was performed on the 6,7-diol unit in compound **1**. Reduction of **2** with DIBAL, oxidative cleavage of the 6,7-diol unit with $NaIO_4$, reduction with $NaBH_4$ and esterification with Ac_2O furnished compound **8**, whose structure was elucidated by analysis of the ^1H NMR spectrum.

Unfortunately, the literature data of related compounds are inconsistent. Taber and Song[25] and also Udding et al.[26] report the synthesis of trisubstituted tetrahydrofurans but it is impossible to resolve their steric configurations from ^1H NMR spectra. Five (*S*,*S*,*R*; *S*,*R*,*S*; *R*,*S*,*R*; *R*,*R*,*R*; and *R*,*S*,*S*) of all eight possible isomers were synthesized but the ^1H NMR spectroscopic data are very confusing. We therefore used further degradation, according model compound 2,5-bis(acetoxymethyl)tetrahydrofuran.[27] Ring fission of **8** was carried out by a mixture of acetic anhydride with a few drops of sulfuric acid in acetic acid and methyl tetracetoxyhexane (**9**) was obtained. Deacetylation and additional oxidative splitting by $NaIO_4$ yielded 2-methyl succinic acid. This compound, as its dimethyl ester (**10**), was compared with *R* and/or *S* enantiomers, both commercially obtained, by means of chiral gas−liquid chromatography

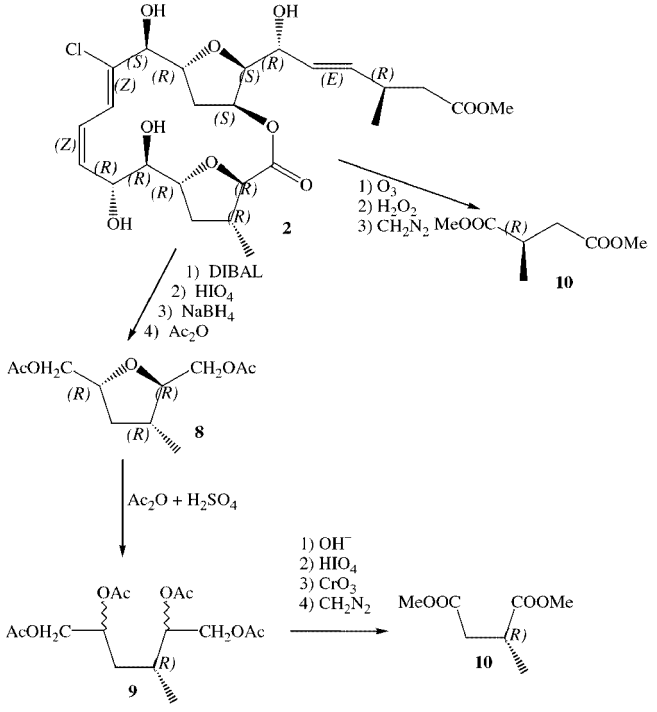


Figure 3. Reaction schema of degradation compounds from chagosensine

Table 2. The presence of degradation products (determined by chiral capillary GC) after oxidation of compound **1** (methylmalonic and succinic acids were also formed during oxidation of **1**, both determined as methyl esters)

Methyl ester of acid	R_t of products after degradation (min^{-1}) Standards	**1**
acetic	2.15	2.17
pyruvic	6.58	6.60
oxalic	8.12	8.11
malonic	11.76	11.77
2*R*-methylsuccinic	14.22	14.23
2*S*-methylsuccinic	14.71	−

(Table 2). Therefore, the absolute configuration at C-3 is *R*. From known relative configurations it is evident that both carbons C-2 and C-5 also have the *R* configuration.

Absolute Configurations at C-6 and C-7

For application of the exciton chirality method, the *p*-methoxycinnamoyl group was chosen as an exciton chromophore of the 6,7-diol in the chagosensine derivative because the UV spectrum of **1** showed a strong absorption at 230 nm (log ε = 4.16). Treatment of **6** with *p*-methoxycinnamoyl chloride afforded the 6,7-bis(*p*-methoxy)cinnamate (**7**). In the ^1H NMR spectrum of **7**, the vicinal coupling constant between 6-H and 7-H was 10.0 Hz, suggesting that 6-H and 7-H had an *anti* relationship to each other. The CD spectrum[28] of **7** disclosed a negative first Cotton effect (λ = 324 nm, Δε −11.3) and a positive second Cotton effect (λ = 289 nm, Δε = +12.1) (Figure 4), indicating 6*R* and 7*R* configurations. The Δε value of the second negative wing is stronger than that of the positive counterpart at 235 nm, which implies that some other exciton interaction must have also contributed besides the major *p*-MeOCinn/*p*-MeOCinn interaction.[29] This additional contribution includes a *p*-MeOCinn/8,10-diene interaction, which is negative at around 235 nm.

Absolute Configuration at C-12 and C-17

The absolute stereochemistries of C-12 and C-17 in **1** were determined by using modified Mosher's methods.[26,27] The acetonide **3** was transformed into the **5a** (*R*)- and **5b** (*S*-MTPA) esters. The ^1H NMR signals of these two esters were assigned based on the 2D NMR spectra, and the Δδ values ($\Delta\delta = \delta_S - \delta_R$) were then calculated and are shown in Figure 2. The Δδ values for 13-H−16-H were negative, while positive Δδ values were observed for 8-H, 9-H, 10-H, 18-H, 19-H, and 20-H, thus indicating that C-12 and C-17 had *S* and *R* configurations, respectively. The magnitude of $J_{16,17}$ = 7.7 Hz suggested that 16-H and 17-H were located in an *anti* arrangement. This information suggested that **1** adopted the conformation shown in Figure 2, and that the relative stereochemistry between C-16 and C-17 was threo. Thus, the absolute stereochemistries of the five stereocenters in **1** were determined to be 12*S*, 13*R*, 15*S*, 16*S*, and 17*R*.

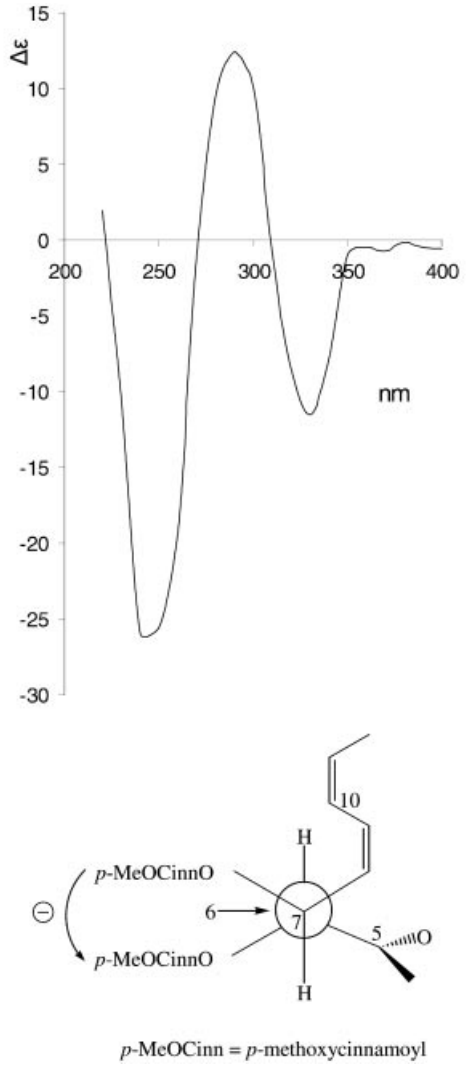


Figure 4. CD spectrum of the 6,7-bis(*p*-methoxycinnamoyl) derivative **7**

Absolute Configuration at C-20

To determine the absolute configuration at C-20 of compound **1**, oxidation with ozone was used to obtain the segment including the methine carbon at C-20. Compound **1** was treated with O_3 followed by oxidation with H_2O_2/HCOOH and esterification with diazomethane. GLC chiral separation afforded a dimethyl ester of methyl succinic acid (**10**), corresponding to the C-19−C-20 segment of **1** (Figure 3). For comparison, both authentic dimethyl esters of methyl succinic acid (*R* and *S*, see Table 2) were commercially obtained. The relative retention time of compound **10** from a natural specimen was identical with that of the commercial *R*-isomer (Table 2), indicating that the absolute configuration at C-20 of compound **1** was *R*. Therefore, the absolute configurations of all 11 chiral centers in compound **1** were elucidated to be 2*R*, 3*R*, 5*R*, 6*R*, 8*R*, 12*S*, 13*R*, 15*S*, 16*S*, 17*R*, and 20*R*.

Experimental Section

General Experimental Procedures: UV spectra were measured in heptane within the range 200−350 nm by a Cary 118 (Varian) apparatus. A Perkin−Elmer Model 1310 (Perkin−Elmer, Norwalk, CT, USA) IR spectrophotometer was used for scanning IR spectroscopy of glycosides as neat films. Circular dichroism (CD) measurements were carried out on a Jasco-500A spectropolarimeter at 24 °C, under dry N_2. NMR spectra were recorded on a Bruker AMX 500 spectrometer (Bruker Analytik, Karlsruhe, Germany) at 500.1 MHz (^{1}H) and 125.7 MHz (^{13}C) in a mixture of deuterated pyridine and CD_3OD (v/v 1:1). High- and low-resolution mass spectra were recorded by using a VG 7070E−HF spectrometer (70 eV). HR-FAB-MS (positive and/or negative ion mode) was performed with a PEG-400 matrix. HPLC was carried out using a Shimadzu gradient LC system (Shimadzu, Kyoto, Japan). Gas chromatography analysis was made on a Hewlett−Packard HP 5980 gas chromatograph (Hewlett−Packard, Czech Republic). An FS capillary column HYDRODEX β-3P ID 0.25 mm, length 25 m, with the stationary phase [heptakis(2,6-di-*O*-methyl-3-*O*-pentyl)-β-cyclodextrin] from Macherey−Nagel GmbH & Co. KG, Düren, Germany was used. Oven temperature: 50 °C to 150 °C at 2 °C/min, then to 240 °C at 5 °C/min, carrier gas helium, 20 cm/s, detector FID, 300 °C, injection of 1 μL mixture in dichloromethane (for standards: containing 0.5 mg/mL of each sample), split (100:1), 300 °C. The following compounds: acetic acid, acetone, malonic, oxalic, pyruvic, (2*R*)- and (2*S*)-methylsuccinic acids were purchased from Sigma−Aldrich (Prague, Czech Republic).

Animal Material: A bright yellow sponge *Leucetta chagosensis* (Family Leucettidae; Order Clathrinida; Subclass Calcinea, Class Calcarea, *Phylum porifera*) were collected by hand (scuba diving) from rocks 11−17 m deep in the Red Sea, Gulf of Aqaba (Eilat, Israel), on October 30, 2001. The voucher specimens are deposited in the Inter-University collection (Eilat). Fresh sponges were placed in ethanol and stored at −10 °C under nitrogen.

Extraction and Isolation of Chagosensine (1): The sponge (ca. 800 g wet weight) was extracted with a mixture of $CHCl_3$/MeOH (1:1) for 24 h. After evaporation, the crude extract was chromatographed in batches of ca. 2 g on an LH-20 column prepared and eluted with $CHCl_3$/MeOH (1:1). The macrolide-containing fractions were combined and the residue (3.67 g), was subjected to C_{18} HPLC [ODS, 5 μm, 10 × 250 mm; eluent, CH_3CN/H_2O (75:25), flow rate, 2.5 mL/min. UV detection at 230 nm] to afford the macrolide chagosensine as a colorless amorphous solid (24 mg, 0.0029% on wet weight), $[\alpha]_D^{23} = -131$ (c = 0.015, CH_2Cl_2).

Methyl Ester 2: Compound **1** (21.6 mg) was dissolved in methanol (5 mL) and treated with excess diazomethane in diethyl ether, and the resulting solution was used for further reactions, yield 21.0 mg (97.3%).

6,7-*O*-Isopropylidene Derivative 3: Compound **2** (10.5 mg) was treated with dimethoxypropane (0.3 mL) and pyridinium *p*-toluenesulfonate (0.3 mL) in CH_2Cl_2 (2.0 mL) at room temperature for 12 h. After evaporating the solvent, the residue was purified using silica-gel TLC (hexane/EtOAc, 6:11) to give acetonide **3**, yield 9.2 mg (77.7%).

Methyl Ether 4: Acetonide **3** (2.9 mg) in chloroform (2 mL) was added to a stirred solution of methyl triflate (1 mL) in di-*tert*-butylpyridine (2 mL). A condenser was then fitted to the flask, and the solution was heated to reflux and stirred for 15 h. The solution was allowed to cool and concentrated ammonium hydroxide (0.5 mL)

was added. After a further 2 h of stirring, the mixture was poured into water and extracted with dichloromethane. The combined organic layers were then washed with 10% hydrochloric acid (3 × 5 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting oil was purified by chromatography eluting with 15% ethyl acetate in hexanes to give 1.75 mg of the methyl ether **4** as a clear oil.

(*S*)-MTPA Ester (5a): (*R*)-(−)-MTPACl (2.0 mg) was added to a CH_2Cl_2 solution (100 μL) of acetonide **3** (3.1 mg), DMAP (1.0 mg), and Et_3N (2 μL) at room temperature, and the mixture was stirred for 3 h. After evaporation of solvent, the residue was purified by silica-gel TLC (hexane/EtOAc, 2:1) to provide the (*S*)-MTPA ester **5a** as a colorless oil, yield 2.0 mg (36.7%).[30,31]

(*R*)-MTPA Ester (5b): Acetonide (**3**) (3.1 mg) was treated with (*S*)-(+)-MTPACl (2.0 mg) by the procedure described above to provide the (*R*)-MTPA ester **5b** as a colorless oil, yield 2.1 mg (38.5%).

***p*-Methoxycinnamate (7):** The pH of a solution of **4** (2.2 mg) in water (2 mL) was adjusted to < 2 with Dowex 50 W (H^+), and the mixture was heated with stirring at 80 °C for 1.5 h. The pH was adjusted to 10 with NH_4OH (5%) and the solution kept at 0 °C for 24 h. The pH of the solution was then adjusted to 7 with Dowex 50 W (H^+), and the water was removed by lyophilization. The crude dimethyl ether (**6**) was dissolved in pyridine (1.0 mL), and 4-*p*-methoxycinnamoyl chloride (20 μL) and a catalytic amount of 4-(dimethylamino)pyridine were added. After 18 h, methanol (2.0 mL) and hexane (1.0 mL) were added, and the reaction solvents were evaporated to dryness. The residue was subjected to TLC (benzene/EtOAc, 9:1) to yield **7** (1.4 mg, 43.3%).

Oxidative Cleavage: Compound **2** (11.5 mg) was dissolved in CH_2Cl_2 (0.2 mL) and treated with a 0.95 M solution of DIBAL in toluene (25 μL) at −78 °C for 1 h. The reaction mixture was partitioned between EtOAc (3 × 1 mL) and 1 M phosphate buffer (1 mL). The organic phase was separated and evaporated in vacuo to afford a crude residue. The residue was dissolved in THF/1 M phosphate buffer (pH 7.2) solution (1:1, 1 mL), $NaIO_4$ (10 mg) was added at room temperature, and the mixture was cooled to 0 °C and stirred for 1 h. After evaporation under reduced pressure, the residue was extracted with EtOAc (3 × 1 mL) and the solvents evaporated. The residue was taken up in EtOH (1 mL) and $NaBH_4$ (12 mg) in EtOH (1 mL) was added at 4 °C. The mixture was stirred at 0 °C for 1 h, 1 M phosphate buffer was added, and the reaction mixture was dried with nitrogen. The residue was dissolved in pyridine (1 mL) and acetic anhydride (1 mL) and stirred at room temperature for 18 h. The mixture was evaporated and partitioned between EtOAc (3 mL) and H_2O (3 mL). The EtOAc layer was washed with brine and dried over $MgSO_4$. After evaporation the residue was passed through a Sep-Pak silica cartridge with hexane/EtOAc (2:1), followed by silica-gel TLC, (eluent hexane/EtOAc, 2:1) to afford 3.5 mg (70.1%) of compound **8** [2,5-bis(acetoxymethyl)-3-methyltetrahydrofuran]. ^1H NMR ($CDCl_3$, ppm) δ = 1.01 (s, 3 H, 23-H); 1.79 (m, 1 H, 4-Ha); 1.86 (m, 1 H, 4-Hb); 2.04 (s, 3 H, Ac); 2.09 (s, 3 H, Ac); 2.10 (m, 1 H, 3-H); 3.90 (m, 1 H, 5-H); 3.94 (m, 1 H, 1-Ha); 4.05 (m, 1 H, 6-Ha); 4.06 (m, 1 H, 1-Hb); 4.08 (m, 1 H, 2-H); 4.42 (m, 1 H, 6-Hb).

Compound **8** (3 mg) was dissolved at 0 °C in the acetolysing reagent, prepared by mixing at 0 °C acetic anhydride (2 mL), acetic acid (1 mL), and concentrated sulfuric acid (0.05 mL),[27] and kept at room temperature for 24 h. It was then poured onto ice, neutralized with sodium hydrogen carbonate, and extracted with diethyl ether. The extract was dried with $MgSO_4$ and evaporated to a syrup, which was subjected to silica gel TLC (MeOH/$CHCl_3$, 4:1) to yield **9** (1,2,5,6-tetraacetoxyhexane; 2.1 mg, 48.5%). ^1H NMR ($CDCl_3$, ppm) δ = 0.97 (d, *J* = 6.8 Hz, 3 H), 1.32 (ddd, *J* = 3.2, 10.0, 14.2 Hz, 1 H), 1.76 (ddd, *J* = 3.8, 10.5, 14.2 Hz, 1 H), 1.86 (m, 1 H), 2.05 (s, 3 H), 2.07 (s, 3 H), 2.08 (s, 3 H), 2.09 (s, 3 H), 3.98 (dd, *J* = 6.3, 11.8 Hz, 1 H), 4.08 (dd, *J* = 7.6, 11.8 Hz, 1 H), 4.23 (dd, *J* = 3.5, 9.2 Hz, 1 H); 4.25 (dd, *J* = 3.7, 11.8 Hz, 1 H), 5.04 (ddd, *J* = 3.7, 4.3, 7.6 Hz, 1 H); 5.18 (m, 1 H). FABMS: *m*/*z* = 333 $[M + H]^+$; 273 $[M + H - AcOH]^+$.

A mixture of compound **9** (2 mg), 1,4-dioxane (1 mL), MeOH (1 mL), and a 1 M aqueous solution of KOH (0.1 mL) was stirred for 2 h at 0 °C and for 1 h at room temperature. The reaction was quenched with a saturated aqueous solution of NH_4Cl (1 mL), and the mixture was concentrated to half its volume under reduced pressure and extracted with $CHCl_3$ (3 × 2 mL). The combined extracts were washed successively with saturated aqueous $NaHCO_3$ (2 × 2 mL), and concentrated to give the crude product as an amorphous solid. The tetrahydroxyhexane was oxidatively split by using $NaIO_4$ (for conditions see above). Further oxidation was carried out with chromic acid (1.25 M), which was added dropwise to a solution of crude diol (2-methyl-1,4-butanediol) in acetone until an orange color persisted, and the reaction had been stirred for 7 h at room temperature. The acetone was removed using a rotary evaporator, and the residue was dissolved in methanol (ca. 1 mL) and treated with excess diazomethane in diethyl ether. The solution was allowed to stand overnight, a few drops of acetic acid were added, and the mixture was concentrated to give **10** (0.5 mg, 51.9%) as a crude oil, which was further separated by chiral GC.

A stream of 4% ozone was passed through a solution of compound **1** (1 mg) in dichloromethane (1 mL) at −78 °C for 5 min. The solution was flushed with nitrogen and concentrated. The residue was dissolved in 90% HCOOH (0.5 mL) and 30% hydrogen peroxide (0.1 mL) was added. After gentle heating the mixture was heated under reflux for 70 min. The mixture was concentrated and the residue was dissolved in methanol (0.5 mL) and treated with excess diazomethane in diethyl ether. The resulting solution of **10** was further separated by chiral GC.

Chagosensine (1): Colorless powder (24.0 mg). $[\alpha]_D^{23} = -131$ (*c* = 0.015, CH_2Cl_2). UV λ_{max} (MeOH, nm) (log ε): 230 (4.16). IR (film, cm^{-1}): ν_{max} = 3650 (OH), 2900, 1735 (C=O), 1680. HRFABMS (*m*/*z*): 517.2153 $[M + H]^+$, calcd. for $[C_{24}H_{33}{}^{35}ClO_{10}+H]^+$ 517.2151; NMR spectra see Tables 1 and 3.

Methyl Ester 2: HRFABMS (*m*/*z*): 531.2313 $[M + H]^+$, calcd. for $[C_{25}H_{35}{}^{35}ClO_{10} + H]^+$ 531.2308; NMR spectra see Tables 1 and 3.

6,7-*O*-Isopropylidene Derivative 3: HRFABMS (*m*/*z*): 571.2625 $[M + H]^+$, calcd. for $[C_{28}H_{39}{}^{35}ClO_{10} + H]^+$ 571.2621; NMR spectra see Tables 1 and 3.

Methyl Ether 4: HRFABMS (*m*/*z*): 599.2938 $[M + H]^+$, calcd. for $[C_{30}H_{43}{}^{35}ClO_{10} + H]^+$ 599.2934; NMR spectra see Tables 1 and 3.

(*S*)-MTPA Ester 5a: HRFABMS (*m*/*z*): 1003.3421 $[M + H]^+$, calcd. for $[C_{48}H_{53}F_6{}^{35}ClO_{14} + H]^+$ 1003.3417; NMR spectra see Tables 1 and 3.

(*R*)-MTPA Ester 5b: HRFABMS (*m*/*z*): 1003.3423 $[M + H]^+$, calcd. for $[C_{48}H_{53}F_6{}^{35}ClO_{14} + H]^+$ 1003.3417; NMR spectra see Tables 1 and 3.

***p*-Methoxycinnamate (7):** HRFABMS (*m*/*z*): 879.3677 $[M + H]^+$, calcd. for $[C_{47}H_{55}{}^{35}ClO_{14} + H]^+$ 879.3670; NMR spectra see Tables 1 and 3.

Table 3. ^{13}C NMR of chagosensine (**1**) and its derivatives **2**−**7**

	1	**2**	**3**	**4**	**5a**	**5b**	**6**	**7**
1	176.5	170.5	170.5	170.5	170.5	170.5	170.5	170.5
2	80.8	80.8	80.8	80.8	80.8	80.8	80.8	80.4
3	36.6	36.6	36.6	36.6	36.6	36.6	36.6	36.1
4	38.0	38.0	38.4	38.4	38.4	38.4	38.0	37.5
5	72.4	72.4	70.5	70.5	70.5	70.5	72.4	70.8
6	75.5	75.5	85.5	85.5	85.5	85.5	75.5	80.1
7	72.0	72.0	74.0	74.0	74.0	74.0	72.0	68.4
8	133.6	133.6	137.3	137.3	137.3	137.3	133.6	133.6
9	128.2	128.2	128.2	128.2	128.2	128.2	128.2	128.0
10	126.9	126.9	126.9	126.9	126.9	126.9	124.5	121.9
11	136.2	136.2	136.2	136.2	136.2	136.2	136.2	136.2
12	61.3	61.3	61.3	65.2	64.2	64.2	65.2	65.2
13	70.7	70.7	70.7	68.5	67.4	67.4	68.5	68.5
14	32.9	32.9	32.9	33.6	33.1	33.1	33.6	33.6
15	72.7	72.7	72.7	73.4	71.7	71.7	73.4	73.4
16	81.8	81.8	81.8	79.3	78.6	78.6	79.3	79.3
17	67.2	67.2	67.2	74.9	74.5	74.5	74.9	74.9
18	128.5	128.5	128.5	128.8	128.8	128.8	128.8	128.8
19	133.4	133.4	133.4	133.4	133.4	133.4	133.4	133.4
20	31.2	30.4	30.4	30.4	30.4	30.4	30.4	30.4
21	47.8	40.2	40.2	40.2	40.2	40.2	40.2	40.2
22	178.5	172.0	172.0	172.0	172.0	172.0	172.0	172.0
23	14.8	14.8	14.8	14.8	14.8	14.8	14.8	14.8
24	19.5	19.5	19.5	19.5	19.5	19.5	19.5	19.5
COOMe	−	51.2	51.2	51.2	51.2	51.2	51.2	51.2
12-OMe	−	−	−	51.6	−	−	51.4	51.3
17-OMe	−	−	−	52.1	−	−	52.2	52.2
Me_2C(O)O	−	−	107.6	107.4	107.5	107.8	−	−
CH_3-	−	−	27.7	27.7	27.8	27.9	−	−
CH_3-	−	−	26.3	26.4	26.6	26.4	−	−
C=O	−	−	−	−	−	−	−	165.0
MeOCinn-C=C	−	−	−	−	−	−	−	117.6
MeOCinn-C=C	−	−	−	−	−	−	−	142.8
MeOCinn	−	−	−	−	−	−	−	127.3
MeOCinn	−	−	−	−	−	−	−	114.0
MeOCinn	−	−	−	−	−	−	−	161.2
MeOCinn	−	−	−	−	−	−	−	56.0
C=O	−	−	−	−	173.0	173.0	−	−
CF3	−	−	−	−	120.8	120.8	−	−
OCH_3	−	−	−	−	48.2	48.2	−	−
MTPA-C	−	−	−	−	102.4	102.4	−	−
MTPA	−	−	−	−	135.0	135.0	−	−
MTPA	−	−	−	−	129.9	129.9	−	−
MTPA	−	−	−	−	128.9	128.9	−	−
MTPA	−	−	−	−	127.3	127.3	−	−

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Received April 17, 2003

