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Tetrahedron: *Asymmetry* 14 (2003) 3225–3232

TETRAHEDRON: *ASYMMETRY*

Enantioselective synthesis of 1-alkyl-substituted 1-phenyl-1,2-ethanediols using a myrtenal-derived chiral auxiliary

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Received 1 July 2003; accepted 25 July 2003

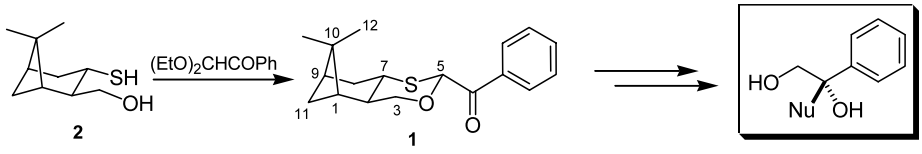
Abstract—The enantioselective synthesis of several 1-phenyl-1,2-ethanodiol derivatives using 2-benzoyl-1,3-oxathiane **1** as a chiral auxiliary is described. Nucleophilic additions of Grignard reagents, methyl lithium and *LS*-Selectride on benzoyloxathiane **1** proceeded in >95% diastereomeric ratio (dr) affording the corresponding tertiary carbinols, which were successively hydrolyzed and reduced to give the title derivatives in >95% enantiomeric excess (ee).

1. Introduction

Substituted 1-phenyl-1,2-ethanediols having an alkyl group at C-1 widely occur in biologically active molecules such as antifungal,[1,2] herbicidal,[3] anticonvulsant,[4] immunosupresor,[5] muscarinic M3 receptor antagonist,[6] hair growth stimulant,[7] antitumoral[8] and antiperspirant compounds.[9,10] Some of these biological activities were described using racemic 1-phenyl-1,2-ethanediol derivatives to prepare the active compound,[4,8–10] and therefore we were encouraged to develop a practical methodology to achieve the enantioselective synthesis of the former molecules. Thus, taking advantage of the recently published synthesis of a new (1*R*)-myrtenal-derived chiral auxiliary,[11] herein is presented an easy synthetic methodology, starting from benzoyloxathiane **1**, for the preparation of enantiomerically pure 1-alkyl-substituted 1-phenyl-1,2-ethanediols, which can be used as key precursors for the preparation of both known and new bioactive compounds.

2. Results and discussion

In a previous paper we described the synthesis of hydroxythiol **2** in both excellent yield and high enantiomeric excess,[11] a compound which was now used as the starting material for the synthesis of the new benzoyl-1,3-oxathiane **1** (Chart 1).[12] Thus, hydroxythiol **2**, which is easely obtained in higher yield and enantiomeric purity than the hydroxythiol derived from (*R*)-(+)-pulegone,[13] was treated with 1.2 equiv. of α,α-diethoxyacetophenone in boiling toluene and in the presence of catalytic amounts of *p*-TsOH, giving benzoyloxathiane **1** in 58% yield. The substantial higher yield obtained in this reaction, as compared to the



2 1

Chart 1.

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doi:10.1016/j.tetasy.2003.07.017

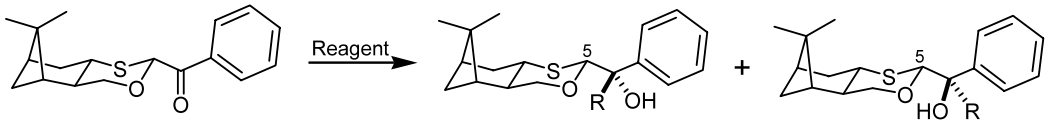
preparation of the structural analogous 2-acetyl-1,3-oxathiane,[11] could be due to the slightly better stability shown by α,α-diethoxyacetophenone, as compared to α,α-dimethoxyacetone under the same acidic reaction conditions. This can be accounted by the presence of more by-products when the later acetal is used as the acylating agent. The (*R*)-configuration of the new stereogenic center, C-5, was assigned by means of NMR NOE experiments, since upon irradiation of H-5, the signals owing to H-3*axial* and H-7 showed 6 and 8% enhancement, respectively. Implicitly, this experiment confirmed the (*R*)- and (*S*)-configuration at C-2 and C-7, respectively. Similarly to the preparation of the structural analogue 2-acetyl-1,3-oxathiane,[11] formation of benzoyloxathiane **1** was accompanied by traces of the corresponding axial epimer.

Table 1 shows diastereoselectivity and chemical yields obtained when benzoyloxathiane **1** was subjected to nucleophilic additions with several organometallic and reducing agents to afford mixtures of adducts **3** and **4**. Chemical yields range from good to excellent. However, when EtMgBr, *i*-PrMgBr and *i*-BuMgBr were used, significant presence of reduction products was observed.[14] It should be emphasized that the hydride provided by the above Grignard reagents yield the same adduct as that formed by addition of LAH, DIBAL and *LS*-Selectride (Table 1, entries 10, 11 and 12). Similarly, addition of MeLi and MeMgBr afforded the same compound (Table 1, entries 1 and 9) revealing that the attack to the carbonyl group by both reagents is taking place on the same molecular face. The yields reported in entries 8, 10 and 11, are described for mixtures of the corresponding epimers.

Diastereoselectivity was measured by means of ^{1}H NMR by integrating H-5 in the crude reaction mixture, since the chemical shifts of this proton appear systematically at lower field for the (*S*) epimer. Notation '≥99:1' as diastereomeric ratio means that only the major adduct was detected. It can be observed that the highest stereoselectivity is obtained in the expected order:[13] Grignard reagents>RLi≥aluminum hydrides. However, the better stereoselectivity observed with MeLi (≅ as MeMgBr) with regard to *n*-BuLi is not yet well understood. Efforts are underway to clarify this behavior. As predictable in this type of heterocyclic systems, major adducts (compounds **3**) are formed in agreement to the preferred nucleophilic attack through the *Re* face of the carbonyl group, according to the Cram chelated model.[15]

In Table 2 are summarized the chemical yields and enantiomeric excess (ee%) obtained after hydrolysis of adducts **3a–c**, **3f**,**g** and **3i**, as well as the subsequent reduction of the corresponding aldehydes. Best results of adduct hydrolysis were achieved by using $AgNO_3$, NCS in MeCN:H_2O for 5 min.[13] Since the intermediate aldehydes were unstable during chromatographic separation, they were transformed, by means of $NaBH_4$ or $LiAlH_4$, to the corresponding diols without further purification. We observed that the milder reductions with $NaBH_4$ were more efficient than reductions using $LiAlH_4$, thus allowing also a better recovery of the chiral auxiliary **2**, probably due to the easier work-up protocol followed in the former. Therefore, yields of most diols shown in Table 2 were obtained from $NaBH_4$ reductions (except entry 7) and after purification by column chromatography. It should be mentioned that hydrolysis of adduct **3g**, and subsequent $LiAlH_4$ reduction of the corresponding aldehyde, furnished a mixture of diol **5g** and the styrene derivative **5k**, which was formed by the conjugated 1,4-addition of hydride. Since this mixture was difficult to separate by column chromatography, it was converted into diol **5j** by means of catalytic hydrogenation. The non-enan-

Table 1. Addition reactions to benzoyloxathiane **1**

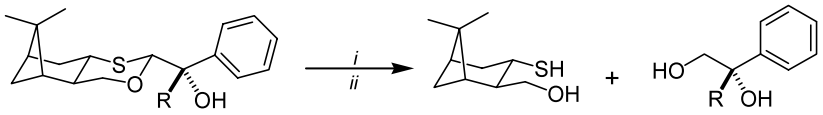


1 **3** **4**

Entry	Reagent	R	Comp. (%)[a]	Ratio **3**:**4**[c]
1	MeMgBr	Me	**3a** (>99)	≥99:1
2	EtMgBr	Et	**3b** (85)	≥99:1
3	*i*-PrMgBr	*i*-Pr	**3c** (60)	≥99:1
4	$PhCH_2MgCl$	$PhCH_2$	**3d** (80)	≥99:1
5	*i*-BuMgBr	*i*-Bu	**3e** (71)	≥99:1
6	CH_2=CHMgBr	CH_2=CH	**3f** (90)	≥99:1
7	PhC≡CMgBr	PhC≡C	**3g** (97)	≥99:1
8	*n*-BuLi	*n*-Bu	**3h** (78)[b]	84:16
9	MeLi	Me	**3a** (>99)	≥99:1
10	LAH	H	**3i** (92)[b]	82:18
11	DIBAL	H	**3i** (70)[b]	89:11
12	*LS*-Selectride	H	**3i** (82)	≥99:1

[a] Calculated after purification by column chromatography.
[b] Calculated as mixture of **3** and **4**.
[c] Determined by ^{1}H NMR integration of H-5 on the crude reaction mixture.

Table 2. Hydrolysis of adducts **3**



3 **2** **5**

Entry	R	Yield (%)[a]	$[\alpha]$[b]	Ee (%)[c]
1	Me	**5a** (92)	+5.7	>98
2	Et	**5b** (75)	−7.2	>98
3	*i*-Pr	**5c** (80)	−19.0	>98
4	CH_2=CH	**5f** (89)	−43.4	>98
5	PhC≡C	**5g** (90)[d]	+11.0	>98
6[e]	$PhCH_2CH_2$	**5j** (90)	+10.6	>98
7[f]	PhCH=CH	**5k** (35)	–[h]	–
8	H	**5i** (73)	+38.6	>98

Reaction conditions: (i) $AgNO_3$, CH_3CN, rt, 1–5 min; (ii) $NaBH_4$, THF. Yield of recovered hydroxythiol: 60–80%.
[a] After column chromatography.
[b] See Section 3 for solvent used.
[c] See Section 3 for ee% of described diols.
[d] Obtained when $NaBH_4$ was used as reducing agent.
[e] Obtained by catalytic hydrogenation (Pd/C) of diol **5g**.
[f] Formed by conjugated addition of $LiAlH_4$ to diol **5g**.
[h] Not measured.

tioselective syntheses of diols **5g**[16] and **5j**[17] were previously described, but complete spectroscopic data and specific rotations were not reported. Taking into account the high diastereoselectivity obtained in the addition of PhC≡CMgBr to benzoyloxathiane **1** (entry 7, Table 1), and assuming no racemization occurs during the subsequent transformations, we are confident that the present optical data for **5g** and **5j** are for the pure enantiomer (see below). On the other hand, diol **5a** was obtained in essentially the same chemical yield and enantiomeric purity as its enantiomer, which was previously prepared through the addition of C_6H_5MgBr to 2-acetyloxathiane,[11] followed by hydrolysis and reduction of the corresponding intermediates.

As can be appreciated in Tables 1 and 2, the enantiomeric excess obtained for each diol was consistent with the diastereomeric ratio observed at the corresponding adduct stage, and therefore, essentially no racemization is taking place during the hydrolysis and reduction conditions. Thus, the (*S*)-absolute configuration of all prepared diols is in agreement with the above mentioned Cram chelated model operating at the nucleophilic addition on benzoyloxathiane **1**. In conclusion, present results describe a really accessible methodology toward the previously non trivial enantioselective synthesis of optically active terminal 1,2-diols bearing a tertiary carbinol as the stereogenic center.

3. Experimental

3.1. General

Melting points were determined on an electrothermal capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Spectrum 2000 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on a Varian Mercury spectrometer at 300 and 75.4 MHz, respectively, using $CDCl_3$ as solvent and TMS as internal standard. The low resolution mass spectra (LRMS) were recorded on HP 5971A or Varian Saturn 2000 GC/Selective Mass Detectors, either using EI (70 eV) or CI, as it is specified. High-resolution FABMS data were collected on a JMS-SX 102 mass spectrometer. Thin-layer chromatograms were done on precoated TLC sheets of silica gel 60 F_{254} (E. Merck). Flash chromatography was carried out using Merck silica gel (230–400 mesh). THF used in the nucleophilic additions was distilled from Na immediately prior to use, and all other reagents were used without further purification. Optical rotations were measured at 589 nm using a 1 dm cell on a JASCO DIP-370 polarimeter.

3.2. (1*S*,2*R*,5*R*,7*S*,9*R*)-5-Benzoyl-10,10-dimethyl-4-oxa-6-thiatricyclo[7.1.1.$0^{2,7}$]undecane 1

A well stirred solution of 3 g (16.1 mmol) of hydroxythiol **2**,[11] 4 g (19.2 mmol) of α,α-diethoxyacetophenone and 300 mg of *p*-TsOH in 200 mL of toluene was refluxed at room temperature for 45 min. The reaction mixture was poured into a cold saturated solution of $NaHCO_3$, extracted with ethyl ether, washed with a saturated solution of $NaHCO_3$ (2×50 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness. The oily residue was flash chromatographed using a mixture of hexane:EtOAc (99:1) as the eluent, obtaining 2.2 g (45%) of benzoyloxathiane **1** as a white solid, mp

67–69°C. $[\alpha]_D^{25}=-68.4$ (*c* 0.19, $CHCl_3$). ^1H NMR: δ 8.11 (bd, 2H, $J=7.4$ Hz, H-*o*), 7.58 (bt, 1H, $J=7.4$ Hz, H-*p*), 7.46 (bt, 2H, $J=7.4$ Hz, H-*m*), 6.22 (s, 1H, H-5), 4.23 (dd, 1H, $J=11.0$, 2.8 Hz, H-3e), 3.99 (dt, 1H, $J=11.0$, 8.8 Hz, H-7), 3.80 (t, 1H, $J=11.0$ Hz, H-3a), 2.63 (m, 2H, H-2, H-11e), 2.40 (dddd, 1H, $J=13.0$, 8.8, 5.0, 2.2 Hz, H-8e), 2.15 (bq, 1H $J=5.0$ Hz, H-9), 1.82 (t, 1H, $J=6.0$ Hz, H-1), 1.79 (ddd, 1H, $J=13.0$, 11.0, 1.4 Hz, H-8a), 1.29 (s, 3H, H-13), 1.22 (s, 3H, H-12), 1.06 (d, 1H, $J=10.0$ Hz, H-11a). ^{13}C NMR: δ 192.1 (C-1′), 133.8 (C-*i*), 133.7 (C-*p*), 129.5 (C-*o*), 128.4 (C-*m*), 86.9 (C-5), 76.4 (C-3), 51.2 (C-2), 45.7 (C-9), 43.4 (C-1), 42.6 (C-7), 39.5 (C-11), 39.0 (C-10), 33.4 (C-8), 29.5 (C-13), 24.6 (C-12). IR (KBr): 2917, 1735, 1692, 1449, 1072, 756 cm^{-1}. EIMS *m*/*z* (rel. int.): 302 (M^+, <1), 197 (100), 35 (2), 77 (2). HRFABMS *m*/*z* 303.1405 (calcd for $C_{18}H_{22}O_2S$+H, 303.1419).

3.2.1. General procedure for the addition of Grignard reagents to benzoyloxathiane 1. To a solution of benzoyloxathiane **1** (1 equiv.) in anhd. THF was added the Grignard reagent (1.5–2 equiv.) at −78°C under a nitrogen atmosphere. After stirring for 2 h at the same temperature, the reaction mixture was allowed to warm up to room temperature and further stirred for 1 h. The reaction mixture was quenched with 10 mL of a saturated solution of ammonium chloride, the THF was eliminated by evaporation and the remaining emulsion was extracted with ethyl ether. The organic layer was washed with a saturated solution of ammonium chloride, dried over anhd. Na_2SO_4 and concentrated to dryness, giving the corresponding pure diastereoisomer **3** (or admixed with **4**) as a colorless oil.

3.3. (1*S*,2*R*,5*R*,7*S*,9*R*)-5-[(1′*S*)-1′-Hydroxy-1′-phenyl-1′-ethyl)]-10,10-dimethyl-4-oxa-6-thiatricyclo[7.1.1.$0^{2,7}$]-undecane 3a

This compound was obtained by the following two procedures:

Method a: According to the above general procedure, to a well-stirred cooled (−78°C) solution of 158 mg (0.52 mmol) of **1** in 5 ml of anhd. THF under a nitrogen atmosphere, 187 mg (1.56 mmol) of methylmagnesium bromide in ethyl ether were added dropwise. After work-up, 166 mg (>99%) of pure **3a** were obtained as a single diastereoisomer (colorless oil).

Method b: A well-stirred cooled (−78°C) solution of 84 mg (0.28 mmol) of benzoyloxathiane **1** in 3 mL of anhydrous THF was treated with 0.42 mmol of MeLi in cyclohexane and stirred under a nitrogen atmosphere for 2 h. The mixture was quenched with 1 mL of a saturated soln. of ammonium chloride and allowed to warm up to room temperature. The THF was evaporated and the residue extracted with 50 mL of ethyl ether. The organic layer was washed with 5% aq. HCl (3×30 mL) and brine (1×30 mL), dried over anhd. Na_2SO_4 and evaporated to dryness. The crude reaction outcome was purified through a Chromatotron system using a mixture of hexane:EtOAc (19:1) as the eluent to give 88 mg (>99%) of **3a** as a colorless oil. $[\alpha]_D^{25}=-62.4$ (*c* 0.21, $CHCl_3$). ^1H NMR: δ 7.50 (dd, 2H, $J=8.1$, 1.2 Hz, H-*o*), 7.36 (t, 1H, $J=7.0$ Hz, H-*p*), 7.29 (t, 2H, $J=8.1$ Hz, H-*m*), 5.11 (s, 1H, H-5), 4.09 (dd, 1H, $J=11.1$, 2.9 Hz, H-3e), 3.68 (t, 1H, $J=11.1$ Hz, H-3a), 3.62 (t, 1H, $J=10.0$, 8.2 Hz, H-7), 2.95 (s, 1H, OH), 2.58 (m, 1H, H-11e), 2.40 (ddd, $J=11.1$, 10.5, 2.9 Hz, H-2), 2.29 (m, 1H, H-8e), 2.10 (q, 1H, $J=5.2$ Hz, H-9), 1.81 (t, 1H, $J=5.9$ Hz, H-1), 1.66 (s, 3H, H-2′), 1.62 (m, 1H, H-8a), 1.24 (s, 3H, H-13), 1.10 (s, 3H, H-12), 0.97 (d, 1H, $J=9.6$ Hz, H-11a). ^{13}C NMR: δ 143.0 (C-*i*), 127.9 (C-*p*), 127.3 (C-*m*), 125.2 (C-*o*), 93.3 (C-5), 76.4 (C-1′), 75.7 (C-3), 51.3 (C-2), 45.5 (C-9), 43.3 (C-1), 40.8 (C-7), 39.3 (C-11), 39.0 (C-10), 33.5 (C-8), 29.6 (C-13), 27.2 (C-2′), 24.5 (C-12). IR (neat): 3501, 2914, 1447, 1057, 758, 736, 699 cm^{-1}. EIMS *m*/*z* (rel. int.): 318 (M^+, <1), 197 (M−121, 100), 135 (32), 121 (39), 107 (68), 93 (72), 79 (81), 43 (85). HRFABMS *m*/*z* 319.1749 (calcd for $C_{19}H_{26}O_2S$+H, 319.1732).

3.4. (1*S*,2*R*,5*R*,7*S*,9*R*)-5-[(1′*S*)-1′-Hydroxy-1′-phenyl-1′-propyl)]-10,10-dimethyl-4-oxa-6-thiatricyclo[7.1.1.$0^{2,7}$]-undecane 3b

A solution of 169 mg (0.56 mmol) of **1** in 5 mL of anhydrous THF was treated with 112 mg (0.84 mmol) of ethylmagnesium bromide in ethyl ether. After work-up 158 mg (85%) of pure **3b** were obtained as a single diastereoisomer (colorless oil). $[\alpha]_D^{25}=-72.8$ (*c* 0.36, $CHCl_3$). ^1H NMR: δ 7.45–7.22 (m, 5H, Ar), 5.14 (s, 1H, H-5), 4.09 (dd, 1H, $J=10.5$, 2.3 Hz, H-3e), 3.7 (t, 1H, $J=10.5$ Hz, H-3a), 3.65 (dt, 1H, $J=10.5$, 9.0 Hz, H-7), 2.77 (bs, 1H, OH), 2.55 (m, 1H, H-11e), 2.40 (bt, 1H, $J=10.5$, H-2), 2.22 (m, 2H, H-2′a, H-8e), 2.08 (q, 1H, $J=5.2$ Hz, H-9), 1.91 (m, 1H, H-2′b), 1.80 (t, 1H, $J=5.9$ Hz, H-1), 1.61 (t, 1H, $J=12.0$ Hz, H-8a), 1.24 (s, 3H, H-13), 1.01 (s, 3H, H-12), 0.96 (d, 1H, $J=9.4$ Hz, H-11a), 0.70 (t, 3H, $J=7.0$ Hz, H-3′). ^{13}C NMR: δ 141.2 (C-*i*), 127.9 (C-*p*), 127.1 (C-*m*), 125.9 (C-*o*), 93.0 (C-5), 78.4 (C-1′), 76.4 (C-3), 51.3 (C-2), 45.5 (C-1), 43.2 (C-9), 40.8 (C-7), 39.3 (C-11), 38.9 (C-10), 33.5 (C-8), 31.8 (C-2′), 29.5 (C-13), 24.6 (C-12), 7.6 (C-3′). IR (neat): 3359, 2933, 1448, 1059, 736, 699 cm^{-1}. CIMS *m*/*z* (rel. int.): 333 (MH^+, 11), 315 (100), 197 (9), 147 (27), 135 (46), 57 (25). HRFABMS *m*/*z* 333.1891 (calcd for $C_{20}H_{28}O_2S$+H, 333.1888).

3.5. (1*S*,2*R*,5*R*,7*S*,9*R*)-5-[(1′*S*)-1′-Hydroxy-2′-methyl-1′-phenyl-1′-propyl)]-10,10-dimethyl-4-oxa-6-thiatricyclo-[7.1.1.$0^{2,7}$]undecane 3c

A solution of 109 mg (0.36 mmol) of **1** in 4 mL of anhydrous THF was treated with 80 mg (0.54 mmol) of *iso*-propylmagnesium bromide in ethyl ether. After work-up 74 mg (60%) of pure **3c** were obtained as a single diastereoisomer (colorless oil). $[\alpha]_D^{25}=-68.1$ (*c* 0.26, $CHCl_3$). ^1H NMR: δ 7.43 (d, 2H, $J=8.4$ Hz, H-*o*), 7.38–7.23 (m, 1H, H-*p*, 2H, H-*m*), 5.43 (s, 1H,

H-5), 4.17 (dd, 1H, $J=10.7$, 3.2 Hz, H-3e), 3.73 (dt, 1H, $J=10.0$, 8.8, H-7), 3.69 (t, 1H, $J=11.1$ Hz, H-3a), 2.83 (s, 1H, OH), 2.59 (m, 1H, H-11e), 2.31 (m, 3H, H-2, H-2′, H-8e), 2.10 (q, 1H, $J=5.0$ Hz, H-9), 1.80 (t, 1H, $J=6.0$ Hz, H-1), 1.60 (m, 1H, H-8a), 1.3 (s, 3H, H-13), 1.10 (s, 3H, H-12), 0.90 (d, 1H, $J=9.4$ Hz, H-11a), 0.85 (d, 3H, $J=6.9$ Hz, H-3′). ^{13}C NMR: δ 140.2 (C-*i*), 127.3 (C-*m*), 127.0 (C-*p*), 126.43 (C-*o*), 91.0 (C-5), 80.0 (C-1′), 76.4 (C-7), 51.3 (C-2′), 45.5 (C-1), 43.2 (C-9), 41.3 (C-7), 39.3 (C-11), 39.0 (C-10), 35.2 (C-2), 33.4 (C-8), 29.6 (C-13), 24.6 (C-12), 17.8 (C-3′a), 17.0 (C-3′b). IR (neat): 3563, 2912, 1448, 734 cm^{-1}. CIMS m/z (rel. int.): 347 (MH^+, 68), 329 (M^+-18, 72), 161 (91), 135 (100), 107 (8). HRFABMS m/z 347.2041 (calcd for $C_{21}H_{30}O_2S$+H, 347.2045).

3.6. (1*S*,2*R*,5*R*,7*S*,9*R*)-5-[(1′*S*)-1′-Hydroxy-1′,2′-diphenyl-1′-ethyl)]-10,10-dimethyl-4-oxa-6-thiatricyclo-[7.1.1.0^{2,7}]undecane 3d

A solution of 120 mg (0.40 mmol) of **1** in 4 mL of anhydrous THF was treated with 90 mg (0.60 mmol) of benzylmagnesium chloride in ethyl ether. After work-up, 126 mg (80%) of pure **3d** were obtained as a single diastereoisomer (colorless oil). $[\alpha]_D^{24}=-86.6$ (*c* 0.26, $CHCl_3$). ^{1}H NMR: δ 7.37–6.81 (m, 10H, Ar), 5.24 (s, 1H, H-5), 4.18 (dd, 1H, $J=10.9$, $J=3.1$ Hz, H-3e), 3.72 (t, 1H, $J=10.9$ Hz, H-3a), 3.63 (dt, 1H, $J=10.5$, 8.8, H-7), 3.35 and 3.26 (AB, 2H, $J=13.5$ Hz, CH_2Ph), 2.53 (m, 1H, H-11e), 2.83 (bs, 1H, OH), 2.58 (m, 1H, H-11e), 2.42 (bt, 1H, $J=10.5$ Hz, H-2), 2.25 (m, 1H, H-8e), 2.20 (bq, 1H, $J=5.4$ Hz, H-9), 1.81 (t, 1H, $J=5.8$ Hz, H-1), 1.63 (m, 1H, H-8a), 1.23 (s, 3H, H-13), 1.16 (s, 3H, H-12), 0.99 (d, 1H, $J=9.5$ Hz, H-11a). ^{13}C NMR: δ 141.6 (C-*i*′), 136.3 (C-*i*), 130.7 (C-*m*′), 127.7 (C-*m*), 127.6 (C-*o*′), 127.3 (C-*p*′), 126.3 (C-*p*), 126.0 (C-*o*), 91.8 (C-5), 78.3 (C-1′), 76.4 (C-3), 51.3 (C-2), 45.5 (C-1), 45.5 (*C*H_2Ph), 43.3 (C-9), 40.9 (C-7), 39.4 (C-11), 39.0 (C-10), 33.5 (C-8), 29.6 (C-13), 24.5 (C-12). IR (neat): 3448, 2920, 1449, 1050, 757, 693, cm^{-1}. EIMS m/z (rel. int.): 394 (M^+, <1), 197 (92), 135 (19), 107 (46), 105 (100), 77 (94), 41 (35).

3.7. (1*S*,2*R*,5*R*,7*S*,9*R*)-5-[(1′*S*)-1′-Hydroxy-3′-methyl-1′-phenyl-1′-butyl)]-10,10-dimethyl-4-oxa-6-thiatricyclo-[7.1.1.0^{2,7}]undecane 3e

A solution of 150 mg (0.50 mmol) of **1** in 5 ml of anhydrous THF was treated with 80 mg (0.75 mmol) of *iso*-butylmagnesium bromide in ethyl ether. After work-up 128 mg (71%) of pure **3e** were obtained as a single diastereoisomer (colorless oil). $[\alpha]_D^{20}=-68.8$ (*c* 0.5, EtOH). ^{1}H NMR: δ 7.46 (d, 1H, $J=7.5$ Hz, H-*o*), 7.37 (t, 2H, $J=7.5$ Hz, H-*p*), 7.28 (t, 2H, $J=7.5$ Hz, H-*m*), 5.08 (s, 1H, H-5), 4.10 (dd, 1H, $J=10.6$, 3.7 Hz, H-3e), 3.68 (t, 1H, $J=10.6$ Hz, H-3a), 3.60 (dt, 1H, $J=10.0$, 8.7 Hz, H-7), 2.77 (s, 1H, OH), 2.55 (m, 1H, H-11e), 2.39 (bt, 1H, $J=10.6$ Hz, H-2), 2.22 (m, 1H, H-8e), 2.10 (m, 2H, H-9, H-2′), 1.94 (m, 2H, H-1, H-2′), 1.58 (m, 1H, H-8a), 1.47 (m, 1H, H-3′), 1.23 (s, 3H, H-13), 1.10 (s, 3H, H-12), 0.96 (d, 1H, $J=10.0$ Hz, H-11a), 0.92 (d, 1H, $J=7.5$ Hz, H-4′a), 0.63 (d, 1H, $J=6.2$ Hz, H-4′b). ^{13}C NMR: δ 141.9 (C-*i*), 127.9 (C-*p*), 127.0 (C-*m*), 125.7 (C-*o*), 94.8 (C-5), 78.6 (C-1′), 76.4 (C-3), 51.4 (C-2), 47.4 (C-2′), 45.5 (C-9), 43.2 (C-1), 40.7 (C-7), 39.4 (C-11), 38.9 (C-10), 33.5 (C-8), 29.6 (C-13), 24.5 (C-12), 24.5 (C-4′b), 24.1 (C-4′a), 24.0 (C-3′). IR (neat): 3564, 2950, 1448, 1057, 682 cm^{-1}. CIMS m/z (rel. int.): 361 (MH^+, 11), 343 (100), 209 (10), 175 (15), 135 (43), 107 (4). HRFABMS m/z 361.2201 (calcd for $C_{22}H_{32}O_2S$+H, 361.2194).

3.8. (1*S*,2*R*,5*R*,7*S*,9*R*)-5-[(1′*S*)-1′-Hydroxy-1′-phenyl-2′-propen-1′-yl)]-10,10-dimethyl-4-oxa-6-thiatricyclo-[7.1.1.0^{2,7}]undecane 3f

Compound **1** (100 mg, 0.33 mmol) in anhydrous THF (5 mL) was treated with vinylmagnesium bromide (65 mg, 0.49 mmol) in ethyl ether. After work-up pure **3f** was obtained as a single diastereoisomer (colorless oil: 98 mg, 90%). $[\alpha]_D^{25}=-68.1$ (*c* 0.26, $CHCl_3$). ^{1}H NMR: δ 7.46 (d, 2H, $J=7.5$ Hz, H-*o*), 7.39–7.22 (m, 3H, Ar), 6.35 (dd, 1H, $J=17.6$, $J=10.5$ Hz, H-2′), 5.43 (d, 1H, $J=17.6$ Hz, H-3′b), 5.34 (s, 1H, H-5), 5.27 (d, 1H, $J=10.5$ Hz, H-3′a), 4.07 (dd, 1H, $J=10.6$, 2.3 Hz, H-3e), 3.68 (t, 1H, $J=11.1$ Hz, H-3a), 3.63 (dt, 1H, $J=9.3$, 8.3 Hz, H-7), 3.05 (s, 1H, OH), 2.53 (m, 1H, H-11e), 2.40 (bt, 1H, $J=9.5$ Hz, H-2), 2.25 (m, 1H, H-8e), 2.07 (q, 1H, $J=5.8$ Hz, H-9), 1.80 (t, 1H, $J=6.0$ Hz, H-1), 1.65 (t, 1H, $J=11.7$ Hz, H-8a), 1.24 (s, 3H, H-13),1.01 (s, 3H, H-12), 0.98 (d, 1H, $J=9.4$ Hz, H-11a). ^{13}C NMR: δ 141.3 (C-*i*), 141.2 (C-2′), 128.0 (C-*m*), 127.5 (C-*p*), 125.6 (C-*o*), 114.5 (C-3′), 92.0 (C-5), 77.8 (C-1′), 76.5 (C-3), 51.2 (C-2), 45.5 (C-1), 43.2 (C-9), 40.8 (C-7), 39.3 (C-11), 38.9 (C-10), 33.4 (C-8), 29.5 (C-13), 24.5 (C-12). IR (neat): 3501, 2914, 1447, 1057, 736, 699 cm^{-1}. EIMS m/z (rel. int.): 330 (M^+, 1), 197 (100), 135 (28), 107 (42), 93 (32), 79 (22). HRFABMS m/z 331.1729 (calcd for $C_{20}H_{26}O_2S$+H, 331.1732).

3.9. (1*S*,2*R*,5*R*,7*S*,9*R*)-5-[(1′*S*)-1′-Hydroxy-1′,3′-diphenyl-2′-propyn-1′-yl)]-10,10-dimethyl-4-oxa-6-thiatricyclo[7.1.1.0^{2,7}]undecane 3g

A solution of compound **1** (100 mg, 0.33 mmol) in anhydrous THF (5 mL) was treated with phenylethynilmagnesium bromide (102 mg, 0.49 mmol) in ethyl ether. After work-up pure **3g** was obtained as a single diastereoisomer, mp 62–65°C (97%). $[\alpha]_D^{25}=-27.1$ (*c* 0.14, $CHCl_3$). ^{1}H NMR: δ 7.75 (dd, 2H, $J=7.8$, 1.5 Hz, H-*o*′), 7.53–7.23 (m, 8H, Ar), 5.29 (s, 1H, H-5), 4.15 (dd, 1H, $J=10.9$, $J=3.1$ Hz, H-3eq), 3.70 (t, 1H, $J=10.9$ Hz, H-3ax), 3.66 (dt, 1H, $J=10.5$, 8.8 Hz, H-7), 3.58 (bs, 1H, OH), 2.53 (m, 1H, H-11e), 2.41 (bt, 1H, $J=10.5$ Hz, H-2), 2.26 (m, 1H, H-8e), 2.10 (q, 1H, $J=5.4$ Hz, H-9), 1.81 (t, 1H, $J=5.8$ Hz, H-1), 1.65 (m, 1H, H-8a), 1.24 (s, 3H, H-13), 1.10 (s, 3H, H-12), 0.99 (d, 1H, $J=9.5$ Hz, H-11a). ^{13}C NMR: δ 139.8 (C-*i*), 131.9 (C-*o*′), 128.5 and 128.3 (C-*p*, C-*p*′), 128.2 and 128.0 (C-*m*, C-*m*′), 126.0 (C-*o*′), 122.4 (C-*i*′), 92.8 (C-5), 90.4 (C-2′), 85.1 (C-3′), 76.6 (C-1′), 74.5 (C-3), 51.1 (C-2), 45.5 (C-1), 43.3 (C-9), 40.9 (C-7), 39.3 (C-11), 39.0 (C-10), 33.4 (C-8), 29.7 (C-13), 24.5 (C-12). IR

(neat): 3448, 2920, 2200, 1449, 1050, 757, 693, cm^{-1}. EIMS m/z (rel. int.): 404 (M^+, 2), 197 (100), 129 (24), 107 (25), 93 (39), 79 (43). HRFABMS m/z 405.1890 (calcd for $C_{26}H_{28}O_2S$+H, 405.1888).

3.10. (1*S*,2*R*,5*R*,7*S*,9*R*)-5-[(1′*S*)-1′-Hydroxy-1′-phenyl-1′-pentyl)]-10,10-dimethyl-4-oxa-6-thiatricyclo[7.1.1.0^{2,7}]-undecane 3h

Following method b to obtain carbinol **3a**, 54 mg (0.18 mmol) of benzoyloxathiane **1** in 2 mL of anhydrous THF were treated with 17 mg (0.26 mmol) of BuLi in cyclohexane and stirred under a nitrogen atmosphere for 2 h. After the usual work-up, the crude reaction was purified through a radial chromatography (Chromatotron apparatus) using a mixture of hexane:EtOAc (19:1) as the eluent to give 28 mg (78%) of a mixture of **3h** and **4h** as a colorless oil. NMR data of major adduct **3h**: ^{1}H NMR: δ 7.50–7.26 (m, 5H, Ar), 5.13 (s, 1H, H-5), 4.11 (dd, 1H, J=11.0, 3.0 Hz, H-3e), 3.68 (t, 1H, J=11.0 Hz, H-3a), 3.62 (dt, 1H, J=10.2, 9.0 Hz, H-7), 2.66 (s, 1H, OH), 2.55 (m, 1H, H-11e), 2.36 (bt, 1H, J=11.0 Hz, H-2), 2.23 (m, 1H, H-8e), 2.13–2.02 (m, 3H, H-9, H-2a′, 2b′), 1.94–172 (m, 3H, H-1, H-3a′, 3b′), 1.61 (m, 1H, H-8a), 1.40–1.12 (m, 2H, H-4a′, 4b′), 1.24 (s, 3H, H-13), 1.11 (s, 3H, H-12), 0.96 (d, 1H, J=9.6 Hz, H-11a), 0.84 (t, 3H, J=7.2 Hz, H-5′). ^{13}C NMR: δ 142.0 (C-*i*), 128.1 (C-*m*), 127.34 (C-*p*), 125.9 (C-*o*), 93.5 (C-5), 78.4 (C-1′), 76.7 (C-3), 51.5 (C-2), 45.8 (C-9), 43.5 (C-1), 41.1 (C-7), 39.6 (C-11), 39.2 (C-10), 39.1 (C-2′), 33.7 (C-8), 29.8 (C-13), 24.7 (C-12), 25.6 (C-3′), 23.3 (C-4′), 14.3 (C-5′).

3.11. (1*S*,2*R*,5*R*,7*S*,9*R*)-5-[(1′*S*)-1′-Hydroxymethyl-phenyl)]-10,10-dimethyl-4-oxa-6-thiatricyclo[7.1.1.0^{2,7}]-undecane 3i

This compound was prepared following the three procedures described in a previous paper.[11]

Method a: A solution of 100 mg (0.33 mmol) of **1** in 5 mL of dry ethyl ether was added to a stirred and cooled (−78°C) suspension of 31 mg (0.82 mmol) of $LiAlH_4$. The mixture was further stirred for 4 h and 50 mL of ethyl ether were added. The reaction was quenched by the slow successive addition of 0.1 mL of EtOH and 0.2 g of cold water. The formed white precipitated was filtered and the organic layer was washed with brine (2×25 mL), dried over Na_2SO_4 and evaporated to dryness, yielding a mixture of **3i** and **4i** in a 41:9 ratio (92 mg, 92%).

Method b: A cold (−78°C) solution of 124 mg (0.41 mmol) of **1** in 2 mL of toluene was treated dropwise with 88 mg (0.62 mmol) of DIBAL in THF and stirred under a nitrogen atmosphere for 2 h. The reaction mixture was quenched with 0.5 mL of a saturated solution of aq. NH_4Cl at −78°C and allowed to warm up to room temperature. Were added 15 mL of ethyl ether, the organic layer was washed with brine (2×5 mL), dried over anhd. Na_2SO_4 and evaporated to dryness. The residue was flash chromatographed using a mixture of hexane:EtOAc (99:1) as the eluent, giving 70 mg (70%) of **3i** as a colorless oil.

Method c: To a cold (−78°C) solution containing 110 mg (0.36 mmol) of **1** in 5 mL of dry toluene were added dropwise 0.54 mmol of *LS*-Selectride in THF and the mixture was stirred under a nitrogen atmosphere for 4 h. The reaction mixture was allowed to warm up to room temperature and stirred overnight, cooled at −78°C and quenched with a saturated solution of aq. NH_4Cl. After reaching room temperature, the organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was treated with 5 mL of cold hexane and the formed white precipitate was filtered. The solvent was evaporated to dryness and the residue was flash chromatographed using a mixture of hexane–EtOAc (99:1) to give 82 mg (82%) of **3i** as a colorless oil. Only adduct **3i** was fully characterized. $[\alpha]_D^{25}=-45.9$ (c 0.22, $CHCl_3$). ^{1}H NMR: δ 7.36 (m, 5H, H-Ar), 5.16 (d, 1H, J=3.5 Hz, H-5), 5.05 (d, 1H, J=3.5 Hz, H-1′), 4.06 (dd, 1H, J=11.1, 2.9 Hz, H-3e), 3.68 (t, 1H, J=11.1 Hz, H-3a), 3.62 (dt, 1H, J=8.8, 10.5 Hz, H-7), 2.84 (bs, 1H, OH), 2.60 (ddd, 1H, J=9.4, 5.9, 1.8 Hz, H-11e), 2.44 (ddd, 1H, J=11.1, 10.5, 2.7 Hz, H-2), 2.27 (m, 1H, H-8e), 2.07 (q, 1H, J=5.5 Hz, H-9), 1.80 (t, 1H, J=6.0 Hz, H-1), 1.69 (m, 1H, H-8a), 1.24 (s, 3H, H-13), 1.10 (s, 3H, H-12), 0.99 (d, 1H, J=9.4 Hz, H-11a). ^{13}C NMR: δ 137.9 (C*i*), 127.2 (C-*m*), 127.0 (C-*p*), 125.3 (C-*o*), 89.7 (C-1′), 75.4 (C-3), 74.3 (C-5), 50.4 (C-2), 44.6 (C-1), 42.7 (C-9), 39.7 (C-7), 38.4 (C-11), 38.0 (C-10), 32.5 (C-8), 28.7 (C-13), 23.4 (C-12). IR (neat): 3446, 2910, 1452, 1054, 698, 649 cm^{-1}. EIMS m/z (rel. int.): 304 (M^+, <1), 197 (100), 115 (20), 107 (44), 79 (65). HRFABMS m/z 305.1546 (calcd for $C_{18}H_{24}O_2S$+H, 305.1575).

3.12. General procedure for the hydrolysis of carbinols 3a–i and successive reduction of the corresponding aldehydes to obtain 1-phenyl-1,2-ethanodiols 5

Method a: Following the procedure described by Eliel et al.,[13] 1 equiv. of carbinol **3** in 5 mL of CH_3CN were treated with 2 equiv. of NCS and $AgNO_3$ in 35 ml of CH_3CN–H_2O (4:1) at 0–4°C during 1–5 min. The work-up was carried out by successively adding solutions of NaCl, Na_2SO_3 and Na_2CO_3 (1 ml, each), the white precipitated was filtered, and the filtrated was extracted with a mixture of hexane:methylene chloride (1:1). The organic layer was dried with anhd. Na_2SO_4, filtered and concentrated to dryness, giving a crude yellowish oil, whose ^{1}H NMR spectrum showed the presence of aldehydes **4** and the expected sultine. This mixture was treated with $LiAlH_4$ without further purification in anhd. ethyl ether at room temperature during 3 h. After the usual work-up and purification through column chromatography, was recovered hydroxythiol **2** (60–80%) and the corresponding diol.

Method b: After having carried out the hydrolysis as described above, the residue was treated with $NaBH_4$ in a mixture of acetonitrile:water (1:1). The resulting mixture was stirred at room temperature for 3 h, 10 ml of hot water were added, stirring continued for 20 min and the mixture was extracted with ethyl ether. The organic layer was dried with anhd. Na_2SO_4, concentrated to dryness and the yellow oily residue was flash chromatographed using a mixture of hexane:ethyl acetate (8:1) as eluent, giving hydroxythiol **2** (65–85%) and the corresponding diol.

3.13. (*S*)-(+)-2-Phenylpropane-1,2-diol 5a

The crude reaction mixture obtained from the hydrolysis of adduct **3a** was treated with $LiAlH_4$ as described in method a. After column chromatography were obtained hydroxythiol **2** (76%) and diol **5a** (92%). $[\alpha]_D^{23}=+5.7$ (*c* 0.45, EtOH), lit.[18] for the (*R*) enantiomer $[\alpha]_D^{23}=-5.8$ (*c* 0.17, EtOH). The remaining spectral data are in agreement with those published.[18]

3.14. (*S*)-(−)-2-Phenylbutane-1,2-diol 5b

The crude reaction mixture obtained from the hydrolysis of adduct **3b** was treated with $NaBH_4$ as described in method b. After column chromatography were obtained hydroxythiol **2** (57%) and diol **5b** (75%). $[\alpha]_D^{25}=-7.2$ (*c* 0.6, EtOH), lit.[19] for the (*R*) enantiomer $[\alpha]_D^{20}=+7.3$ (*c* 0.7, EtOH). The remaining spectral data are in agreement with those published.[19]

3.15. (*S*)-(−)-3-Methyl-2-phenylbutane-1,2-diol 5c

The crude reaction mixture obtained from the hydrolysis of adduct **3c** was treated with $NaBH_4$ as described in method b. After column chromatography were obtained hydroxythiol **2** (62%) and diol **5c** (42 mg, 80%). $[\alpha]_D^{20}=-19.5$ (*c* 0.21, EtOH), lit.[20] for the (*R*) enantiomer $[\alpha]_D^{25}=+16.0$ (*c* 1.6, EtOH). The remaining spectral data are in agreement with those published.[20]

3.16. (*S*)-(−)-2-Phenylbut-3-ene-1,2-diol 5f

The crude reaction mixture obtained from the hydrolysis of adduct **3f** was treated with $NaBH_4$ as described in method b. After column chromatography were obtained hydroxythiol **2** (74%) and diol **5f** (89%). $[\alpha]_D^{20}=-43.4$ (*c* 0.20, EtOH), lit.[19] $[\alpha]_D^{20}=-39.9$ (*c* 1.0, EtOH). The remaining spectral data are in agreement with those published.[19]

3.17. (*S*)-(+)-2,4-Diphenylbut-3-yne-1,2-diol 5g

The crude reaction mixture obtained from the hydrolysis of adduct **3g** was treated with $NaBH_4$ as described in method b. After column chromatography were obtained hydroxythiol **2** (80%) and diol **5g** (90%). $[\alpha]_D^{20}=+11.0$ (*c* 0.15, EtOH). ^{1}H NMR: δ 7.26–7.73 (m, 10H, Ar), 3.86 (dd, 1H, $J=11.2$, 6.1 Hz, H-1a), 3.75 (dd, 1H, $J=11.2$, 8.0 Hz, H-1b), 3.18 (bs, 1H, OH), 2.23 (bdd, 1H, $J=8.0$, 6.1 Hz, OH). ^{13}C NMR: δ 140.9 (C-1′), 132.1 (C-2″, C-6″), 129.1–128.6 (C-2′, C-3′, C-5′, C-6′, C-3″, C-5″), 126.1 (C-4′), 122.2 (C-1″), 89.4 (C-3), 86.9 (C-4), 74.5 (C-2), 72.4 (C-1). CIMS *m*/*z* (rel. int.): 239 (M^++H, 1), 221 (100), 207 (12), 193 (13), 143 (12).

3.18. (*S*)-*trans*-2,4-Diphenylbut-3-ene-1,2-diol 5k

The crude reaction mixture obtained from the hydrolysis of adduct **3g** was treated with $LiAlH_4$ as described in method a. From this mixture was characterized diol **5k**, which was formed from **3g** by 1,4-conjugated addition of hydride. Colorless oil (35%, estimated by ^{1}H NMR from crude reaction). ^{1}H NMR: δ 7.22–7.53 (m, 5H, Ar), 6.72 (d, 1H, $J=16.0$ Hz, H-3), 6.46 (d, 1H, $J=16.0$ Hz, H-4), 3.87 (d, 2H, $J=6.2$ Hz, H-1a, H-1b), 2.95 (bs, 1H, OH), 1.86 (bt, 1H, $J=6.2$ Hz, OH).

3.19. (*S*)-(+)-2,4-Diphenylbutane-1,2-diol 5j

The mixture of diols **5g** and **5k**, obtained above, was hydrogenated over Pd/C (5%) in EtOAc (30 psi) at room temperature for 72 h. The catalyst was eliminated by filtration, and the filtrate was evaporated to dryness to give diol **5j** as a colorless oil (90%). $[\alpha]_D^{23}=+10.6$ (*c* 0.15, EtOH). ^{1}H NMR: δ 7.02–7.49 (m, 10H, Ar), 3.86 (d, 1H, $J=11.0$ Hz, H-1a), 3.72 (d, 1H, $J=11.0$ Hz, H-1b), 2.66 (m, 1H, H-4a), 2.34 (m, 1H, H-4b), 2.11–2.39 (m, 2H, H-3a, H-3b). ^{13}C NMR: δ 143.3 (C-1″), 142.4 (C-1′), 128.8 (C-3′), 128.6 (C-2′), 128.5 (C-6′), 127.5 (C-7′), 126.0 (C-8′), 125.8 (C-4′), 77.5 (C-2), 71.1 (C-1), 40.6 (C-3), 29.7 (C-4). EIMS *m*/*z* (rel. int.): 224 (M^+−18, <1), 211 (100), 120 (10), 105 (20), 91 (62).

3.20. (*S*)-(+)-1-Phenylethane-1,2-diol 5i

The crude reaction mixture obtained from the hydrolysis of adduct **3i** was treated with $NaBH_4$ as described in method b. After column chromatography were obtained hydroxythiol **2** (78%) and diol **5i** (73%). $[\alpha]_D^{23}=+38.6$ (*c* 0.18, EtOH), lit.[21] for the (*R*) enantiomer $[\alpha]_D^{23}=-38.4$ (*c* 1.12, EtOH). ^{1}H NMR: δ 7.28–7.38 (m, 5H, Ar), 4.83 (dd, 1H, $J=8.0$, 3.6 Hz, H-2), 3.76 (dd, 2H, $J=11.3$, 3.6 Hz, H-1b), 3.67 (dd, 2H, $J=11.3$, 8.0 Hz, H-1b), 2.62 (bs, 1H, OH), 1.64 (bs, 1H, OH).

Acknowledgements

The authors wish to thank QFB Fernando Labarrios for MS measurements. L.G.Z. acknowledges CGPI/IPN (grant 20020683) and CONACyT (35013E). L.C.-G. and M.E.V.-D. thank CONACyT (grants 92069 and 125225, respectively) and CGPI/IPN (PIFI) postgraduate fellowships. P.V.-P. thanks Institutional Fellowship (CGPI/IPN).

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