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Spirofungins A and B: a reassignment of Kiyota's spiroketals

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Abstract—In this letter, we present our results obtained in attempts to synthesize the initially proposed structure of the spiroketal core of spirofungin B. Based on these results, we propose a reassignment for the structures of the spiroketals obtained by Kiyota's group.

1. Introduction

Spirofungins A (**1**) and B (**2**) (Fig. 1) were isolated as a 4:1 mixture from the culture filtrate and extracts of *Streptomyces violaceusniger* Tü 4113 as new polyketide–spiroketal-type antibiotics[1] related to reveromycins.[2] Spirofungins A and B showed high inhibition activity against yeasts such as the human pathogen *Candida albicans* and a moderate antifungal activity against filamental fungi such as *Botritis cinerea* and *Mucor miehei*.

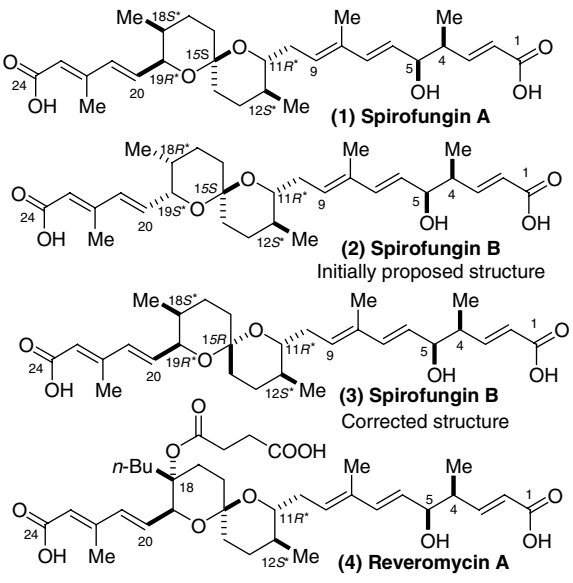

Figure 1. Spirofungins A and B and reveromycin A.

Recently, Rizzacasa and co-workers reported the total synthesis of spirofungin B (**2**) and found that the NMR data for the synthetic material did not match that of the natural product.[3] A revised structure for (**2**) that is epimeric with (**1**) at the C15 spiroketal center was then proposed.[3] Thus, spirofungin B would be a spiroketal (**3**) with a single anomeric stabilization.[4] This reassignment was supported by our report[5] dealing with the synthesis of the spiroketals for spirofungins A and B, and by further results of Rychnovsky and La Cruz.[6] In addition, Shimizu et al.[7] recently reported the first total synthesis of both spirofungins A and B and the reassigned structure for spirofungin B, which confirmed the structures and the previous reassignment made by Rizzacasa and co-workers.[3]

2. Results and discussion

In the course of our synthesis of the initially proposed structure of spirofungin B (Dias's group), the spiroketal (**8**) was obtained by treatment of precursor (**7**) with HF–pyridine in THF (Scheme 1).[5] The spiroketal precursor (**7**) was obtained from the coupling reaction between the lithiated hydrazone obtained from (**5**) and alkyl iodide (**6**).[5] Removal of the –PMB protecting group

Keywords: Spiroketal core; Reassignment of stereochemistry.
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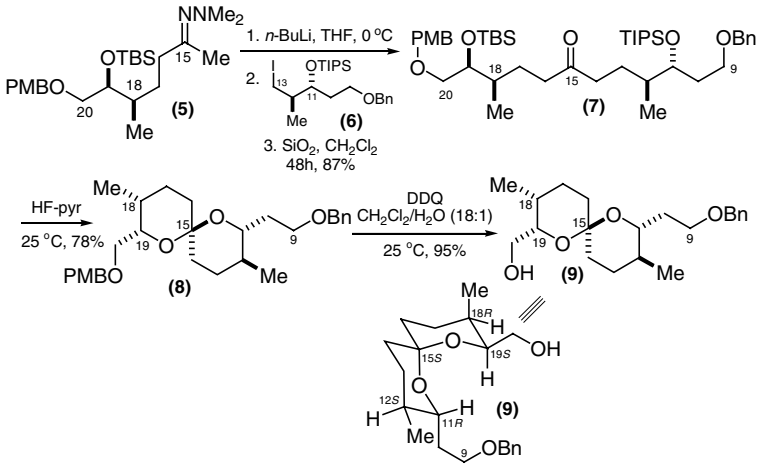


Scheme 1. Synthesis of spiroketal (**9**).[5]

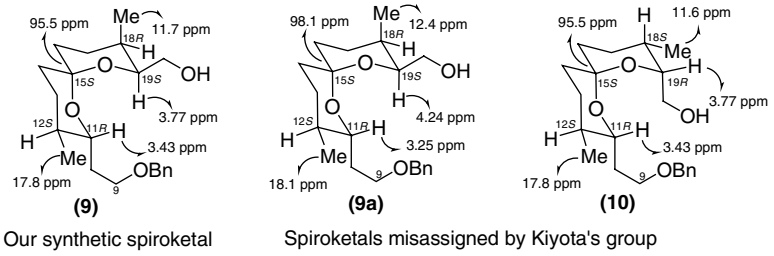


Figure 2. Spiroketals **9**, **9a**, and **10**.[5,8]

was accomplished by treatment of (**8**) with DDQ in CH_2Cl_2/H_2O to give spiroketal (**9**) in 95% yield.

This same spiroketal (**9a**), lacking the –PMB protecting group at C20, has been reported earlier by Kiyota's group,[8] together with another compound assigned as the spiroketal core of spirofungin A (**10**) (Fig. 2).

An extensive comparison of the ^{1}H and ^{13}C NMR data of our synthetic (**9**), with the compounds obtained by Kiyota and co-workers, showed that the chemical shifts did not match with data reported for (**9a**) (Fig. 2, Tables 1 and 2). We have observed a chemical shift for the spiro carbon at 95.5 ppm[5] in **9**, while Kiyota and co-workers described a chemical shift for C15 at 98.1 ppm in **9a** (Fig. 2).[8] In our compound, axial and equatorial positioned methyl groups appear at 11.7 and 17.8 ppm, respectively, while in **9a** methyl groups appear at 12.4 and 18.1 ppm. This same analysis was extended to the ^{1}H NMR spectroscopic data. In particular, chemical shifts for H11 and H19 in our compound (3.43 and 3.77 ppm, respectively) were significantly different from those found in compound **9a** (3.25 ppm for H11 and 4.24 ppm for H19).

At the same time, for the structure of spiroketal **10**, where the stereogenic centers in C18 and C19 have been changed, compared with (**9**) and (**9a**), it is possible to observe a chemical shift for C15 at 95.5 ppm, but both methyl groups with distinct chemical shifts (11.6 and 17.8 ppm) were equatorially positioned. ^{1}H NMR spectra show chemical shifts for H11 and H19 at 3.43 and 3.77 ppm, respectively. Curiously, we noticed that data assigned for our synthetic compound matched very well with those assigned for the spirofungin A spiroketal core (**10**). These results suggest that structures for the spiroketals obtained by Kiyota's group were misassigned.

Analysis of some previously published results shows that it is possible to make a distinction between the spiroketal that presents double anomeric stabilization and that which presents a single anomeric stabilization, based on chemical shifts of the spiroketal carbon in the ^{13}C NMR spectra.[3,9] On going from the mono to the double stabilized spiroketal a shielding effect on the ^{13}C chemical shift of the spirocarbon is observed. It is important to notice that this analysis can be used only to compare spiroketals, which are epimeric at the spirocarbon. This fact was first observed by Deslongchamps and co-workers[9] and was recently discussed in detail by Rizzacasa and co-workers.[3]

In a recent letter, Tan and co-workers[10] reported a series of spiroketals with single and double anomeric stabilization, in which the trend for a slightly downfield shift of the anomeric carbon can be found (Fig. 3). Among several examples the epimeric spiroketal partners **11** and **12** as well as **13** and **14** showed the spiro carbon in monostabilized spiroketal deshielded related with the same carbon in double stabilized spiroketal.[10]

Table 1. ^{13}C NMR ($CDCl_3$) data for (+)-(**9**), (**9a**), and (**10**)

C Numbered	(+)-(**9**)[a] δ (^{13}C), 75 MHz	(**9a**)[b] δ (^{13}C), 125 MHz	(**10**)[b] δ (^{13}C), 125 MHz
9	67.2	67.8	67.1
10	33.3	34.5	33.2
11	71.3	75.5	71.3
12	35.2	36.1	35.1
12-Me	17.8	18.1	17.8
13	26.7	30.2	26.6
14	30.3	37.2	30.2
15	95.5	98.1	95.5
16	35.7	23.4	35.6
17	28.2	26.5	28.1
18	28.3	29.0	28.1
18-Me	11.7	12.4	11.6
19	71.7	73.5	71.7
20	64.6	65.2	64.6

[a] Data for our synthetic spiroketal.
[b] Data extracted from Ref. 8.

Table 2. ^{1}H NMR ($CDCl_3$) data for (+)-(**9**), (**9a**), and (**10**)

H Numbered	(+)-(**9**)[a] δ (^{1}H), 500 MHz	(**9a**)[b] δ (^{1}H), 500 MHz	(**10**)[b] δ (^{1}H), 500 MHz
9	a: 3.64, b: 3.73	a: 3.65, b: 3.72	a: 3.65, b: 3.74
10	2.05	a: 2.03, b: 1.65	2.06
11	3.43	3.25	3.43
12	1.33	1.37	1.33
12-Me	0.84	0.86	0.85
13	a: 1.36, b: 2.03	a: 1.31, b: 1.65	a: 1.35, b: 2.03
14	1.41	a: 1.56, b: 1.64	1.41
15	—	—	—
16	1.65	a: 1.37, b: 2.07	1.66
17	a: 1.51, b: 1.55	a: 1.33, b: 1.82	a: 1.52, b: 1.55
18	1.63	1.73	1.65
18-Me	0.88	0.92	0.89
19	3.77	4.24	3.77
20	a: 3.38, b: 3.55	a: 3.48, b: 3.63	a: 3.39, b: 3.56

[a] Data for our synthetic spiroketal.
[b] Data extracted from Ref. 8.

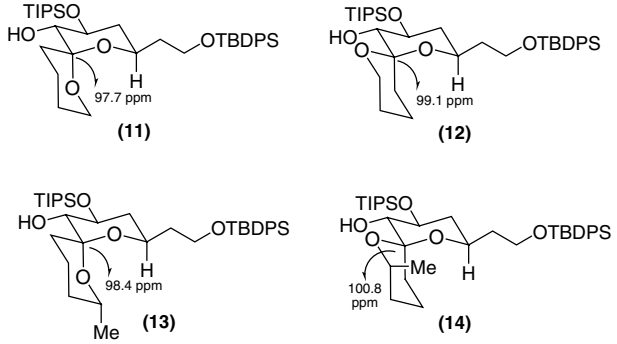


Figure 3. Tan's spiroketals partners.[10]

In their synthesis of the spiroketals of spirofungins A and B, Shimizu and co-workers[11] obtained a mixture of spiroketals (**15**) and (**16**) in a ratio of 1.5:1.0, isomeric at the spiro center (Fig. 3).[3] The spirofungin A spiroketal core presents chemical shifts for C15 at 96.8 ppm, for equatorial methyl groups at 15.0 and 18.0 ppm and for H11 and H19 at 3.91 and 3.81 ppm. There is no data reported for C15 to spirofungin B spiroketal core, but axial and equatorial methyl groups appear at 11.3 and 17.8 and H11 and H19 appear at 3.27 and 4.58 ppm (Fig. 4).[3]

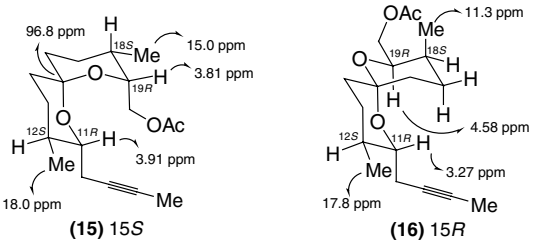


Figure 4. Shimizu's spiroketals of spirofungins A and B.[3]

Comparable chemical shift differences are also observed for H11 and H19 in spirofungins A and B.[1–3] A deshielding effect of C15 can be observed going from the mono

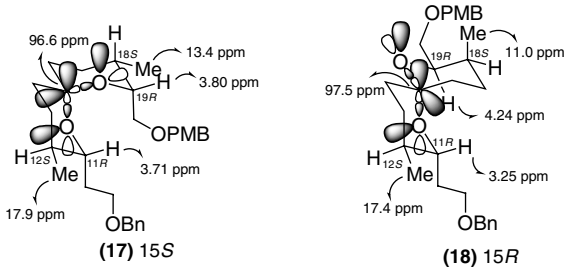


Figure 5. Dias's spiroketals of spirofungins A and B.[5]

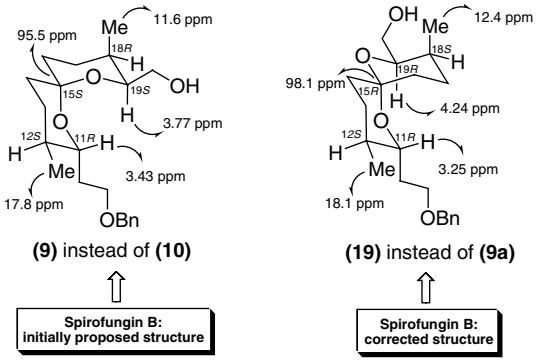


Figure 6. Corrected structures for Kiyota's spiroketals.[14]

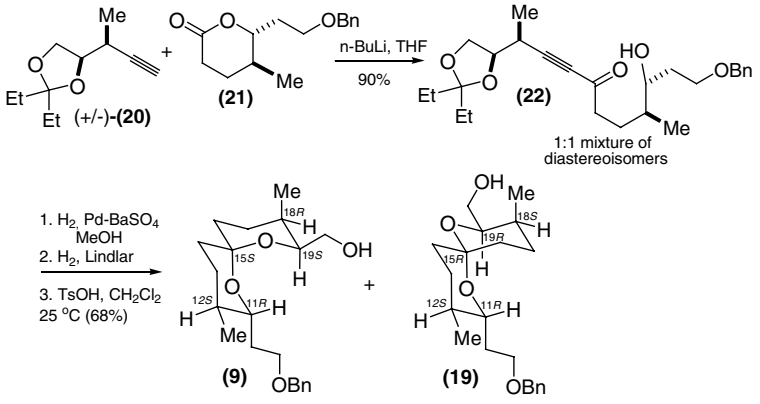
(**3**) to the double stabilized spiroketal (**2**) and a shielding effect of H11 with concomitant deshielding effect of H19 is observed going in this same direction.[3,12] This same trend can be found again in the synthesis of the spiroketal fragment of reveromycin A by Theodorakis and co-workers.[13]

In our studies directed toward the total synthesis of spirofungins A and B,[5] we have obtained spiroketals (**17**) and (**18**) in a ratio of 1.0:2.3, respectively (Fig. 5). We have observed a deshielding effect on spiro carbon when a comparison is made between the double stabilized spiroketal **17**, in which C15 appears at 96.6 ppm, and the mono-stabilized spiroketal **18**, in which C15 appears at 97.5 ppm. We can observe a trend to a slightly downfield shift of the spiro carbon when going from an axial–axial to an axial–equatorial oxygen orientation. At the same time, the chemical shift for H19 in the minor isomer **17** is upfield from the corresponding chemical shift in the preferred isomer **18**, where the axial oxygen deshields the axial H19[12] and the opposite change in chemical shift is evident for H11.

We believe these effects can be explained based on a strong hyperconjugative anomeric type interaction between the axial oxygen lone pair (nonbonding electronic orbital) with the σ^* antibonding orbital (σ^* C–O). In compound **18**, we have just one interaction of this type, promoting the deshielding effect of H19. As there is no reciprocity of this effect, H11 presents an increased shielding due to the increased electronic density of the oxygen between C11 and C15. This same explanation can be extended to the chemical shifts observed for C15 in mono- and double-stabilized spiroketals. In double stabilized spiroketals, C15 is subjected to two-hyperconjugative interactions while in mono-stabilized spiroketals there is only one.

Based on our results and all these observations we propose a new stereochemical assignment for Kiyota's spiroketals (Fig. 6). Data assigned for structure (**10**), which was supposed to result in spirofungin A, corresponds in fact with the initially proposed structure of the spirofungin B spiroketal core. This observation is in perfect agreement with the data and structure of the spiroketal (**9**) obtained in our group.[5] Data assigned for (**9a**) corresponds to the spiroketal present in the corrected structure of spirofungin B, which has a C15 epimeric center related with spirofungin A and shows one single anomeric stabilization.[14]

In addition, in the original work, Kiyota and co-workers[8] have used a racemic mixture of alkyne **20** in a coupling reaction with chiral lactone **21** leading to hydroxy ketone **22** as a 1:1 mixture of diastereoisomers (Scheme 2). They have isolated only two of the four possible spiroketal isomers from an acid catalyzed spiroketalization of this 1:1 mixture, in a combined yield of 68%, with no mention to the remaining 32% missing yield. At least one more spiroketal, the one related to the spirofungin A core should have been isolated based on the literature precedents.[3,5,13]



Scheme 2. Corrected synthesis of spiroketals **9** and **19** by Kiyota et al.

Kiyota's group will describe further improvement of the work discussed in Scheme 2 in due course.

3. Conclusions

These results suggest that the structures proposed for Kiyota's spiroketals were misassigned. We propose a reassignment in which the absolute configurations in (**10**) are C(18*R*) and C(19*S*), the same structure found in spiroketal (**9**) obtained in our group, while (**9a**) corresponds with the corrected spirofungin B spiroketal core (**19**) which has a C(15*R*) epimeric structure related to (**10**).

4. Experimental

4.1. General

All reactions were carried out under an atmosphere of argon or nitrogen in flame-dried glassware with magnetic stirring. Dichloromethane was distilled from CaH_2. THF was distilled from sodium/benzophenone ketyl. Oxalyl chloride was distilled immediately prior to use. TLC plates were silica gel 60 (GF 5–40-μm). Visualization was accomplished with either a UV lamp or I_2 staining. Chromatography on silica gel (230–400 mesh) was performed using a forced-flow of the indicated solvent system (*flash* chromatography). Visualization was accomplished with UV light and heated phosphomolybdic acid or by I_2 staining. ^{1}H NMR spectra were recorded on either a Varian Gemini 300 (300 MHz) or a Varian Inova 500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm) unless otherwise indicated. Data are reported as ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, st = sextet, apt = apparent triplet, m = multiplet, b = broad, br s = broad singlet, br d = broad doublet, dq = doublet of quartets, dt = doublet of triplets, td = triplet of doublets, apqt = apparent quintet, apdt = apparent doublet of triplets, number of hydrogens, coupling constant(s) in hertz. Proton-decoupled ^{13}C NMR spectra were recorded on a Varian Gemini 300 (75 MHz) spectrometer and are recorded in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm) unless otherwise indicated. Infrared spectra were recorded on a Perkin–Elmer 1600 FTIR spectrophotometer. Mass spectra were recorded on a VGAutoespec-Micromass. Optical rotations were measured on a Polamat A polarimeter from Carl Zeiss Jena, using a 1 mL quartz cell, with sodium lamps, and are reported as follows: $[\alpha]t$ (°C) λ, (*c* g/100 mL, solvent).

4.2. (2*S*,3*R*,9*S*,10*R*)-1-(4-Methoxybenzyloxy)-12-(benzyloxy)-2-(*tert*-butyldimethylsililoxy)-3,9-dimethyl-10-(triisopropylsilyloxy)dodecan-6-one (+)-(7)

A solution of 0.47 mL of *n*-BuLi (2.50 M in hexanes, 1.17 mmol) was added dropwise to a solution of 463 mg (1.06 mmol) of dimethylhydrazone (**5**) in 1.5 mL of THF at −78 °C under Ar. After 30 min of stirring at 0 °C, a solution of 573 mg (1.17 mmol) of the iodide (**6**) in 0.8 mL of THF was added by cannula, and the resulting mixture was stirred at 0 °C overnight (18 h). Saturated aqueous NH_4Cl (5 mL) was added to quench the reaction and the mixture was warmed to ambient temperature. The aqueous layer was extracted three times with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Purification on silica gel (EtOAc/hexanes 5–20%) after standing on a silica gel column for 36 h, to hydrolyze the dialkyl hydrazone, provided the desired ketone (+)-**7** in 65% yield as a pale yellow oil. TLC (EtOAc–hexanes, 15:85) R_f 0.53; $[\alpha]_D^{20}$ +1.44 (*c* 2.08, $CHCl_3$); IR (film) 2948, 2860, 1716, 1614, 1511, 1467, 1365, 1246, 1170, 1100, 1037, 958, 887 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (m, 5H), 7.24 (d, *J* 8.7 Hz, 2H), 6.87 (d, *J* 8.7 Hz, 2H), 4.51 (d, *J* 11.3 Hz, 1H), 4.48 (d, *J* 11.0 Hz, 1H), 4.45 (d, *J* 11.0 Hz, 1H), 4.38 (d, *J* 11.3 Hz, 1H), 3.91 (dt, *J* 7.3, 3.7 Hz, 1H), 3.80 (s, 3H), 3.74 (td, *J* 4.4, 2.9 Hz, 1H), 3.56 (t, *J* 6.8 Hz, 2H), 3.39 (dd, *J* 9.5, 4.9 Hz, 1H), 3.34 (dd, *J* 9.5, 6.0 Hz, 1H), 2.39 (m, 4H), 1.71 (m, 4H), 1.66 (m, 2H), 1.37 (m, 2H), 1.06 (m, 21H), 0.89 (d, *J* 6.9 Hz, 3H), 0.87 (s, 9H), 0.82 (d, *J* 6.6 Hz, 3H), 0.036 (s, 3H), 0.032 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.0, 159.0, 138.5, 130.4, 129.1, 128.2, 127.6, 127.4, 113.6, 74.1, 73.0, 72.9, 72.7, 67.6, 55.1, 40.9, 40.8, 38.4, 35.9, 32.4, 27.5, 26.6, 25.8, 18.2, 14.0, 13.5, 12.8, −4.16, −4.95.

4.3. Spiroketal (+)-(8)

To a solution of 100 mg (0.132 mmol) of (+)-(**7**) in 3 mL of THF in a polyethylene flask, was added 0.25 mL of 48% aqueous solution HF. After 18 h at room temperature the reaction was diluted with Et_2O and neutralized by the slow addiction of $NaHCO_3$ (powder). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by *flash* chromatography (EtOAc/hexanes 10%) provided 49.7 mg of the spiroketal (+)-(**8**) as a colorless oil in 78% yield. TLC (EtOAc–hexanes, 10:90) R_f 0.46; $[\alpha]_D^{20}$ +33.5 (*c* 1.07, $CHCl_3$); IR (film) 2929, 2854, 1513, 1456, 1369, 1246, 1089, 989, 823 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (t, *J* 7.2 Hz, 2H), 7.32 (t, *J* 7.2 Hz, 2H), 7.28 (t, *J* 7.2 Hz, 1H), 7.25 (d, *J* 8.5 Hz, 2H), 6.87 (d, *J* 8.5 Hz, 2H), 4.55 (d, *J* 11.9 Hz, 1H), 4.52 (d, *J* 11.7 Hz, 1H), 4.50 (d, *J* 11.9 Hz, 1H), 4.41 (d, *J* 11.7 Hz, 1H), 3.98 (td, *J* 6.4, 2.4 Hz, 1H), 3.81 (s, 3H), 3.70 (dd, *J* 7.6, 6.1 Hz, 2H), 3.48 (td, *J* 10.1, 2.4 Hz, 1H), 3.46 (dd, *J* 9.8, 7.0 Hz, 1H), 3.39 (dd, *J* 9.8, 5.80 Hz, 1H), 2.06 (m, 2H), 1.79 (m, 1H), 1.64 (m, 3H), 1.60 (m, 1H), 1.48 (m, 2H), 1.39 (m, 2H), 1.33 (m, 1H), 0.89 (d, *J* 7.0 Hz, 3H), 0.84 (d, *J* 6.7, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.9, 138.6, 130.9, 128.9, 128.2, 127.7, 127.4, 113.6, 73.1, 72.8, 71.6, 71.2, 69.9, 67.6, 55.2, 35.7, 35.1, 33.4, 30.2, 28.0, 27.9, 26.3, 25.8, 17.8, 11.1; HRMS calcd for $C_{29}H_{40}O_5$: 468.2876, found: 468.3230.

4.4. Spiroketal (+)-(9)

To a solution of 30 mg (0.064 mmol) of the spiroketal (+)-(**8**) in 3 mL of a 18:1 mixture CH_2Cl_2/water at

25 °C was added 16.2 mg (0.070 mmol) of DDQ. After 15 min the mixture was diluted with 5 mL of Et_2O and washed with two portions of 5 mL of $NaHCO_3$. The organic extract was dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification by *flash* chromatography (EtOAc–hexanes, 15:85) provided 21 mg of the spiroketal (+)-(**9**) in 95% yield as a colorless oil. TLC (EtOAc–hexanes, 15:85) R_f 0.28; $[\alpha]_D^{20}$ +45 (*c* 0.16, *i*-PrOH); IR (film) 3055, 2935, 2877, 2305, 1720, 1609, 1454, 1379, 1263, 1091, 983, 895 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.35 (m, 4H), 7.28 (m, 1H), 4.52 (d, *J* 11.9 Hz, 1H), 4.49 (d, *J* 11.9 Hz, 1H), 4.50 (d, *J* 11.9 Hz, 1H), 3.77 (ddd, *J* 8.8, 3.9, 2.4 Hz, 1H), 3.73 (dd, *J* 8.8, 6.4 Hz, 1H), 3.64 (ddd, *J* 9.0, 7.0, 4.3 Hz, 1H), 3.55 (dd, *J* 11.3, 8.5 Hz, 1H), 3.43 (td, *J* 10.0, 2.3 Hz, 1H), 3.38 (dd, *J* 11.3, 4.0 Hz, 1H) 2.05 (m, 2H), 1.64 (m, 2H), 1.57 (m, 1H), 1.48 (m, 2H), 1.41 (ddd, *J* 13.7, 4.4, 2.4 Hz, 2H), 1.36 (dt, *J* 4.4, 2.4 Hz, 1H), 1.33 (m, 2H), 0.88 (d, *J* 6.9 Hz, 3H), 0.84 (d, *J* 6.4, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 128.2, 127.6, 127.4, 95.5, 73.0, 71.7, 71.3, 67.2, 64.6, 35.7, 35.2, 33.3, 30.3, 28.3, 28.2, 26.7, 17.8, 11.7; HRMS calcd for $C_{21}H_{32}O_4$: 348.2301, found: 348.2077.

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14. The observed NOE proposed between H11 and H19 in the wrong spiroketal (**9a**) by Kiyota et al. could well be observed between these same hydrogens in the corrected spiroketal **18**, as a similar NOE has been described by Theodorakis et al. in the synthesis of the spiroketals of reveromycin A (see Ref. 13).