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Enantioselective synthesis of γ-lactones from thioglycolic acid: Syntheses of (−)-muricatacin and 5-*epi*-(−)-muricatacin †

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Abstract

An approach for the enantioselective synthesis of functionalized γ-lactones and its application to the syntheses of (−)-muricatacin **1a** and 5-*epi*-(−)-muricatacin **1b** is reported. A sequential oxidation of the intermediate **4** with *m*-chloroperoxybenzoic acid was conducted to realize the reaction mechanism.

1. Introduction

Functionalized γ- and δ-lactones have attracted substantial attention in recent years due to the fact that they are important building blocks for natural product synthesis and many of them possess important biological activity.[1] (−)-Muricatacin **1a**, isolated from the seeds of *Annona muricata*, is a functionalized γ-lactone which shows some cytotoxicity on human tumor cell lines.[2] Syntheses of muricatacin and its isomer also attracted the attention of several synthetic groups.[1,3] We have reported an enantioselective synthesis of D-daunosaminide through a functionalized γ-lactone from thioglycolic acid employing (1*R*)-(+)-camphor as the chiral auxiliary with a high degree of asymmetric induction.[4] As a continuation of these studies, we report here an approach to the enantioselective synthesis of functionalized γ-lactones and its application to the syntheses of (−)-muricatacin **1a** and 5-*epi*-(−)-muricatacin **1b** from thioglycolic acid employing (1*R*)-(+)-camphor as the chiral auxiliary.

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† Dedicated to Professor Hsien-Ju Tien on the occasion of his 65th birthday.

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2. Results and discussion

A retrosynthesis of functionalized γ-lactones and (−)-muricatacin **1a** is shown in Scheme 1. Synthesis of a γ-lactone and (−)-muricatacin requires an enantioselective *cis*-dihydroxylation of the C_4–C_5 double bond followed by a lactonization on intermediate **2**. Intermediate **2** could be prepared from the alkylation of a chiral acetate with 1-halo-2-pentadecene. We have shown that chiral oxathiolanone **3** could be used as a chiral acetate equivalent.[4] Thus, chiral oxathiolanone **3**, prepared from the condensation of thioglycolic acid and (1*R*)-(+)-camphor,[5] was treated with lithium diisopropylamide followed by a 1-iodo-2-alkene to give the corresponding alkylation product **4** in moderate to good yields with good diastereoselectivity (Eq. 1 and Table 1).

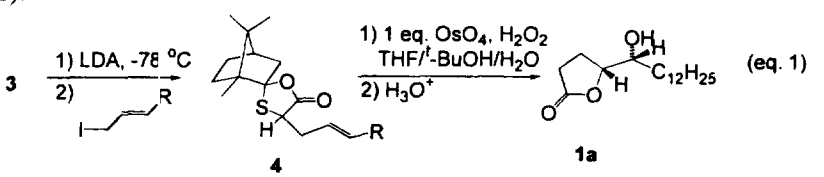
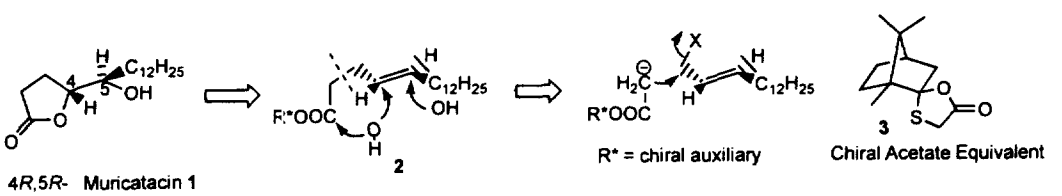


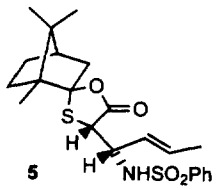
Table 1
Diastereoselective alkylation of oxathiolanone **3**

entry	alkenyl iodide	product	yield(%)	ratio(α:β)
1	R = H	**4a**	89	104:1
2	R = CH_3	**4b**	85	20:1
3	R = Ph	**4c**	74	25:1
4	R = $C_{12}H_{25}$	**4d**	47	7:1

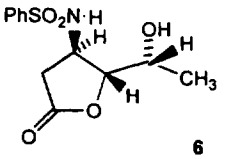


Scheme 1.

Treatment of **4dα** with 10% OsO_4 and excess H_2O_2 at 25°C for 24 hours gave no sign of the formation of γ-lactone. When **4dα** was treated with an equimolar amount of OsO_4 and excess H_2O_2 at 25°C for 48 h followed by acidification with hydrochloric acid, a γ-lactone was obtained in 29% yield. This result is in contrast to our previous observation where compound **5** upon treatment with 10% OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) gave γ-lactone **6** in 65% yield directly.



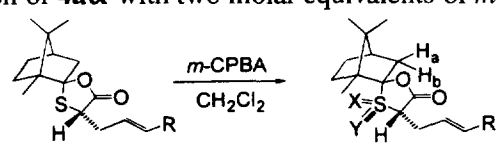
5



6

From comparison of our spectral data and specific rotation for the product from OsO_4 mediated oxidation with those reported in the literature, we assigned our product as (−)-muricatacin **1a** with 81% enantiomeric excess.[3a] Treatment of **4dα** with three molar equivalents of *m*-chloroperoxybenzoic acid (*m*-CPBA) at 25°C for 9 h also gave a γ-lactone in 58% yield. After comparison of the spectral data and specific rotation for this γ-lactone with that for (−)-muricatacin **1a** and its diastereomer, we assigned this product as 5-*epi*-(−)-muricatacin **1b** with 88% enantiomeric excess.[3a]

Oxidation of **4cα** with one equimolar amount of *m*-CPBA at 25°C gave oxidation products **7a–c**, which is consistent with a random oxidation of sulfide to sulfoxide and sulfone with a slight preference for the formation of sulfoxide **7a**. Assignments for **7a** and **7b** were judged from the ^1H NMR chemical shifts of H_a and H_b. One would observe a deshielding effect for H_a and a shielding effect for H_b by the S=O group in their ^1H NMR spectra, due to the spatial arrangement of S=O. H_a in **7a** will appear further downfield than in **7b**, and H_b in **7a** will appear further upfield than in **7b** in their ^1H NMR spectra. Oxidation of **4aα** with two molar equivalents of *m*-CPBA at 25°C gave **7d** in 93% yield (Eq. 2).

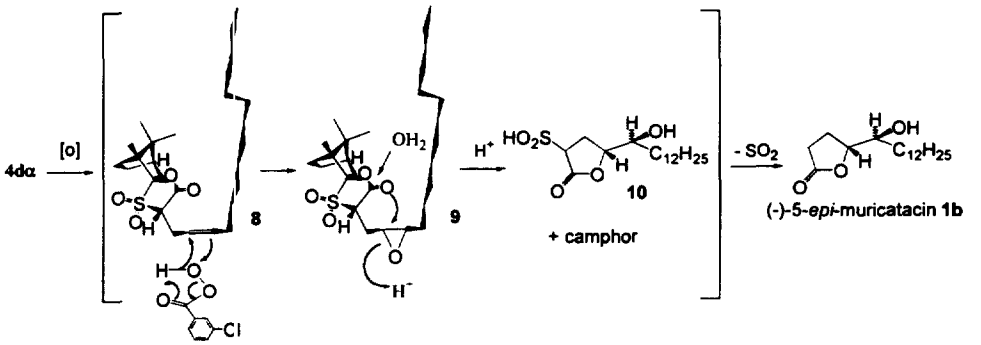


4aα R = H
4cα R = Ph

7a R = Ph, X = O, Y = lone pair (57%)
7b R = Ph, X = lone pair, Y = O (17%)
7c R = Ph, X = Y = O (15%)
7d R = H, X = Y = O (93%)

(eq. 2)

Neither reaction gave the C=C bond epoxidized product. Thus it is reasonable to assume that *m*-CPBA oxidation of **4dα** to 5-*epi*-(−)-muricatacin **1b** proceeded as shown in Scheme 2. At the early stage of oxidation, the sulfide moiety of **4dα** was oxidized to give the corresponding sulfone **8**. Conformational analysis of **8** based on MM2 calculation reveals that the most stable conformation[6] for **8** is a saxophone-shaped molecule with the $CH_2CH{=}CHCH_2$ moiety sitting at the bottom (Fig. 1). Since a sulfone is a rather non-directing functionality for *m*-CPBA oxidation,[7] the oxidation of the double bond should proceed from the convex face of the molecule to give epoxide **9**. Epoxide **9** then underwent an acid promoted ring opening of the epoxide function followed by a translactonization to give **10**. Intermediate **10** was unstable and lost sulfur dioxide[8] to give **1b** as the product. Similarly, OsO_4 promoted oxidation of **4dα** to **1a** proceeded as depicted in Scheme 3. The sulfonyl group-directed stereoselective *cis*-dihydroxylation[9] of **8**, though not as selective as the sulfone intermediate derived from **5**, gave osmate **11** which, upon acid promoted translactonization and sulfur dioxide extrusion, gave **1a** as the product. The difference in the level of enantioselectivity between these cases is presumably due to the dihedral angle of S–C–C–C= in **5** being a better fit for osmium tetraoxide promoted *cis*-dihydroxylation.[10]



Scheme 2.

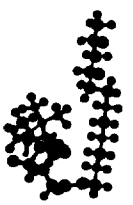
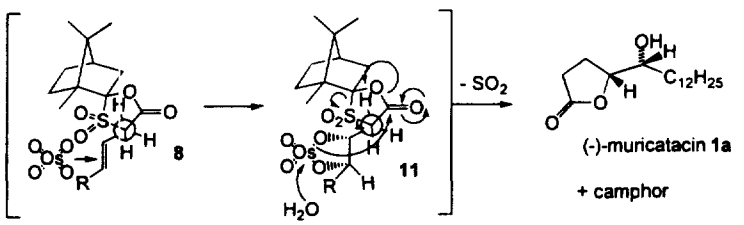


Fig. 1. Conformational analysis of **8** based on MM2 calculation



Scheme 3.

3. Conclusion

Although the yields for the enantioselective synthesis of (−)-muricatacin and 5-*epi*-(−)-muricatacin by our synthetic sequence are not high at the current stage, the compounds could be prepared in a very short synthetic sequence with high enantioselectivity. A sequential oxidation of compounds **4** reveals that the oxidation of a sulfide group to a sulfone group is faster than the oxidation of a double bond to an epoxide. More work has to be done to realize the unusual behavior of chiral 1,3-oxathiolan-5-ones, derived from camphor and thioglycoloic acid, upon oxidation that is either promoted or mediated by osmium tetraoxide.

4. Experimental

Unless otherwise noted, infrared spectra were run on neat liquids. The NMR spectra were run at 300 MHz for ^{1}H NMR, 75 MHz for ^{13}C NMR in $CDCl_3$ solution, and were referenced to the internal standard (TMS) in ppm units. Mass spectra were measured with the high-resolution electron impact technique on a JEOL JMS-HX110 mass spectrometer. Optical rotations were measured on a JASCO DIP-360 polarimeter. Column chromatography was performed on Merck 9385 Kieselgel 60 silica gel.

4.1. General procedure for the alkylation of 3

To a stirred tetrahydrofuran solution containing lithium diisopropylamide (0.50 mmol, 1 M) was slowly added a solution of 1,3-oxathiolan-5-one **3** (113 mg, 0.50 mmol) in tetrahydrofuran (1 mL) at −78°C. After 30 min, 1-iodo-2-alkene (0.50 mmol) was added. The reaction mixture was stirred for an additional 1 h at −78°C and neutralized with 5% aqueous oxalic acid solution to pH 5–6. The aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed with brine (2×20mL), water (2×20mL), dried over anhydrous sodium sulfate, and then concentrated *in vacuo*. The residue was purified by column chromatography (hexanes–ethyl acetate) to give the corresponding 4-alkylation products. Two isomeric products could be separated by HLPC (Merck Lichrosorb Si 60 7μm; ethyl acetate:hexanes=1:100; 2 mL/min.).

4.1.1. (1R,2S,4′S)-2-(1,7,7-Trimethylbicyclo[2.2.1]heptane)-spiro-2′-[4′-(2-propenyl)-1′,3′-oxathiolan-5′-one] **4aα**

$[\alpha]_D^{28}$ +7.5 (*c* 2, $CHCl_3$); IR: ν 1760 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.73–5.85 (m, 1H), 5.09–5.18 (m, 2H), 3.98 (dd, *J*=9.6, 3.9 Hz, 1H), 2.90–2.94 (m, 1H), 2.52–2.58 (m, 1H), 2.38–2.42 (m, 1H), 2.05 (d, *J*=13.8 Hz, 1H), 1.84 (t, *J*=4.5 Hz, 1H), 1.16–1.73 (m, 4H), 1.02 (s, 3H), 0.91 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.1 (C), 134.1 (CH), 117.9 (CH_2), 99.1 (C), 53.8 (C), 50.0 (CH_2), 48.8 (C), 45.5 (CH), 45.2 (CH), 36.1 (CH_2), 31.7 (CH_2), 26.5 (CH_2), 20.97 (CH_3), 20.3 (CH_3), 9.7 (CH_3); MS (70 eV, *m/z*): 266 (M^+), 815, 153, 110, 95, 86.

4.1.2. (1R,2S,4′S)-2-(1,7,7-Trimethylbicyclo[2.2.1]heptane)-spiro-2′-[4′-(2-butenyl)-1′,3′-oxathiolan-5′-one] **4bα**

$[\alpha]_D^{20}$ −63.8 (*c* 6.65, $CHCl_3$); IR: ν 1765 cm^{-1}; ^1H NMR: δ 5.46–5.54 (m, 1H), 5.32–5.39 (m, 1H), 3.78 (dd, *J*=8.7, 4.3 Hz, 1H), 2.60–2.66 (m, 1H), 2.49 (ddd, *J*=14.4, 4.4, 3.4 Hz, 1H), 2.31–2.39 (m, 1H), 1.81 (d, *J*=14.4 Hz, 1H), 1.74–1.86 (m, 1H), 1.73 (t, *J*=4.4 Hz, 1H), 1.44–1.64 (m, 1H), 1.00–1.09 (m, 1H), 0.96 (s, 3H), 0.82 (s, 3H), 0.80 (s, 3H); ^{13}C NMR: δ 174.0 (C), 129.0 (CH), 126.1 (CH_2), 99.1 (C), 54.9 (C), 50.1 (CH_2), 48.4 (C), 47.4 (CH), 45.0 (CH), 37.1 (CH_2), 31.4 (CH_2), 26.4 (CH_2), 21.0 (CH_3), 20.2 (CH_3), 17.7 (CH_3), 9.5 (CH_3); HRMS (70 eV, *m/z*) for $C_{16}H_{24}O_2S$ calcd 280.1497, found 280.1497.

4.1.3. (1R,2S,4′R)-2-(1,7,7-Trimethylbicyclo[2.2.1]heptane)-spiro-2′-[4′-(2-butenyl)-1′,3′-oxathiolan-5′-one] **4bβ**

$[\alpha]_D^{20}$ +93.7 (*c* 0.85, $CHCl_3$); IR: ν 1767 cm^{-1}; ^1H NMR: δ 5.54–5.56 (m, 1H), 5.39–5.42 (m, 1H), 3.94 (dd, *J*=9.6, 3.9 Hz, 1H), 2.80–2.82 (m, 1H), 2.54 (ddd, *J*=13.7, 4.4, 3.2 Hz, 1H), 2.33–2.35 (m, 1H), 2.04 (d, *J*=13.7 Hz, 1H), 2.02–2.06 (m, 1H), 1.84 (t, *J*=4.4 Hz, 1H), 1.46–1.75 (m, 1H), 1.16–1.23 (m, 1H), 1.02 (s, 3H), 0.90 (s, 3H), 0.80 (s, 3H); ^{13}C NMR: δ 174.2 (C), 128.7 (CH), 126.7 (CH), 98.9 (C), 53.8 (C), 50.1 (CH_2), 48.7 (C), 46.3 (CH), 45.2 (CH), 35.0 (CH_2), 31.6 (CH_2), 26.5 (CH_2), 20.9 (CH_3), 20.3 (CH_3), 17.8 (CH_3), 9.7 (CH_3); HRMS (70 eV, *m/z*) for $C_{16}H_{24}O_2S$ calcd 280.1497, found 280.1489.

4.1.4. (1R,2S,4′S)-2-(1,7,7-Trimethylbicyclo[2.2.1]heptane)-spiro-2′-[4′-(3-phenyl-2-pentenyl)-1′,3′-oxathiolan-5′-one] **4cα**

$[\alpha]_D^{20}$ −91.2 (*c* 6.97, $CHCl_3$); IR: ν 3023, 1762 cm^{-1}; ^1H NMR: δ 7.21–7.36 (m, 5H), 6.50 (d, *J*=15.8 Hz, 1H), 6.18 (dt, *J*=15.8, 7.1 Hz, 1H), 3.99 (dd, *J*=8.8, 4.4 Hz, 1H), 2.93–2.94 (m, 1H), 2.58 (ddd, *J*=14.4, 4.6, 3.0 Hz, 1H), 2.54–2.68 (m, 1H), 1.89 (d, *J*=14.4 Hz, 1H), 1.79 (t, *J*=4.6 Hz, 1H), 1.53–1.71 (m, 1H), 1.07–1.11 (m, 1H), 1.04 (s, 3H), 0.89 (s, 6H); ^{13}C NMR: δ 174.4 (C), 136.8 (C), 133.7 (CH), 128.5 (CH), 127.5 (CH), 126.3 (CH), 125.0 (CH), 99.8 (C), 55.3 (C), 50.3 (CH_2), 48.7 (C),

47.6 (CH), 45.3 (CH), 37.7 (CH_2), 31.6 (CH_2), 26.7 (CH_2), 21.3 (CH_3), 20.5 (CH_3), 9.8 (CH_3); HRMS (70 eV, *m/z*) for $C_{21}H_{26}O_2S$ calcd 342.1653, found 342.1647.

4.1.5. (1R,2S,4′R)-2-(1,7,7-Trimethylbicyclo[2.2.1]heptane)-spiro-2′-[4′-(3-phenyl-2-pentenyl)-1′,3′-oxathiolan-5′-one] ***4cβ***

$[\alpha]_D^{20}$ +77.6 (*c* 1.84, $CHCl_3$); IR: ν 3024, 1763 cm^{-1}; ^1H NMR: δ 7.26–7.41 (m, 5H), 6.56 (d, *J*=15.8 Hz, 1H), 6.22 (dt, *J*=15.8, 7.1 Hz, 1H), 4.13 (dd, *J*=9.3, 4.1 Hz, 1H), 3.10–3.13 (m, 1H), 2.59–2.67 (m, 2H), 2.12 (d, *J*=13.7 Hz, 1H), 1.91 (t, *J*=4.4 Hz, 1H), 1.52–1.80 (m, 3H), 1.24–1.31 (m, 1H), 1.10 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H); ^{13}C NMR: δ 174.0 (C), 136.8 (C), 133.1 (CH), 128.5 (CH), 127.4 (CH), 126.2 (CH), 125.5 (CH), 99.1 (C), 53.8 (C), 50.0 (CH_2), 48.7 (C), 46.1 (CH), 45.2 (CH), 35.3 (CH_2), 31.6 (CH_2), 26.4 (CH_2), 20.9 (CH_3), 20.3 (CH_3), 9.7 (CH_3); HRMS (70 eV, *m/z*) for $C_{21}H_{26}O_2S$ calcd 342.1653, found 342.1658.

4.1.6. (1R,2S,4′S)-2-(1,7,7-Trimethylbicyclo[2.2.1]heptane)-spiro-2′-[4′-(2-pentadecenyl)-1′,3′-oxathiolan-5′-one] ***4dα***

$[\alpha]_D^{25}$ −32.9 (*c* 0.61, $CHCl_3$); IR ($CHCl_3$): 1770 cm^{-1}; ^1H NMR: δ 5.48–5.61 (m, 1H), 5.30–5.42 (m, 1H), 3.83 (dd, *J*=8.9, 4.4 Hz, 1H), 2.65–2.75 (m, 1H), 2.55 (ddd, *J*=13.6, 3.7, 3.4 Hz, 1H), 2.35–2.45 (m, 1H), 1.95–2.00 (m, 2H), 1.85 (d, *J*=13.6 Hz, 1H), 1.77 (t, *J*=4.4 Hz, 1H), 1.46–1.73 (m, 3H), 1.16–1.35 (m, 20H), 1.06–1.14 (m, 1H), 1.05 (s, 3H), 0.86 (s, 3H), 0.84 (s, 3H), 0.83 (t, *J*=6.9 Hz, 3H); ^{13}C NMR: δ 174.3 (C), 133.7 (CH), 124.7 (CH), 99.1 (C), 53.9 (C), 50.1 (CH_2), 48.8 (C), 46.3 (CH), 45.3 (CH), 31.9 (CH_2), 31.7 (CH_2), 29.7 (3×CH_2), 29.5 (3×CH_2), 29.4 (3×CH_2), 27.5 (CH_2), 26.5 (CH_2), 22.7 (CH_2), 20.9 (CH_3), 20.4 (CH_3), 14.1 (CH_3), 9.3 (CH_3); HRMS (70 eV, *m/z*) for $C_{27}H_{46}O_2S$ calcd 434.3218, found 434.4314.

4.1.7. (1R,2S,4′R)-2-(1,7,7-Trimethylbicyclo-[2.2.1]heptane)-spiro-2′-[4′-(2-pentadecenyl)-1′,3′-oxathiolan-5′-one] ***4dβ***

$[\alpha]_D^{25}$ +48.7 (*c* 0.40, $CHCl_3$); IR ($CHCl_3$): 1770 cm^{-1}; ^1H NMR: δ 5.48–5.61 (m, 1H), 5.38–5.42 (m, 1H), 3.94 (dd, *J*=9.6, 3.9 Hz, 1H), 2.78–2.92 (m, 1H), 2.53 (ddd, *J*=13.7, 4.2, 3.9 Hz, 1H), 2.25–2.41 (m, 1H), 2.04 (d, *J*=13.7 Hz, 1H), 1.90–1.99 (m, 2H), 1.83 (t, *J*=4.1 Hz, 1H), 1.39–1.70 (m, 3H), 1.19–1.35 (m, 20H), 1.05–1.14 (m, 1H), 1.01 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H), 0.85 (t, *J*=6.9 Hz, 3H); ^{13}C NMR: δ 174.2 (C), 134.4 (CH), 125.4 (CH), 98.9 (C), 53.8 (C), 50.1 (CH_2), 48.8 (C), 46.3 (CH), 45.2 (CH), 35.1 (CH_2), 32.4 (CH_2), 31.9 (CH_2), 31.7 (CH_2), 29.6 (3×CH_2), 29.5 (3×CH_2), 29.3 (CH_2), 29.1 (CH_2), 26.4 (CH_2), 22.7 (CH_2), 20.9 (CH_3), 20.3 (CH_3), 14.1 (CH_3), 9.7 (CH_3); HRMS (70 eV, *m/z*) for $C_{27}H_{46}O_2S$ calcd 434.3218, found 434.4315.

4.2. Oxidation of ***4cα*** *with one equivalent of* m-*chloroperoxybenzoic acid*

To a dichloromethane solution (1 mL) containing **4cα** (49.1 mg, 0.143 mmol) was slowly added *m*-chloroperoxybenzoic acid (80% purity, 29.1 mg, 0.135 mmol) in dichloromethane (1 mL) at −10°C. The mixture was allowed to warm to 25°C with stirring for 3 h, then saturated sodium sulfite solution (1 mL) was added. The aqueous layer was extracted with dichloromethane (3×5 mL). The combined organic layers were washed with brine, dried over sodium sulfate, then concentrated *in vacuo*. The residue was purified on a silica gel column eluted with EtOAc:hexanes (1:9) to give **7a** (29.1 mg, 0.081 mmol, 57%), **7b** (8.8 mg, 0.0246 mmol, 17%), and **7c** (8.0 mg, 0.0215 mmol, 15%).

4.2.1. (1R,2S,3′S,4′S)-2-(1,7,7-Trimethylbicyclo[2.2.1]heptane)-spiro-2′-[4′-(3-phenyl-2-pentenyl)-1′, 3′-oxathiolan-5′-one] S-oxide ***7a***

$[\alpha]_D^{25}$ +11.2 (*c* 2.1, $CHCl_3$); IR: ν 3025, 1780 cm^{-1}; ^1H NMR: δ 7.21–7.38 (m, 5H), 6.65 (d, *J*=15.8 Hz, 1H), 6.25 (dt, *J*=15.8, 7.1 Hz, 1H), 3.74 (dd, *J*=6.0, 6.0 Hz, 1H), 2.91–3.20 (m, 2H), 2.63 (d, *J*=15.6 Hz, 1H), 1.95–2.05 (m, 2H), 1.55–1.79 (m, 3H), 1.15–1.29 (m, 1H), 1.08 (s, 3H), 0.93 (s, 3H), 0.90 (s, 3H); ^{13}C NMR: δ 166.4 (C), 136.5 (C), 135.0 (CH), 128.6 (2×CH), 127.8 (CH), 126.4 (2×CH), 122.7 (CH), 105.0 (C), 63.8 (CH), 52.6 (C), 51.3 (C), 44.9 (CH), 33.3 (CH_2), 30.6 (CH_2), 29.5 (CH_2), 25.3 (CH_2), 20.1 (CH_3), 19.5 (CH_3), 10.4 (CH_3); HRMS (70 eV, *m/z*) for $C_{21}H_{26}O_3S$ calcd 358.1602, found 358.1599.

4.2.2. (1R,2S,3′R,4′S)-2-(1,7,7-Trimethylbicyclo[2.2.1]heptane)-spiro-2′-[4′-(3-phenyl-2-pentenyl)-1′, 3′-oxathiolan-5′-one] S-oxide ***7b***

$[\alpha]_D^{25}$ −38.0 (*c* 1.00, $CHCl_3$); IR: ν 3025, 1779 cm^{-1}; ^1H NMR: δ 7.21–7.42 (m, 5H), 6.65 (d, *J*=15.5 Hz, 1H), 6.30 (dt, *J*=15.6, 8.4 Hz, 1H), 3.59 (dd, *J*=7.4, 7.4 Hz, 1H), 2.92–2.98 (m, 1H), 2.53 (d, *J*=15.3 Hz, 1H), 2.18 (dt, *J*=15.3, 4.1 Hz, 1H), 1.99 (t, *J*=4.0 Hz, 1H), 1.63–1.91 (m, 3H), 1.24–1.47 (m, 2H), 1.10 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H); ^{13}C NMR: δ 171.1 (C), 136.5 (C), 134.4 (CH), 128.6 (CH), 127.8 (2×CH), 126.4 (2×CH), 124.0 (CH), 109.8 (C), 60.9 (CH), 53.1 (C), 51.8 (C), 43.9 (CH), 37.3 (CH_2), 31.3 (CH_2), 26.7 (CH_2), 26.5 (CH_2), 20.2 (CH_3), 20.1 (CH_3), 11.1 (CH_3); HRMS (70 eV, *m/z*) for $C_{21}H_{26}O_3S$ calcd 358.1602, found 358.1602.

4.2.3. (1R,2S,4′S)-2-(1,7,7-Trimethylbicyclo[2.2.1]-heptane)-spiro-2′-[4′-(3-phenyl-2-pentenyl)-1′,3′-oxathiolan-5′-one] S,S-dioxide ***7c***

$[\alpha]_D^{25}$ +72.8 (*c* 0.40, $CHCl_3$); IR: ν 3030, 1778 cm^{-1}; ^1H NMR: δ 7.21–7.39 (m, 5H), 6.62 (d, *J*=15.8 Hz, 1H), 6.26 (dt, *J*=15.8, 6.5 Hz, 1H), 3.51 (dd, *J*=11.0, 4.3 Hz, 1H), 2.85–3.06 (m, 2H), 2.06–2.15 (m, 1H), 1.85–2.05 (m, 3H), 1.43–1.58 (m, 2H), 1.17–1.25 (m, 1H), 1.12 (s, 3H), 1.03 (s, 3H), 0.92 (s, 3H); ^{13}C NMR: δ 171.8 (C), 136.5 (C), 134.4 (CH), 128.6 (2×CH), 126.3 (2×CH), 124.0 (CH), 103.7 (C), 60.9 (CH), 53.4 (C), 50.7 (C), 44.6 (CH), 40.7 (CH_2), 31.2 (CH_2), 25.9 (CH_2), 25.6 (CH_2), 20.6 (CH_2), 20.0 (CH_3), 19.5 (CH_3), 10.3 (CH_3); HRMS (70 eV, *m/z*) for $C_{21}H_{26}O_4S$ calcd 374.1511, found 374.1554.

4.3. Oxidation of ***4aα*** *with two equivalents of* m-*chloroperoxybenzoic acid*

To a dichloromethane solution (1 mL) containing **4aα** (100 mg, 0.377 mmol) was slowly added *m*-chloroperoxybenzoic acid (80% purity, 160 mg, 0.74 mmol) in dichloromethane (2 mL) at −10°C. The mixture was allowed to warm to 25°C with stirring for 14 h, then saturated sodium sulfite solution (1 mL) was added. The aqueous layer was extracted with dichloromethane (3×5 mL). The combined organic layer was washed with brine, dried over sodium sulfate, then concentrated *in vacuo*. The residue was purified on a silica gel column eluted with EtOAc:hexanes (1:9) to give **7d** (104 mg, 93%).

4.3.1. (1R,2S,4′S)-2-(1,7,7-Trimethylbicyclo[2.2.1]-heptane)-spiro-2′-[4′-(2-propenyl)-1′,3′-oxathiolan-5′-one] S,S-dioxide ***7d***

$[\alpha]_D^{25}$ +181.3 (*c* 1.49, $CHCl_3$); IR: ν 1784 cm^{-1}; ^1H NMR: δ 5.81–5.96 (m, 1H), 5.18–5.31 (m, 2H), 3.44 (dd, *J*=11.0, 4.1 Hz, 1H), 2.76–2.91 (m, 2H), 1.96–2.13 (m, 2H), 1.78–1.95 (m, 3H), 1.44–1.60 (m, 1H), 1.15–1.23 (m, 1H), 1.09 (s, 3H), 1.02 (s, 3H), 0.89 (s, 3H); ^{13}C NMR: δ 171.9 (C), 132.8 (CH), 119.2 (CH), 103.6 (C), 60.2 (CH), 53.4 (C), 50.7 (C), 44.6 (CH), 40.6 (CH_2), 31.2 (CH_2), 26.9 (CH_2),

26.1 (CH_2), 20.0 (CH_3), 19.4 (CH_3), 10.3 (CH_3); HRMS (70 eV, *m/z*) for $C_{15}H_{22}O_4S$ calcd 298.1239, found 298.1243.

4.4. 5-epi-(−)-Muricatacin *1b*

To a dichloromethane solution (2 mL) containing **4dα** (106.4 mg, 0.245 mmol) was slowly added *m*-chloroperoxybenzoic acid (80% purity, 174 mg, 0.80 mmol) in dichloromethane (2 mL) at −10°C. The mixture was allowed to warm to 25°C with stirring for 10 h, then saturated sodium sulfite solution (1 mL) was added. The aqueous layer was extracted with dichloromethane (3×5 mL). The combined organic layers were washed with brine, dried over sodium sulfate, then concentrated *in vacuo*. The residue was purified on a silica gel column eluted with EtOAc:hexanes (1:3) to give **1b** (40.7 mg, 58%). **1b**: $[\alpha]_D^{25}$ −11.0 (*c* 0.40, $CHCl_3$); IR: ν ($CHCl_3$) 3431, 1767 cm^{-1}; ^1H NMR, δ 0.85 (t, *J*=7.0 Hz, 3H), 1.15–1.28 (m, 20H), 1.30–1.46 (m, 2H), 1.51 (br, 1H), 2.13–2.30 (m, 2H), 2.42–2.65 (m, 2H), 3.90 (m, 1H), 4.41 (dt, *J*=7.6, 3.2 Hz, 1H); ^{13}C NMR: δ 14.1 (CH_3), 21.1 (CH_2), 22.7 (CH_2), 25.6 (CH_2), 28.7 (CH_2), 29.3 (CH_2), 29.5 (3×CH_2), 29.6 (3×CH_2), 31.9 (2×CH_2), 71.4 (CH), 82.8 (CH), 177.4 (C); HRMS for $C_{17}H_{32}O_3$, calcd 284.2351, found 284.2351.

4.5. (−)-Muricatacin *1a*

To a tetrahydrofuran solution (25 mL) containing **4dα** (89.2 mg, 0.206 mmol) was added 1% aqueous OsO_4 solution (5.2 mL) and 30% H_2O_2 (0.05 mL) at 25°C. The mixture was allowed to stir for 24 h, then saturated sodium sulfite solution (5 mL) was added and the solution was acidified to pH 2 with HCl. The aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic layer was washed with brine, dried over sodium sulfate, then concentrated *in vacuo*. The residue was purified on a silica gel column eluted with EtOAc:hexanes (1:3) to give **1a** (30.6 mg). The product was further purified with HPLC (Merck Lichrosorb Si 60, 7μm; ethyl acetate:hexanes=1:3) to give pure **1a** (17.2 mg, 29%). **1a**: $[\alpha]_D^{25}$ −20.5 (*c* 0.5, $CHCl_3$); IR: ν ($CHCl_3$) 3432, 1767 cm^{-1}; ^1H NMR: δ 0.85 (t, *J*=7.0 Hz, 3H), 1.11–1.44 (m, 20H), 1.46–1.54 (m, 2H), 1.88 (br, 1H), 2.03–2.29 (m, 2H), 2.46–2.65 (m, 2H), 3.55 (m, 1H), 4.39 (dt, *J*=7.3, 4.7 Hz, 1H); ^{13}C NMR: δ 14.1 (CH_3), 22.7 (CH_2), 24.1 (CH_2), 25.4 (CH_2), 28.7 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (3×CH_2), 29.6 (CH_2), 31.9 (CH_2), 33.0 (CH_2), 73.7 (CH), 82.9 (CH), 177.1 (C); HRMS for $C_{17}H_{32}O_3$, calcd 284.2351, found 284.2368.

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