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ASYMMETRIC SYNTHESIS OF CRYPTOFOLIONE AND DETERMINATION OF ITS ABSOLUTE CONFIGURATION†

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Abstract – Two possible stereoisomers of cryptofolione, isolated from the *Cryptocarya* species in South Africa and Brazil, were synthesized in an enantioselective manner by using asymmetric hetero Diels-Alder reaction as the key steps. Comparative evaluation of the ^{1}H NMR, ^{13}C NMR, CD spectra, and specific rotation of the synthetic compounds with those reported in the literature was performed to establish the absolute configuration of cryptofolione to be [6*R*,10*S*,12*R*].

Naturally occurring 6-substituted 5,6-dihydro-α-pyrones have been observed in several botanical families and fungi species.[1] Among them, 6-(ω-arylalkenyl)-5,6-dihydro-α-pyrones bearing no substituent at C4 are characteristics of *Cryptocarya* species (Lauraceae).[2] These α-pyrones are biosynthesized as secondary metabolites *via* a mixed acetate-shikimate pathway[3] and structurally characterized by 5,6-dihydro-α-pyrone, 1,3-diol or 1,3,5-triol, and *trans*-styryl skeletons. cryptofolione (**1**), a class of 6-(ω-arylalkenyl)-5,6-dihydro-α-pyrones, has been recently isolated from branch and stem bark of the *Cryptocarya* species such as *C. myrtifolia* by Drewes *et al.*[2a] and *C. moschata* by Cavalheiro *et al.*[4,5] The bioactivities of this compound have been evaluated to show moderate tripanocidal and leishmancidal effects *in vitro*.[6] The configuration of their pyrone unit has been reported to be *R* based on their CD spectra[4] and the relative configurations of diol or triol units on the C6-side chain have been determined by ^{13}C NMR spectral analysis for some compounds.[7] However, their whole stereochemistries still remain unestablished. Thus, in order to determine the stereochemistry of this class of compounds in a synthetic way,[8] we examined the synthesis of cryptofolione (**1**) by using asymmetric hetero Diels-Alder reaction and diastereoselective reduction, the stereochemistries of which have been established unequivocally, as key steps. Based on ^{13}C NMR spectral analysis, the relative configuration of the 1,3-diol unit has been

†This paper is dedicated to the memory of the late Professor Emeritus Kenji Koga.

proposed to be *anti*.[2a,4,7] Since the configuration of the α-pyrone unit is *R*, the stereochemistry of **1** is either 6*R*,10*S*,12*R* or 6*R*,10*R*,12*S* (Figure 1).

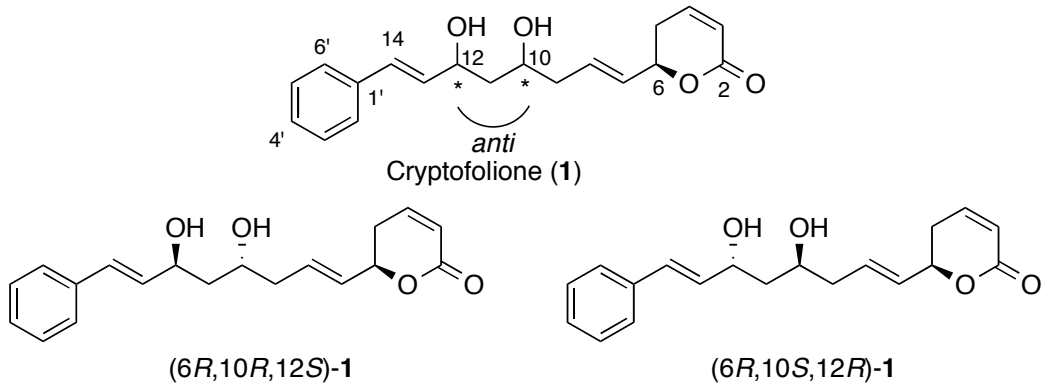
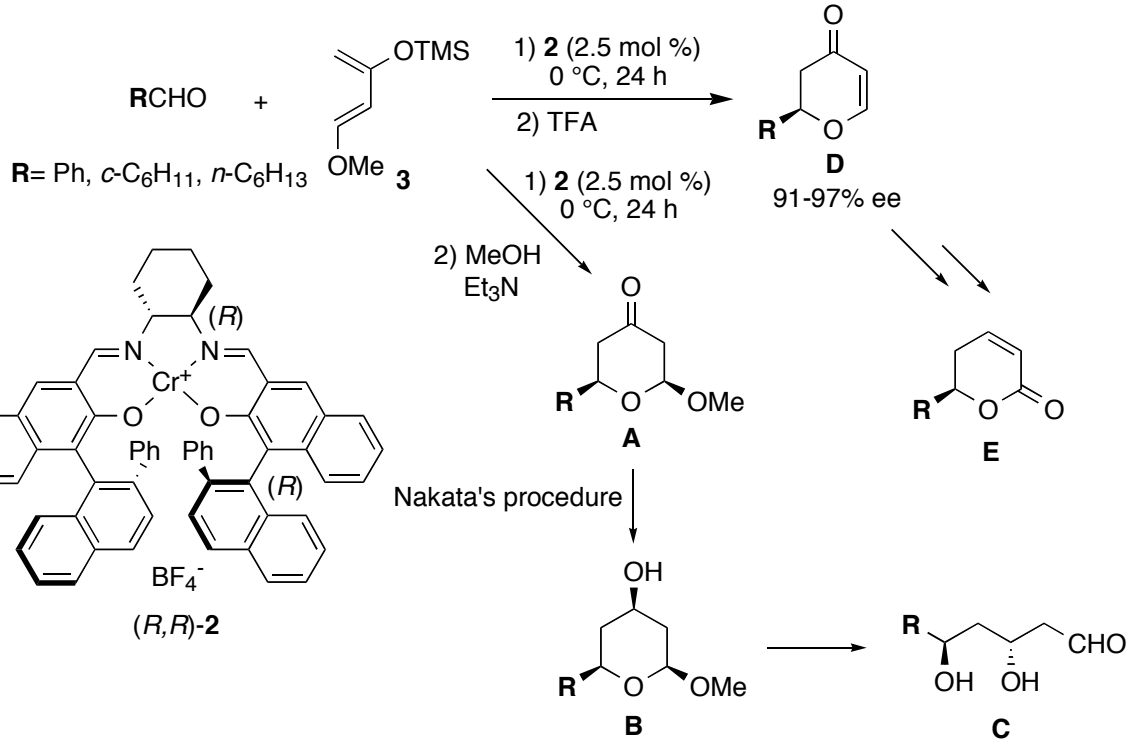


Figure 1. Two possible stereoisomers, (6*R*,10*R*,12*S*)-**1** and (6*R*,10*S*,12*S*)-**1**, for cryptofolione.

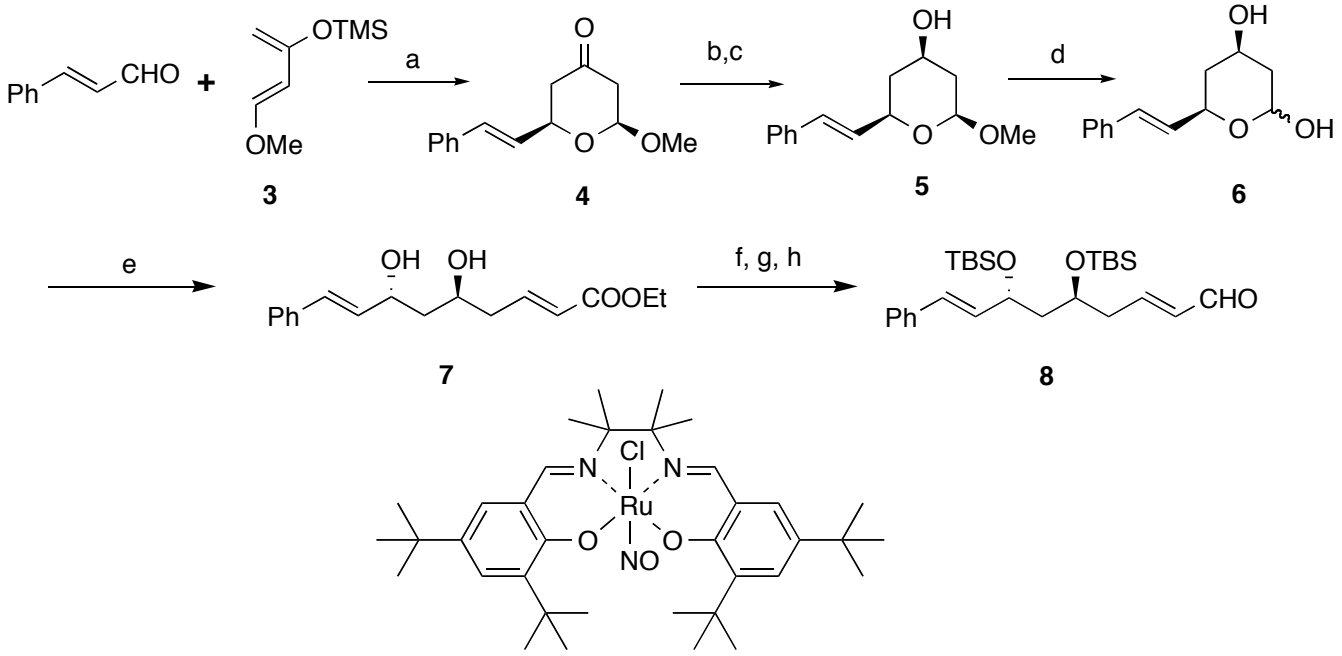
We have recently reported that second-generation (salen)chromium complex (**2**)[9] is an efficient catalyst for asymmetric hetero Diels-Alder (AHDA) reactions of Danishefsky diene (**3**) and aldehydes.[10] The reactions proceed with high enantioselectivity greater than 90% ee and their stereochemistry is predictable from the catalyst used. The quenching the AHDA reactions with methanol and triethylamine[11] gives 2-methoxy-γ-pyrones (**A**) that can be stereoselectively reduced to give 4,6-*cis*-4-hydroxy-2-methoxytetrahydropyrans (**B**) according to Nakata's procedure.[12] Ring-opening of compounds (**B**) gives 3,5-*anti*-diols (**C**). On the other hand, the treatment of the AHDA reaction



Scheme 1

mixture with trifluoroacetic acid (TFA) gives 6-substituted 2,3-dehydro-γ-pyrones (**D**) that are readily converted to the corresponding α-pyrones (**E**) according to the reported procedure[13] (Scheme 1). Thus, we expected that two possible stereoisomers of **1** could be synthesized by using AHDA reaction as the key step. To use the 1,3-diol unit as the common intermediate for the synthesis of the two isomers, we planned to synthesize 6*R*,10*S*,12*R*-**1** (**1**$_R$) and the enantiomer of 6*R*,10*R*,12*S*-**1** (**1**$_S$).

The synthesis started with AHDA reaction of cinnamyl aldehyde with diene (**3**) using complex (**2**) as the catalyst (Scheme 2). The reaction gave 2-methoxy-γ-pyrone (**4**) of 95% ee, when the reaction was quenched with methanol in the presence of triethylamine. The product was reduced with $LiAlH_4$[12] to give the corresponding *cis*-alcohol (**5**), the recrystallization of which from toluene gave optically pure **5** in 74% yield. Compound (**5**) was hydrolyzed under acidic conditions to lactol (**6**) which was subjected to Wittig reaction using PPh_3=CHCHO. However, the reaction was slow and the yield of the corresponding α,β-unsaturated aldehyde was low (<30%) even after a prolonged reaction time. Consequently, **6** was treated with the anion of triethyl phosphonoacetate, and α,β-unsaturated ester (**7**) corresponding to the C6-C6' fragment of **1** (or its enantiomer) was obtained in a quantitative yield. We next attempted to protect the 1,3-diol as acetonide,[13] but the reaction gave a 1:1 mixture of the corresponding acetonide and **7**, even if an excess amount of 2,2'-dimethoxypropane in the presence of a strong acid like *p*-toluenesulfonic acid was used. This result probably supports that the configuration of the 1,3-diol is *anti*, because the acetonization of *anti*-1,3-diol causes the undesired 1,3-diaxial repulsion



3 **4** **5** **6** **7** **8**

Ru-salen complex

Scheme 2. Reaction conditions: a) (*R*,*R*)-**2** (2.5 mol %), CH_2Cl_2, 0 °C, 24 h, then MeOH, Et_3N (quant., 95% ee); b) $LiAlH_4$, -78 °C, THF (quant.); c) recrystallization from toluene (74%,100% ee); d) 0.025 M HCl (H_2O : MeCN = 1 : 2), 50 °C (80 %); e) $(EtO)_2P(O)CH_2COOEt$ (3 eq.), NaH, -30 ° C, THF (quant.); f) TBSCl, imidazole; g) DIBAL, -78 °C; h) Ru-salen (2 mol%), air (O_2), visible light (58 % for 3 steps)

(Figure 2). Therefore, compound (**7**) was protected as *t*-butyldimethylsilyl (TBS) ethers and transformed to aldehyde (**8**) by DIBAL reduction and subsequent aerobic oxidation catalyzed by Ru-salen complex.[14] AHDA reactions of **8** with **3** using **2** or ***ent*-2** as the catalyst gave γ-pyrones ($\mathbf{9}_R$) and ($\mathbf{9}_S$) together with a small amounts (<5 %) of their diastereomers ($\mathbf{9}_S$ and $\mathbf{9}_R$), respectively, after the reaction mixture was treated with TFA (Scheme 3).[10] γ-Pyrones ($\mathbf{9}_R$) and ($\mathbf{9}_S$) were converted into the corresponding α-pyrones ($\mathbf{10}_R$ and $\mathbf{10}_S$), respectively, by the following sequence:[15] i) reduction by Luche's method,[16] ii) acidic transformation of enol ether to methyl acetal associated with double bond migration,[17] and c) Jones oxidation. Treatment of α-pyrones ($\mathbf{10}_R$ and $\mathbf{10}_S$) with acetic acid-water gave $\mathbf{1}_R$ and $\mathbf{1}_S$, respectively.[18] Isomerically pure $\mathbf{1}_R$ and $\mathbf{1}_S$ were obtained by HPLC separation (DAICEL CHIRALCEL AS-H x 2, hexane/2-propanol = 7/3, 0.7 mL/min) and subjected to the following experiments for characterization.

^{1}H and ^{13}C NMR spectra of $\mathbf{1}_R$ and $\mathbf{1}_S$ were recorded at 200 and 270 MHz (^{1}H NMR) and at 68 or 100 MHz (^{13}C NMR) and compared with those of cryptofolione (**1**). Both the ^{13}C NMR spectral data of $\mathbf{1}_R$ and $\mathbf{1}_S$ were found to be almost identical and to agree with the reported one[2a,4] for cryptofolione (**1**) (Table 1). ^{1}H NMR spectra of $\mathbf{1}_R$ and $\mathbf{1}_S$ are also very similar to one another (Figure 3). CD measurements of $\mathbf{1}_R$ and $\mathbf{1}_S$ showed positive and negative cotton effects, indicating that their C6-configurations are *R* and *S*,

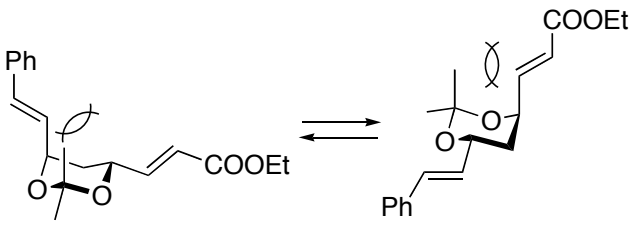
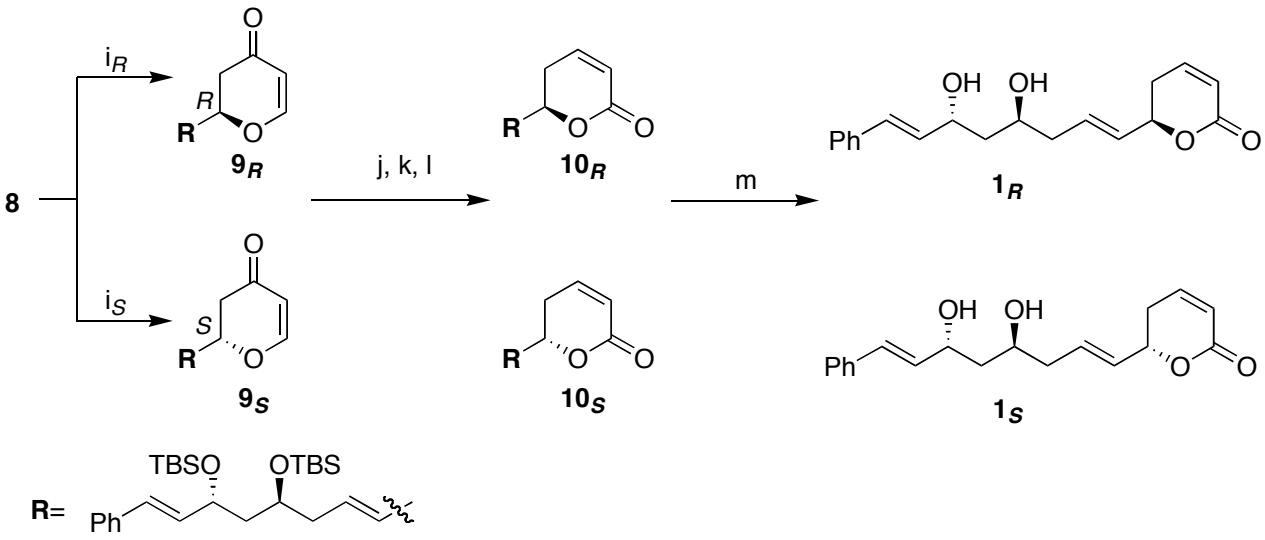


Figure 2



Scheme 3. Reaction conditions: i_R) **2** (2.5 mol %), CH_2Cl_2, 0 °C, 24 h, then TFA (79%); i_S) ***ent*-2** (2.5 mol %), CH_2Cl_2, 0 °C, 24 h, then TFA (63%); j) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, -78 °C; k) MeOH, PPTS, rt; l) Jones oxidation, 0 °C ($\mathbf{10}_R$: 30 % from $\mathbf{9}_R$, $\mathbf{10}_S$: 38 % from $\mathbf{9}_S$); m) AcOH : H_2O : THF= 3 : 1 : 1, rt ($\mathbf{1}_R$: 81 %, $\mathbf{1}_S$: 83 %)

Table 1. Chemical shifts (^{13}C NMR) for **1**, $\mathbf{1}_R$, and $\mathbf{1}_S$

C	**1**[a] (ppm)	$\mathbf{1}_R$[b] (ppm)	$\mathbf{1}_S$[c] (ppm)	C	**1**[a] (ppm)	$\mathbf{1}_R$[b] (ppm)	$\mathbf{1}_S$[c] (ppm)
2	164.3	164.0	164.1	11	42.3	42.1	42.2
3	121.3	121.5	121.5	12	70.1	70.5	70.3
4	145.1	144.7	144.8	13	129.7	130.0	130.0
5	29.6	29.7	29.7	14	131.9	131.6	131.7
6	78.0	77.8	77.9	1'	136.7	136.5	136.6
7	129.6	130.0	130.0	2'/6'	126.4	126.5	126.4
8	131.3	131.0	131.1	3'/5'	128.6	128.6	128.6
9	40.4	40.4	40.4	4'	127.6	127.7	127.7
10	68.0	68.2	68.1				

a) Data (50 MHz, $CDCl_3$) extracted from reference 2a.
b) 68 MHz, $CDCl_3$.
c) 100 MHz, $CDCl_3$.

respectively, as expected from the sense of asymmetric induction of AHDA reactions (CD curves of $\mathbf{1}_R$ and $\mathbf{1}_S$ were observed at 278 and 276 nm, respectively).[4] Furthermore, the molecular structure of $\mathbf{1}_S$ was determined by X-Ray crystallography, establishing the stereochemistry of $\mathbf{1}_S$ to be the supposed 6*S*,10*S*,12*R* in conjunction with the above CD spectral analysis (Figure 4).[19] Thus, the structures of $\mathbf{1}_R$ and $\mathbf{1}_S$ were confirmed to be 6*R*,10*S*,12*R* and 6*S*,10*S*,12*R*, respectively. Finally, comparative evaluation for the specific rotations of **1** ($[\alpha]_D^{23}$ +57° (c 0.52, CH_2Cl_2)[2a], $\mathbf{1}_R$ ($[\alpha]_D^{24}$ +48° (c 0.011, CH_2Cl_2), and $\mathbf{1}_S$ ($[\alpha]_D^{24}$ –14° (c 0.034, CH_2Cl_2) was performed to strongly suggest the absolute configuration of cryptofolione to be 6*R*,10*S*,12*R*.[20]

In conclusion, we have synthesized two possible stereoisomers of cryptofolione by using Cr(salen)-catalyzed AHDA reaction as the key steps. Their absolute configurations were rationally determined based on the sense of asymmetric induction of AHDA reactions and were also deduced from a combination of CD measurement and X-Ray crystallographic analysis. Comparison of the specific rotations of the synthetic samples with the one of natural product led to the establishment of the absolute configuration of cryptofolione for the first time.

ACKNOWLEDGEMENTS

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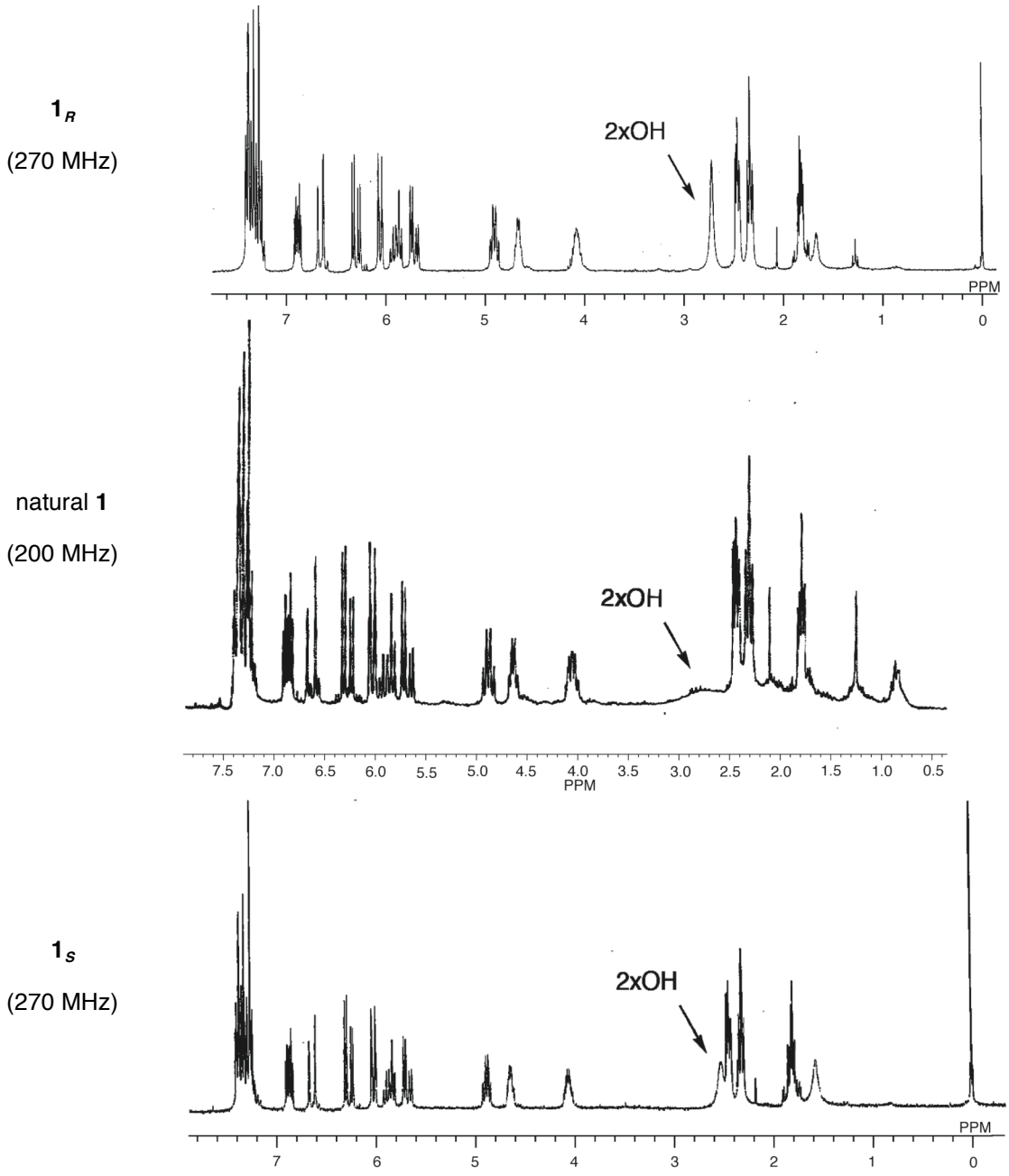

Figure 3. ^{1}H NMR spectral data of natural **1**, $\mathbf{1}_R$, and $\mathbf{1}_S$

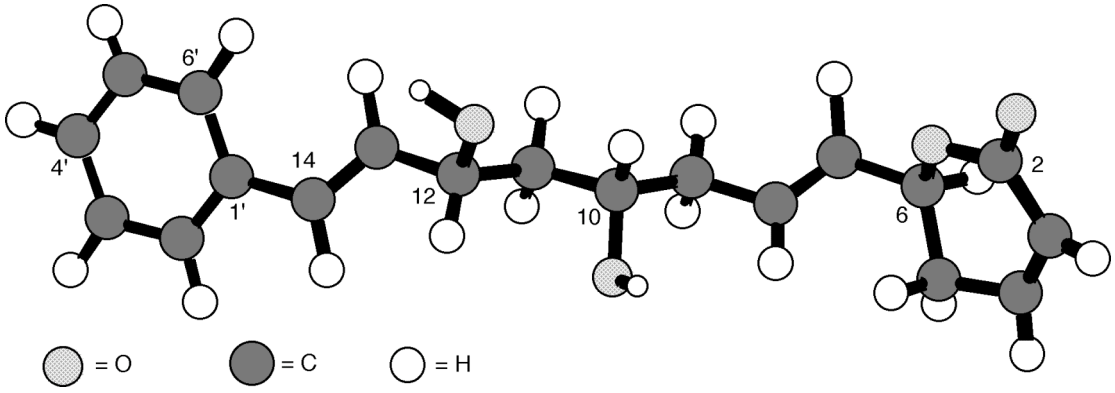

Figure 4. A Chem3D diagram for the X-Ray structure of $\mathbf{1}_S$.

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19. Crystallographic data for $\mathbf{1}_S$: Recrystallized from tetrahydrofuran-hexane, $C_{19}H_{22}O_4$, M = 314.37,

monoclinic, space group $P2_1$, a = 10.653(2) Å, b = 6.0862(9) Å, c = 13.182(2) Å, V = 850.0(2) Å^3, Z = 2, Dc = 1.228, μ(Mo-Ka) = 0.85, R = 0.054, Rw = 0.046 for 1541 reflections and 207 variables, GOF = 0.99. Data were collected on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo-Ka at –90 °C. Structural analysis was performed using the teXsan crystallographic software package. The structure was solved by heavy atom Patterson methods and expanded using Fourier techniques. Hydrogen and all non-hydrogen atoms were refined isotropically and anisotropically, respectively.

20. Although this result indicates that the specific rotations of both (6*R*,10*R*,12*S*)-**1** and (6*R*,10*S*,12*R*)-**1** have the same plus sign as the natural product, the absolute value for the former stereoisomer is more comparable with that reported for cryptofolione.