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^{1}H and ^{13}C NMR Assignments and Stereochemistry of *d,l*-Isospongiadiol and Six Spongian Intermediates

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ABSTRACT: Long-range (LR COSY, RELAY, TOCSY, HMBC) and neighbor (COSY, HMQC) 2D correlation NMR methods were used in tandem to derive complete ^{1}H and ^{13}C NMR assignments for synthetic *d,l*-isospongiadiol and six spongian intermediates obtained from a novel free-radical tandem cyclization process. The ^{13}C NMR spectra of synthetic *d,l*-isospongiadiol are identical with those reported previously for natural isospongiadiol, whereas the ^{1}H NMR spectra reflect solvent differences. NOESY and difference NOE data demonstrate that synthetic *d,l*-isospongiadiol and the spongian intermediates have the desired 19β-methylene and 18α-, 17β- and 20β-methyl stereoselectivity at the stereogenic centers, and that rings A–C are in chair conformations. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{1}H NMR; ^{13}C NMR; LRCOSY; HMBC; NOESY; isospongiadiol; spongian intermediates; stereochemistry

INTRODUCTION

The non-steroidal furanoditerpenes spongiadiol (**1**), epispongiadol (**2**) and isospongiadiol (**3**) isolated from *Spongia* species collected in Australian[1] and Caribbean[2] waters are known to possess antiviral and antitumor activity. These unusual diterpenes commonly feature 18α-, 17β- and 20β-methyl groups, but exist in nature at small quantities and their isolation requires extensive separation efforts. Our laboratories are exploring synthetic routes[3–5] to rare terpenes with biological activity. In this paper, we report a detailed NMR study of synthetic *d,l*-isospongiadiol (**3**) and six spongian intermediates (**5**, **5a**, **5b**, **5c**, **8** and **9**) obtained from novel, biomimetic free-radical cyclizations of polyenes.[3–6]

In one step, three stereoselective 6-*endo* tandem cyclizations of polyene **4** introduce five chiral centers in **5** with very high selectivity to form the rings of the spongian skeleton.

Intermediate **5** with an exocyclic C-14 methylene is transformed to spongian analog **6** via spongian intermediates **5a–c**.

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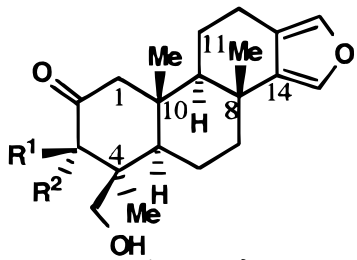

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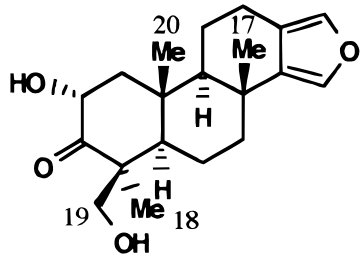

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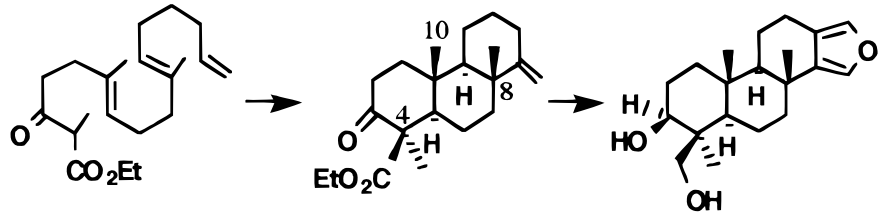

4 **5** **6**

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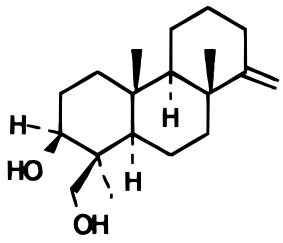

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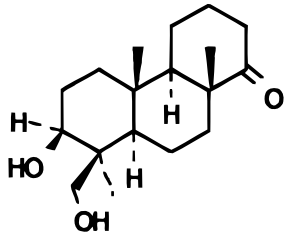

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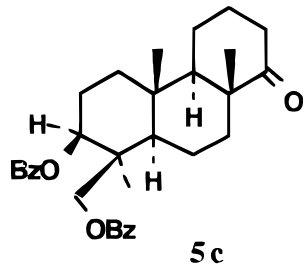


5c

The analogous stereoselective tandem cyclizations of polyene **7** introduce six chiral centers in spongian intermediate **8** while concomitantly introducing an exocyclic C-13 methylene for conversion to epoxide **9**. The C-13 epoxide and C-14 methylene are transformed to the furan ring via an oxidation step, and hydroxylation at C-2 in analog **10** gives *d,l*-isospongiadiol (**3**).

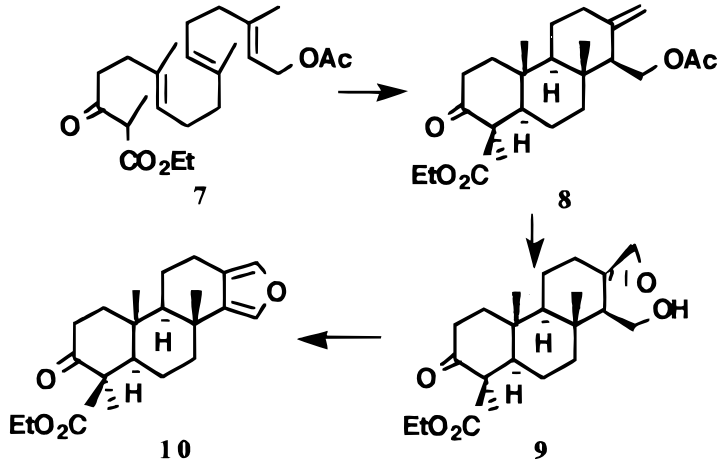
Complete ^{1}H and ^{13}C NMR assignments were derived for spongian intermediates **5** and **5a–c**, **8** and **9** and synthetic *d,l*-isospongiadiol (**3**) from long-range (LR COSY, RELAY, TOCSY, HMBC) and neighbor (COSY, HMQC) 2D NMR scalar correlations.[7–14] 2D NOESY,[15] 1D difference NOE (NOEDS),[16,17] observed coupling constants and long-range coupling results are consistent with chair conformations of the tricyclic rings with the desired 19β-methylene, 18α-, 17β- and 20β-methyl, and 5α- and 9α-methine stereoselectivity at the key chiral centers. The ^{13}C NMR spectral data for synthetic *d,l*-isospongiadiol (**3**) were found to be identical with those of natural isospongiadiol[1] whereas the ^{1}H NMR spectral data reflect solvent differences.

EXPERIMENTAL

The syntheses of compounds **5** and **5a–c**, **8**, **9** and **3** have been described elsewhere.[3–5] Spongian intermediates **5** and **5a–c**, **8** and **9** are named in this paper as substituted phenanthrenes,[5] while synthetic *d,l*-isospongiadiol (**3**) is named relative to the original naming of the spongian skeleton.[1] The equatorial 4-CH_3 and angular 8-CH_3 and 10-CH_3 groups in the phenanthrene nomenclature are formally identical with the 18-CH_3, 17-CH_3 and 20-CH_3 groups in the spongian nomenclature.

NMR data were recorded at 28 °C for 5–8 mg samples dissolved in $CDCl_3$ or $CDCl_3$–C_6D_6 mixtures in 5 mm NMR tubes using a Varian Unity 500 MHz NMR spectrometer equipped with a Sun Sparc 2 data system and a 5 mm Varian inverse probe. ^{1}H spectra were obtained with a spectral width (SW) of 5 kHz, a 67° pulse flip angle (6 μs), a 4.8 s acquisition time (AT), a 2 s relaxation delay (RD) and digitized with 48K points giving a digital resolution of 0.208 Hz per point. COSY,[7,8] long-range COSY (LR COSY)[8,9] and RELAY[10] data were recorded in the absolute value mode with a 4.5 kHz SW, 2K points, 1 s RD and 32 scans per increment; 512 time increments were collected and zero-filled to 2K points with sine-bell weighting in both dimensions before Fourier transformation, followed by symmetrization of the 2D matrix. TOCSY[11] and NOESY[15] data were collected in the phase-sensitive mode using two sets of 256 time-incremented spectra with Gaussian weighting in both dimensions, 32 scans per increment, 1 s delay and a mixing time of 70 ms in TOCSY and 500 ms in NOESY. The 2D matrix after zero-filling was 2K × 2K and was not symmetrized. The 1D difference NOE spectra (NOEDS)[16,17] used 15 s of low-power (estimated 0.2 mW) presaturation to build up the steady-state NOE. To improve FID subtraction, samples were thermally equilibrated in the magnet for over 1 h before recording data, and the NOEDS were obtained in an interleaved manner with four scans accumulated for each FID and looping around 20 times to achieve a good signal-to-noise ratio with 80 scans per FID.

^{1}H-decoupled ^{13}C spectra were recorded with a 30 007 Hz SW, a 60° pulse flip angle (6 μs), a 1.6 s repeat time and digitized into 78 080 points to give a digital resolution of 0.769 Hz per point. Single-bond ^{1}H, ^{13}C



chemical shift correlation spectra were recorded in the inverse mode using ^{1}H detection based on the HMQC method[12,13] with ^{13}C decoupling using GARP1.[18] A BIRD filter was used to suppress unwanted signals. Two sets of 256 time increments were obtained in the phase-sensitive mode, processed using Gaussian functions and zero-filled to a final size of 2K × 2K; 48 transients were obtained per time increment and the RD was 1.2 s.

^{1}H-detected multiple bond correlation spectra (HMBC)[13,14] were recorded in the phase-sensitive mode without ^{13}C decoupling during acquisition. The HMBC spectra were plotted in a mixed mode [absolute value in f_2 (^{1}H) and phase sensitive in f_1 (^{13}C)]. A shifted Gaussian weighting function was used along f_2 and a cosine weighting function was used along f_1. Two sets of 256 time increments were zero-filled to a final size of 2K × 2K. The RD was 1.2 s, the filter delay corresponded to an average $^1J_{CH}$ of 140 Hz and 64 transients were obtained per increment. The long range ^{1}H–^{13}C couplings were allowed to evolve for a delay of 83 ms corresponding to an average $^nJ_{CH}$ of 6.3 Hz.

RESULTS AND DISCUSSION

Spongian Intermediates With Five Chiral Centers

The NMR analysis of **5** is started in the A-ring by noting that its ^{1}H NMR spectrum showed a well resolved six-line resonance at 2.94 ppm (dt, J = 14.6, 6.6 Hz) which arises from H-2β in the axial orientation to the 3-carbonyl (Fig. 1). A COSY experiment then identified H-2α, H-1α and H-1β (Fig. 1). The ^{1}H NMR spectra of **5a–c** analogously showed a well resolved H-3 resonance at >3.3 ppm, which allowed the tracing of COSY or TOCSY connectivities to H-2β, H-2α, H-1β and H-1α (Table 1).

The COSY spectra for **5** and **5a–c** revealed off-diagonal connectivities at two of the three methyl singlets. For example, the 1.02 and 1.11 ppm methyl singlets

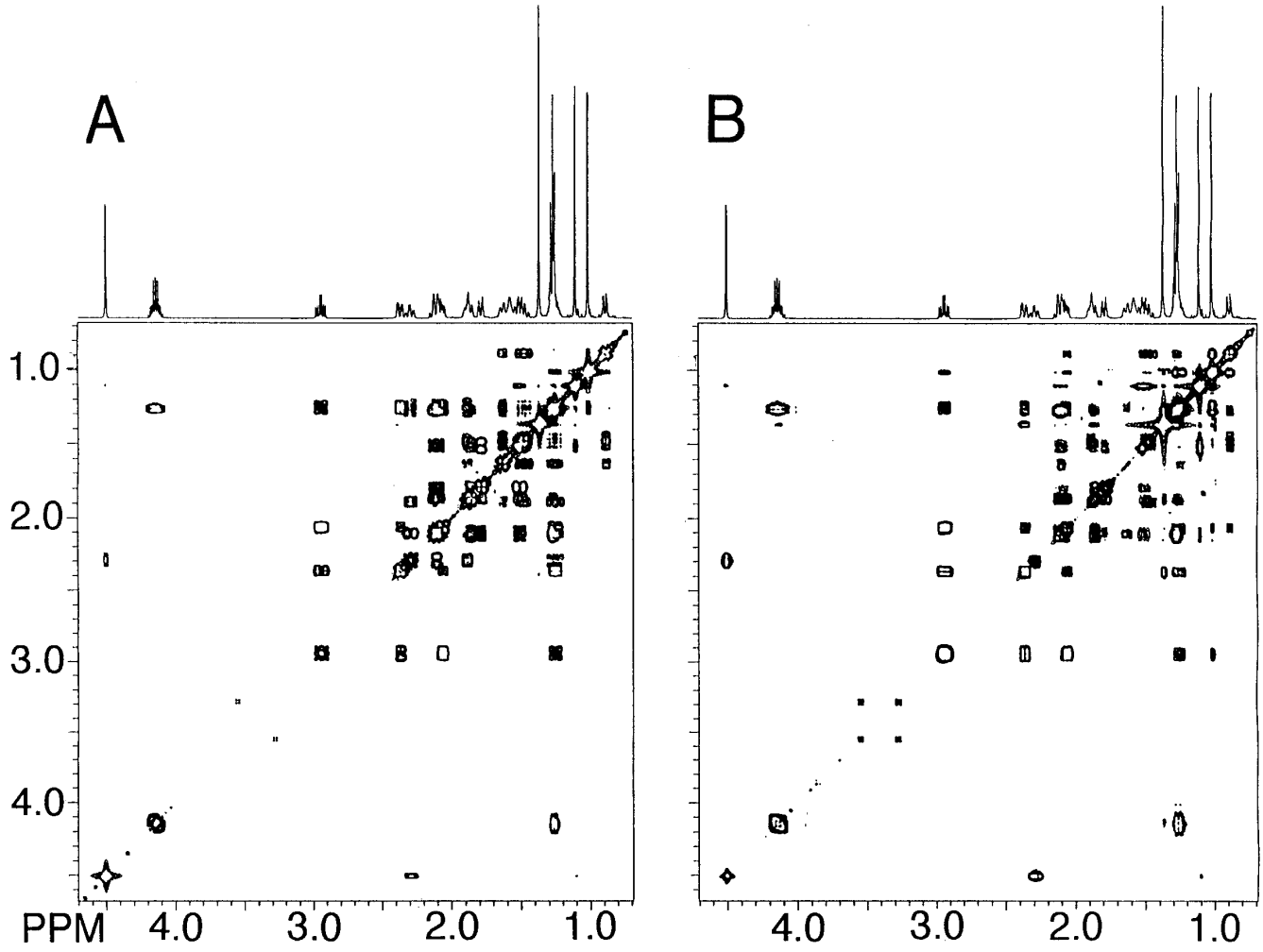


Figure 1. 500 MHz ^{1}H NMR spectra of spongian intermediate **5** in $CDCl_3$ at 28 °C. (A) Standard 2D COSY featuring long-range correlations from angular 10-CH_3 (1.02 ppm) to H-1α (*ca.* 1.27 ppm) and to H-9α (resolved doublet-of-doublets at 0.89 ppm) and from angular 8-CH_3 (1.11 ppm) to H-7α (1.51 ppm). (B) Long-range COSY with a 0.3 s delay to optimize for small couplings. The long-range correlations previously seen are enhanced. Diagnostic correlations are detected from (1) the angular 10-CH_3 to H-2β and H-1β, (2) the angular 8-CH_3 to H-11β and H-13β and (3) the equatorial 4-CH_3 to H-6α and H-2α.

Table 1. ^{1}H NMR assignments of spongian intermediates **5** and **5a–c**[a]

Position	δH [(mult), *J* (Hz)]			
	5[b]	**5a**	**5b**	**5c**[c]
1α	~1.27 [m]	0.94 [m, 13, 3.5]	0.99 [m]	~1.24 [m]
1β	2.06	~1.73 [m]	~1.78 [m]	~1.89 [m]
2α	2.367 [dq, 4.7, 2.3]	~1.72 [m]	~1.75 [m]	~1.92 [m]
2β	2.94 [dt, 14.6, 6.6]	~1.82 [m]	1.832 [m]	~1.91 [m]
3		3.408 [dd, 12, 4.5]	3.411 [dd, 11.5, 4.4]	4.87 [dd, 11.5, 5.6]
4-CH_3	1.369 [s]	1.241 [s]	1.231 [s]	1.227 [s]
4-CH_2-OH		4.198 [d, 11.1]	4.180 [d, 11.1]	4.534 [d, 11.8]
4-CH_2-OH		3.374 [d, 11.1]	3.359 [d, 11.1]	4.737 [d]
5α	~1.27 [m]	0.896 [m]	0.866 [dd, 12.4, 1.8]	~1.16 [m]
6α	1.864 [m]	~1.73 [m]	~1.75 [m]	~1.91 [m]
6β	2.109 [m]	1.407 [m]	1.32 [dddd, 13, 3.5]	~1.65 [m]
7α	1.512 [m]	1.550 [m]	~1.63 [m]	~1.63 [m]
7β	1.787 [dt, 13.1, 3.4]	~1.73 [m]	~1.71 [m]	~1.71 [m]
8-CH_3	1.107 [s]	1.021 [s]	1.115 [s]	1.156 [s]
9α	0.889 [dd, 12.4, 2.7]	0.845 [dd, 12.4, 2.5]	1.049 [dd, 11.9, 3.0]	~1.16 [m]
10-CH_3	1.015 [s]	0.826 [s]	0.902 [s]	1.076 [s]
11α	1.633 [dq, 13, 2.3]	~1.59 [m]	~1.63 [m]	~1.66 [m]
11β	1.480 [dddd, 13, 2.3]	~1.38 [m]	~1.69 [m]	~1.76 [m]
12α	~1.27 [m]	~1.24 [m]	~1.51 [m]	~1.54 [m]
12β	1.893 [m]	~1.87 [m]	2.059 [m]	2.093 [m]
13α	2.109 [m]	2.080 [m]	2.186 [m]	2.221 [m, 14, 3.8]
13β	2.295 [dtt, 13.7, 5, 1.4]	2.265 [dtt, 13.7, 5, 1]	2.543 [ddd, 14, 6.9]	2.543 [ddd, 14, 6.9]
14-CH_2	4.510 [d, 1.4]	4.489 [d, 1.4]		

[a] Chemical shifts in $CDCl_3$ at 28 °C relative to internal TMS.
[b] Additional side-chain ester ^{1}H signals in **5** at 1.287 ppm (t) and 4.147 ppm (m).
[c] Additional aromatic blocking group ^{1}H signals in **5c** at 7.22, 7.38, 7.45, 7.54, 7.96 and 8.00 ppm.

in **5** showed COSY cross peaks to multiplets at *ca.* 1.27 and 1.51 ppm, respectively (Fig. 1). Since H-1α, H-5α, H-12α and the ethyl triplet overlap at *ca.* 1.27 ppm, and H-7α and H-11β overlap at *ca.* 1.5 ppm (Fig. 1), interpretation of the methyl cross peaks from COSY alone was ambiguous. The three methyl resonances in **5** and **5a–c** were instead distinguished using COSY optimized for long-range couplings.[8,9] The 1.02 ppm methyl resonance in **5** (Fig. 1), for example, showed new four- or five-bond connectivities to H-2β (2.94 ppm) and H-1β (2.06 ppm) and an enhanced cross peak to H-9α (0.89 ppm), which clearly established its assignment to the angular 10-CH_3 group. The 1.11 ppm methyl signal (Fig. 1) was established as the angular 8-CH_3 group from long-range cross peaks to H-11β (1.48 ppm) and H-13β (2.30 ppm). With the angular 10-CH_3 and 8-CH_3 groups assigned, the COSY connectivities to the *ca.* 1.27 and 1.15 ppm multiplets (which were enhanced in LR COSY) are recognized as diagnostic four-bond 'W-type' couplings from the angular methyl groups to H-1α and H-7α similar to diagnostic 18-CH_3 to H-12α and 19-CH_3 to H-1α couplings observed for many steroids.[19] The remaining 1.37 ppm methyl signal in **5** was established as the equatorial 4-CH_3 signal from four- or five-bond connectivities to H-6α (1.86 ppm) and H-2α (2.37 ppm) (Fig. 1). Analogous LRCOSY data for **5a–c** revealed an additional long-range correlation from the 4-CH_3 signal to the C-4 CH_2. The methyl ^{1}H signals in **5** and **5a–c** resonate at various positions with each substituent change (Table 1). Each methyl group in **5** and **5a–c** was therefore assigned based on its individual LR COSY behavior.

With the methyl resonances assigned, the B-ring assignments for **5** and **5a** and **b** were obtained by locating the COSY connectivity from the angular 8-CH_3 to H-7α (Fig. 1) and tracing cross peaks to H-7β, H-6α and H-6β. The H-5α resonance, which was a resolved doublet-of-doublets in **5b** (0.86 ppm, J = 12.4, 1.8 Hz), was then identified either in TOCSY or RELAY or in further COSY traces from either H-6α or H-6β. The B-ring ^{1}H resonances in **5c** were severely overlapped with other ^{1}H signals in the 1D NMR spectrum and gave highly congested 2D COSY/TOCSY data. Heteronuclear data in this one case (see below) were essential to establish reliable B-ring assignments.

The C-ring assignments in **5** and **5a–c** were derived by locating the COSY cross peak (Fig. 1) from the angular 10-CH_3 to H-9α (resolved double doublet; 0.89 ppm, J = 12.4, 2.7 Hz in **5**; 0.85 ppm, J = 12.4, 2.5 Hz in **5a**; 1.05 ppm, J = 11.9, 3.0 Hz in **5b**) and tracing COSY connections to H-11β and H-11α. The COSY correlation from the exocyclic H-14 CH_2 doublet in **5** and **5a** (*ca.* 4.5 ppm, J = 1.4 Hz) located H-13β, which in turn allowed the COSY identification of H-13α, H-12α and H-12β (Fig. 1). The network of nine proton spins from H-9 to H-14 was then verified from TOCSY spectra. Compounds **5b** and **c** feature a C-14 carbonyl and H-13β moves downfield to *ca.* 2.5 ppm. COSY or

TOCSY data then located the remaining six protons in the C-ring of **5b** and **c**.

After associating protons and carbons via ^{1}H–^{13}C HMQC, uncertainties in quaternary and B-ring (C-6, C-7) assignments were overcome by recording ^{1}H–^{13}C HMBC spectra. Scrutiny of the HMBC data revealed strong $^{3}J_{CH}$ connectivities from the 10-CH_3 proton signal to C-5, C-9 and C-1 and a $^{2}J_{CH}$ correlation to the 38.0 ppm quaternary carbon signal (C-10). Multi-bond cross peaks from the 8-CH_3 proton signal identified the C-8 quaternary, C-9 methine and C-7 methylene resonances in all four intermediates **5** and **5a**–**c**. A multi-bond correlation was also detected from the 8-CH_3 to C-14 in **5** and **5a**. The multi-bond correlation to C-7 served to validate the H-7, H-6 assignments of **5** and **5a** and **b** and was essential to the H-7, H-6 assignments in **5c** owing to the highly congested nature of its ^{1}H spectra. HMBC correlations from the 4-CH_3 proton signal in **5** revealed multi-bond connectivities to C-3, C-5, the ester carboxyl and the C-4 quaternary signal (57.6 ppm). In **5a**–**c**, multi-bond correlations were detected from the 4-CH_3 proton signal to C-3, C-5, 4-CH_2 and the C-4 quaternary signal (*ca.* 41 ppm). The detection of the multi-bond correlations established the integrity of the skeletal structure of these spongian intermediates. Other multi-bond responses, e.g. long-range correlations from H-2β to C-3 and C-1 in **5**, served as checks of the validity of the ^{1}H and ^{13}C assignments listed in Tables 1 and 2. A remaining ambiguity, due to poor digitization in the HMQC spectrum, to resolve overlapped 13.8 and 13.9 ppm ^{13}C methyl signals of **5** was addressed by recording two separate ^{13}C spectra at high digital resolution while individually ^{1}H-decoupling the ethyl and 10-CH_3 ^{1}H signals.

Spongian Intermediates with Six Chiral Centers

The ^{1}H NMR spectra of spongian intermediates **9** and **8** (Figs 2 and 5) in $CDCl_3$ showed a six-line multiplet at 2.95 ppm (**9**, dt, J = 14.8, 6.7 Hz) from H-2β similar to that seen for spongian intermediate **5** (Fig. 1). A COSY experiment then allowed identification of the other A-ring resonances (H-1β, H-1α and H-2α), the five B-ring multiplets (H-5 to H-7), and the five C-ring multiplets (H-9 to H-12). LRCOSY results were diagnostic for differentiating the methyl signals. For example, the 0.99 ppm methyl signal in **9** (Fig. 2) showed four- or five-bond connectivities to H-1α (*ca.* 1.35 ppm), H-1β (2.09 ppm)I and H-2β (2.95 ppm) which established its assignment to the angular 10-CH_3 group. The 0.91 ppm methyl signal (Fig. 2) was similarly established as the angular 8-CH_3 group from diagnostic long-range cross peaks to H-7α (*ca.* 1.27 ppm), H-11β (1.57 ppm) and H-14α (*ca.* 1.86 ppm). The remaining 1.37 ppm methyl signal was then assigned to the equatorial 4-CH_3 group and this assignment was confirmed by the observation of weak four-bond connectivities to H-2α (2.41 ppm) and H-6α (*ca.* 1.86 ppm). With methyl groups and ring multiplets firmly established, well dispersed COSY cross peaks for **9** (Fig. 2) allowed a straightforward identification of the H-13 epoxy (3.21 and 2.72 ppm), H-14 methylene (4.34 and 4.20 ppm) and hydroxyl (3.01 ppm) protons (Table 3).

Table 2. ^{13}C NMR assignments of spongian intermediates **5** and **5a–c**[a]

		δC (ppm)			
Position	Multiplicity	**5**[b]	**5a**	**5b**	**5c**[c]
1	t	40.662	38.234	38.183	38.285
2	t	36.626	27.843	27.655	23.706
3	s	208.846	80.869	80.604	80.577
4	s	57.634	40.053	42.933	41.913
4-CH_3	q	20.923	22.453	22.420	22.511
4-CH_2OH	t		64.450	64.294	65.500
5	d	58.156	56.237	55.595	55.941
6	t	20.522	18.562	17.809	18.745
7	t	38.659	39.278	34.766	34.820
8	s	39.988	37.554	49.104	49.085
8-CH_3	q	21.008	21.360	19.645	19.554
9	d	57.184	58.417	57.763	57.642
10	s	38.095	38.095	37.946	38.106
10-CH_3	q	13.846	16.802	17.091	16.588
11	t	21.627	21.360	20.242	20.257
12	t	28.541	28.656	26.172	26.111
13	t	32.998	33.117	37.574	37.563
14	s	150.692	160.214	215.498	215.221
14-CH_2	t	102.975	102.654		

[a] Chemical shifts in $CDCl_3$ at 28 °C relative to internal TMS.
[b] Additional side-chain ester ^{13}C signals in **5** at 13.886 (q), 60.976 (t) and 173.693 (s) ppm.
[c] Additional aromatic blocking group ^{13}C signals in **5c** at 128.272, 128.472, 132.906, 132.975, 129.742, 129.682 (all d multiplicity) and at 130.283 and 130.432 ppm (s multiplicity).

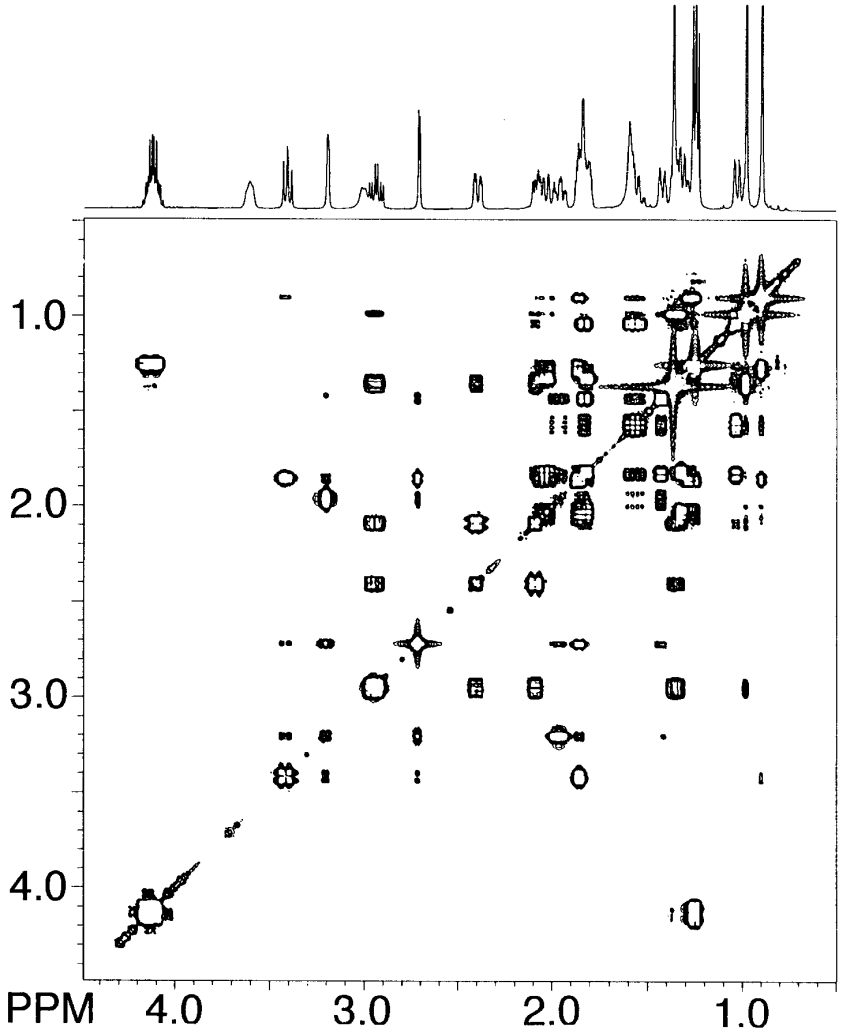


Figure 2. Partial 500 MHz ^{1}H 2D long-range COSY NMR spectra of spongian intermediate **9** in $CDCl_3$ at 28 °C. Diagnostic four- and five-bond connectivities are detected from (1) the angular 10-CH_3 (0.99 ppm) to H-2β, H-1β and H-1α, (2) the angular 8-CH_3 (0.91 ppm) to H-7α, H-11β and H-14α and (3) the equatorial 4-CH_3 to H-6α and H-2α.

After associating the protons and carbons via HMQC (Table 3), an HMBC experiment revealed that the 4-CH_3 resonance in **9** (1.37 ppm) was related to the C-3 carbonyl carbon (208 ppm), C-5 methine (57.5 ppm) and C-4 quaternary carbon (57.4 ppm). The HMBC data also established multi-bond relationships between the 8-CH_3 resonance (0.91 ppm) and the C-7 methylene, C-9 and C-14 methines and the C-8 quaternary carbon (39.1 ppm) in **9**. Further scrutiny of the HMBC data for **9** revealed strong multi-bond connectivities from the 10-CH_3 signal (0.99 ppm) to the C-1 methylene, C-5 and C-9 methines and C-10 quaternary carbon signal (37.7 ppm). The detection of these and other multi-bond responses validated the ^{1}H and ^{13}C assignments (Table 3) and established the skeletal integrity of the spongian intermediates.

d,l-Isospongiadiol (3)

The ^{1}H NMR spectrum of synthetic *d,l*-isospongiadiol (**3**) in $CDCl_3$ (Table 4) revealed the furan moiety at 7.08 (br. s) and 7.05 (br. s), three methyl singlets at 1.30, 1.26 and 1.25 ppm, an AB quartet (assigned to the 19-CH_2 protons) at 4.14 and 3.66 ppm (J = 11 Hz), a resolved eight-line multiplet at 4.61 ppm (ddd, J = 12, 6.3, 2.5 Hz), and a distinct doublet at 3.63 ppm (J = 2.5 Hz). The positions and lineshapes of the furan and AB quartet accorded with the corresponding resonances in the ^{1}H NMR spectrum of natural isospongiadiol[1] which was recorded in a 2:1 C_6D_6–$CDCl_3$ mixture. The NMR spectra also showed considerable differences. The ^{1}H NMR spectrum of natural isospongiadiol lacked the doublet at 3.63 ppm, showed the methyl singlets resonating at 1.11, 0.99 and 0.86 ppm and revealed a simple double doublet (H-2β) resonating at 4.40 ppm. The ^{13}C NMR spectra of synthetic *d,l*-isospongiadiol and natural isospongiadiol, in contrast, were virtually identical (Table 5).

A ^{1}H NMR spectrum of synthetic *d,l*-isospongiadiol (**3**) in 2:1 C_6D_6–$CDCl_3$ at 28 °C was therefore recorded to approximate more closely the observation conditions of the natural material[1] (temperature not given). The three methyl singlets shifted upfield to 1.14, 1.08 and 0.95 ppm and the eight-line multiplet shifted upfield to 4.41 ppm with its small coupling increasing from 2.5 to

Table 3. ^{1}H and ^{13}C NMR assignments of spongian intermediates **8** and **9**[a]

Position	δH [(mult), J (Hz)]		δC (ppm)	
	8	**9**	**8**	**9**
1α	~1.33 [m]	~1.35 [m]	40.835	40.700
1β	2.085 [ddd, 13, 6.6, 2.3]	2.093 [ddd, 13, 5.6, 2.3]		
2α	2.389 [ddd, 15, 4.8, 2.3]	2.407 [ddd, 15, 4.8, 2.3]	36.577	36.476
2β	2.950 [dt, 14.6, 6.6]	2.951 [dt, 14.8, 6.7]		
3			208.556	208.127
4			57.498	57.396
4-CH_3	1.363 [s]	1.370 [s]	20.886	20.876
4-$CO_2CH_2CH_3$			173.568	
4-$CO_2CH_2CH_3$	4.132 [m]	4.132 [m]	61.085	61.096
4-$CO_2CH_2CH_3$	1.254 [t, 7]	1.259 [t, 7]	13.938	13.924
7β	1.908 [dt, 13, 3.3]	~1.82 [m]		
8			38.987	39.156
8-CH_3	0.812 [s]	0.906 [s]	15.764	16.364
10			37.890	37.710
10-CH_3	1.015 [s]	0.989 [s]	13.866	13.869
11β	1.419 [qd, 13, 4.3]	1.570 [qd, 13, 4]		
12α	~ 2.02 [m]	1.968 [tq, 15, 4.6, 1.8]	37.312	35.955
12β	2.418 [dq, 13, 4, 2.4]	1.433 [dq, 12.5, 3.5]		
13			146.047	61.318
13-C*H*H	4.870 [d, 0.8]	3.206 [dd, 3.5, 2]	107.619	51.674
13-CH*H*	4.548 [d, 0.8]	2.721 [d, 3.6]		
14	~2.02 [m]	~1.86 [m]	54.826	54.449
14-C*H*HOR	4.338 [dd, 11, 3.8]	4.338 [dt, 11, 3.3]	61.372	58.729
14-CH*H*OR	4.195 [dd, 11, 9]	4.195 [dd, 11, 9]		
14-CHHO*H*		3.009 [d, 10.7]		
14-CHHO*C*CH_3			171.376	
14-CHHOC*C*H_3	2.019 [s]		21.108	

[a] Chemical shifts in $CDCl_3$ at 28 °C relative to internal TMS.

3.6 Hz (ddd, $J = 12$, 6.6, 3.6 Hz). The simple doublet moved slightly upfield to 3.620 ppm, and its coupling constant changed to 3.6 Hz concomitant with the coupling constant change in the eight-line multiplet. It became clear from this evidence that the 4.41 ppm eight-line multiplet and the 3.62 ppm doublet arose from the H-2β and 2-OH in the A-ring, respectively.

The three methyl singlets were again differentiated in two ways: an HMBC experiment (Fig. 3) revealed that the carbonyl carbon (C-3, 214 ppm) was related to the 19-CH_2 (3.72 and 3.23 ppm), 2-OH (3.62 ppm), H-1β (2.44 ppm, dd, $J = 12.6$, 6.5 Hz) and 18-CH_3 (1.14 ppm) protons. The HMBC data also showed the furan C-14 carbon (136.8 ppm) to be connected to the furan H-16 (6.93 ppm), H-12β (2.59 ppm, dd, $J = 16.1$, 6.1 Hz) and 17-CH_3 (1.08 ppm) protons. The 20-CH_3 resonance (0.95 ppm) was uniquely related to the carbon (C-1, 49.6 ppm) bearing the methylene protons at 2.44 (H-1β) and 0.95 (H-1α) ppm. An LRCOSY experiment revealed diagnostic four- or five-bond connectivities between (1) the 18-CH_3 singlet and the 19-CH_2 proton at 3.72 ppm, (2) the 17-CH_3 singlet and the H-11β proton at 1.47 ppm and (3) the 20-CH_3 singlet and the H-2β proton at 4.41 ppm. COSY and HMQC experiments then completed the ^{1}H (Table 4) and ^{13}C (Table 5) assignments of *d,l*-isospongiadiol (**3**).

Stereochemical Determination

Interpretation of 2D NOESY (Fig. 4) or NOEDS (Fig. 5) results allowed the determination of the relative stereochemical configuration of the chiral centers within **5** and **5a–c**, **8**, **9** and **3**. In the spongian intermediates with five chiral centers, **5** and **5a–c**, NOE enhancements were seen between (1) the angular 10-CH_3 group and the proton groups H-2β (axial), H-6β (axial), H-1β (equatorial), H-11β (axial), 8-CH_3 and C-4 methylene (methyleneoxy in **5**), (2) the angular 8-CH_3 group and the proton groups H-13β (axial), H-6β (axial), H-7β (equatorial), H-11β (axial) and 10-CH_3, (3) the 4-CH_3 group and the proton groups H-5α (axial), H-6α (equatorial), the C-4 methylene and H-3α (axial) in **5a–c** and (4) H-9α (axial) and the proton groups H-5α (axial), H-12α (axial) and H-7α (axial).

In the spongian intermediates with six chiral centers, **8** and **9**, and in *d,l*-isospongiadiol (**3**), the following NOE dipolar interactions were detected: (1) from the angular 10-CH_3 (20-CH_3 in **3**) group [Fig. 5(A)] to H-2β (axial), H-6β (axial), H-1β (equatorial), H-11β (axial), 8-CH_3 (17-CH_3 in **3**) and C-19 methylene (in **3**); (2) from the angular 8-CH_3 (17-CH_3 in **3**) group to H-6β (axial), H-7β (equatorial, H-11β (axial), 10-CH_3 (20-CH_3 in **3**) and to one H-13 epoxy (in **9**) and one

Table 4. ^{1}H NMR assignments of isospongiadiol (**3**)

Position	δH [(mult), *J* (Hz)]		
	d,*l*[a]	*d*,*l*[b]	Natural[c]
1α	1.20 [m]	~0.95 [m]	~0.90 [dd, 12.6]
1β	2.637 [dd, 12.4, 6.6]	2.438 [dd, 12.6, 6.5]	2.36 [dd, 12.6, 6.5]
2-OH	3.625 [d, 2.5]	3.620 [d, 3.6]	
2β	4.612 [ddd, 12, 6.3, 2.5]	4.412 [ddd, 12, 6.6, 3.6]	~4.40 [dd, 12.6, 6.5]
5α	1.405 [m]	1.024 [m]	0.95 [m]
6α	~1.71 [m]	~1.31 [m]	~1.28 [m]
6β	1.71 [dddd, 13, 3.5]	1.379 [m]	~1.28 [m]
7α	~1.58 [m]	~1.28 [m]	~1.19 [m]
7β	2.165 [dt, 12, 3]	1.879 [dt, 12, 3]	~1.77 [m]
9α	~1.24 [m]	0.915 [dd, 12, 6]	0.80 [br. d, 11.4]
11α	1.836 [dd, 13, 7]	1.570 [dd, 13, 7]	1.45 [m]
11β	~1.70 [m]	1.468 [m]	1.37 [m]
12α	2.455 [m]	2.272 [m]	2.19 [m]
12β	2.793 [dd, 16.1, 6.1]	2.593 [dd, 16.1, 6.1]	2.50 [dd, 16.1, 6.1]
15-CH	7.077 [br. s]	6.957 [d, 1.0]	6.89 [br. s]
16-CH	7.048 [br. s]	6.933 [br. m]	6.87 [br. s]
17-CH_3	1.264 [s]	1.077 [s]	0.99 [s]
18-CH_3	1.301 [s]	1.138 [s]	1.11 [s]
19-C*H*H	4.135 [d, 11]	3.723 [dd, 11, 6]	3.70 [d, 11]
19-CH*H*	3.664 [d, 11]	3.233 [dd, 11, 4.6]	3.16 [d, 11]
20-CH_3	1.254 [s]	0.948 [s]	0.86 [s]

[a] Data in $CDCl_3$ at 28 °C relative to internal TMS.
[b] Data in 2:1 C_6D_6–$CDCl_3$ at 28 °C.
[c] From Ref. 1. Data in 2:1 C_6D_6–$CDCl_3$. Temperature not given.

Table 5. ^{13}C NMR assignments of isospongiadiol (**4**)

Position	Multiplicity	δC (ppm)		
		d,*l*[a]	*d*,*l*[b]	Natural[c]
1	t	49.501	49.619	49.8
2	t	69.921	69.835	70.0
3	s	214.033	213.782	214.1
4	s	54.514	54.383	54.6
5	d	58.697	58.310	58.4
6	t	20.041	19.938	20.0
7	t	41.153	41.015	41.1
8	s	34.327	34.233	34.3
9	d	55.872	55.505	55.5
10	s	38.018	37.795	37.9
11	t	18.796	18.759	18.9
12	t	20.500	20.522	20.6
13	s	119.369	119.403	119.5
14	s	136.663	136.778	136.9
15-CH	d	135.072	135.095	135.2
16-CH	d	137.027	137.135	137.2
17-CH_3	q	26.369	26.277	26.4
18-CH_3	q	19.299	19.233	19.4
19-CH_2	t	65.687	65.470	65.5
20-CH_3	q	17.573	17.368	17.5

[a] Data in $CDCl_3$ at 28 °C relative to internal TMS.
[b] Data in 2:1 C_6D_6–$CDCl_3$ at 28 °C.
[c] From Ref. 1. Data in 2:1 C_6D_6–$CDCl_3$. Temperature not given.

H-14 methylene proton (in **8** and **9**; see below); and (3) from the equatorial 4-CH_3 (18-CH_3 in **3**) group to H-5α (axial), H-6α (equatorial) and the C-19 methylene in **3**.

The multiple 1,3-diaxial and distinct axial–equatorial (10-CH_3 to H-1β; 8-CH_3 to H-7β; 4-CH_3 to H-5α) NOE enhancements from both β-face and α-face substituents diagnostically define[19] the three cyclohexane rings in **5** and **5a–c**, **8**, **9** and **3** to adopt chair conformations with *trans* A/B and B/C ring junctures. The resolved *ca.* 12 Hz diaxial couplings between H-9α and H-11β in **5** and **5a** and **b**, **8**, **9** and **3** and between H-5α and H-6β in **5b** and **9** provide further evidence that the B- and C-rings are in chair structures. Also, the diagnostic COSY couplings from the 10-CH_3 to H-1α and H-9α and from the 8-CH_3 to H-7α in spongian intermediates **5** and **5a–c**, **8** and **9** are similar to the diagnostic 18-CH_3 to H-12α and 19-CH_3 to H-1α couplings observed for many steroidal rings in chair structures.[19]

The assignment of the β-configuration of the C-14 methyleneacetoxy substituent in **8** was based on the following NOE results: first, irradiation of H-9α gave NOE enhancements only to H-5α and H-14α [Fig. 5(B)]. Second, irradiation of the 8-CH_3 (0.81 ppm) showed enhancement of only one of the C-14 methylene protons (4.19 ppm). Irradiation of the C-14 methylene at 4.19 ppm showed enhancements of the 8-CH_3 (0.81 ppm), the second C-14 methylene proton (4.34 ppm),

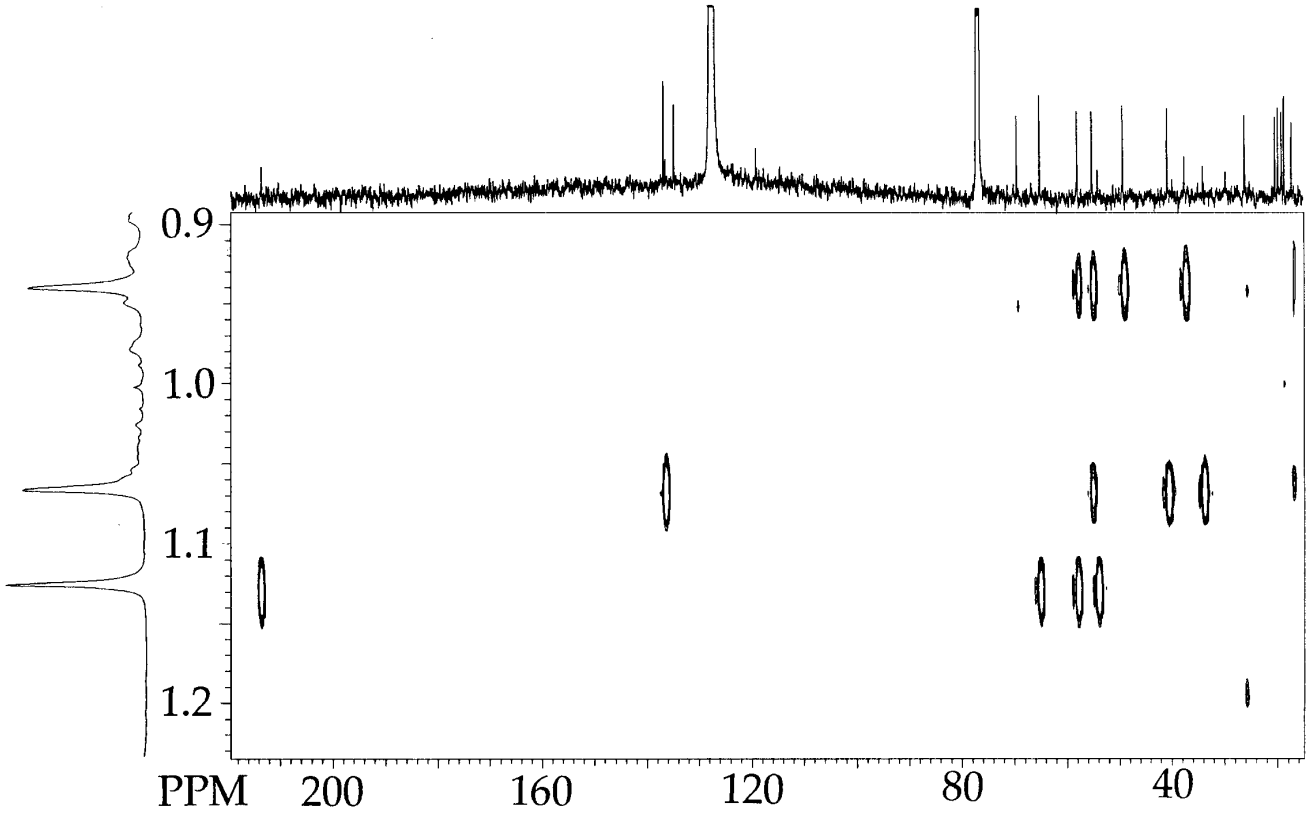


Figure 3. HMBC of synthetic *d,l*-isospongiadiol (**3**) in 2 : 1 C_6D_6–$CDCl_3$ at 28 °C showing multi-bond correlations from the angular 17- and 20-CH_3 and equatorial 18-CH_3 proton resonances.

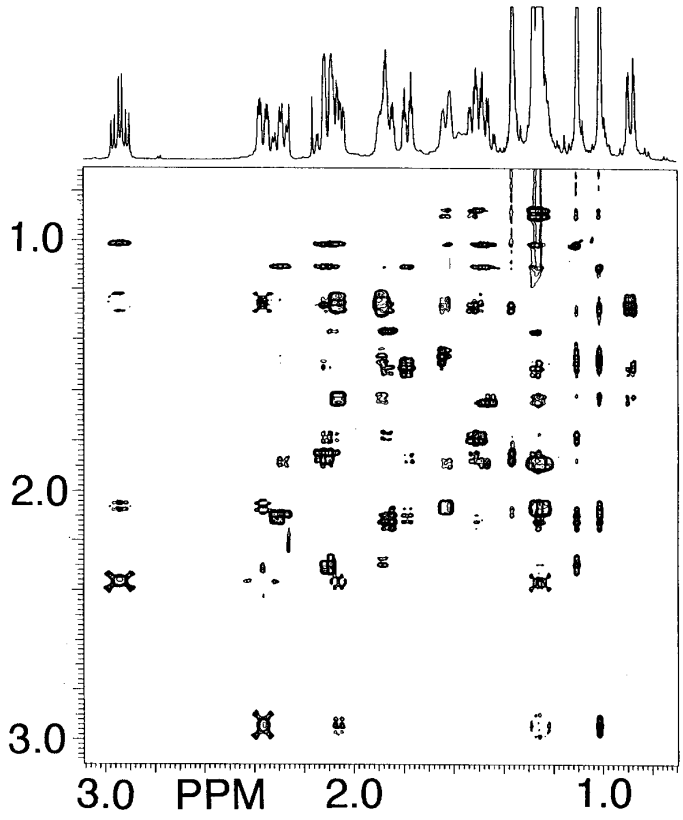


Figure 4. Partial 500 MHz ^{1}H 2D NOESY NMR spectra of spongian intermediate **5** in $CDCl_3$ at 28 °C. With the diagonal peaks phased negatively, the NOE cross peaks phased positively. The diagonal peaks are omitted from the 2D plot for clarity purposes. Diagnostic NOESY cross peaks are detected from (1) the 10-CH_3 (1.02 ppm) to the angular 8-CH_3, H-11β (axial), H-6β (axial) and H-2β, (2) the 8-CH_3 to the angular 10-CH_3, H-11β (axial), H-6β (axial), H-7β (equatorial) and H-13β (axial), (3) the equatorial 4-CH_3 to H-5α, H-6α and the methyleneoxy protons of the ethyl ester and (4) H-9α (axial) to H-5α (axial), H-7α (axial) and H-12α (axial). The mixing time was 500 ms.

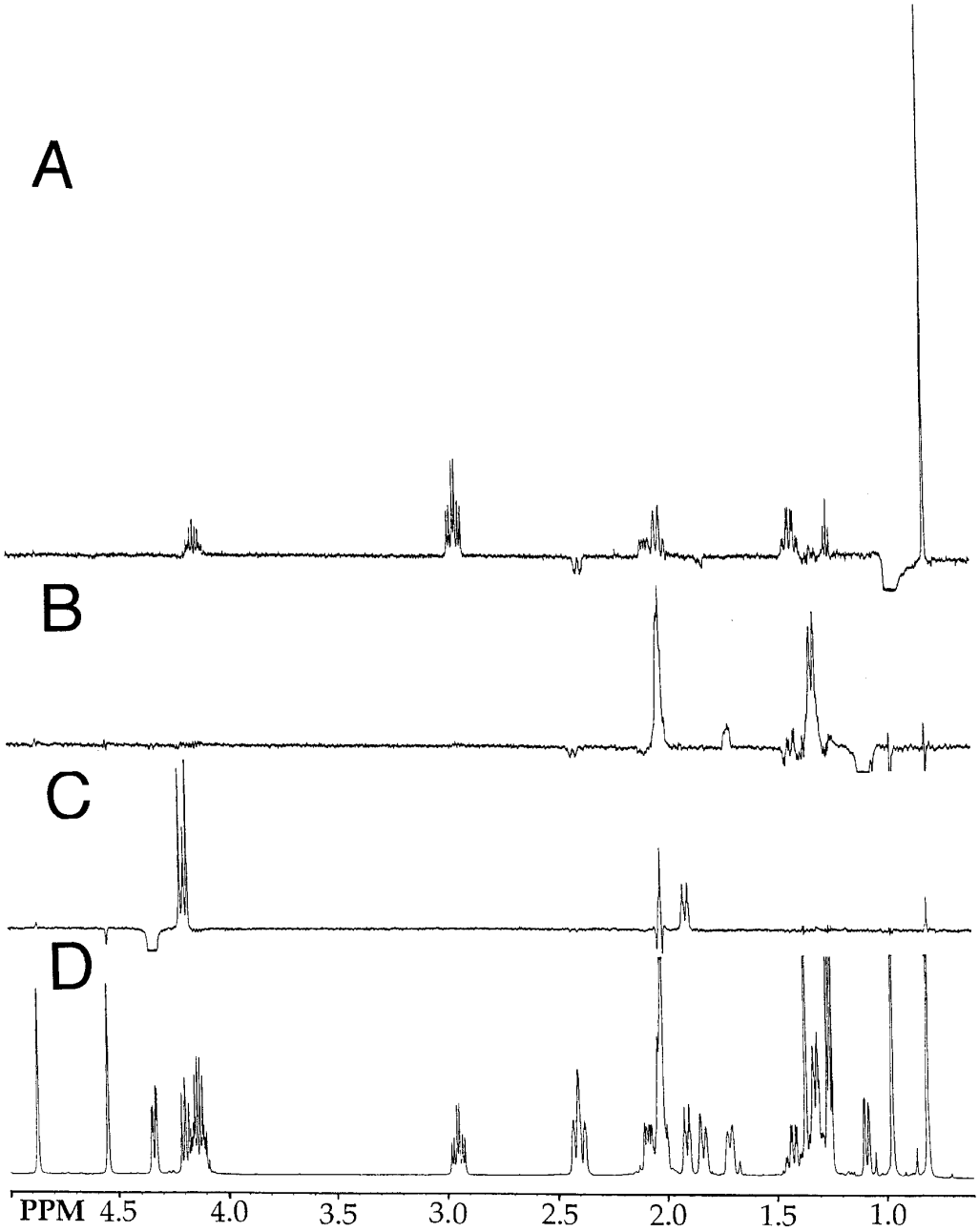


Figure 5. 500 MHz ^{1}H NMR spectra of spongian intermediate **8** in $CDCl_3$ at 28 °C. (A–C) difference NOE spectra: (A) irradiation of the 10-CH_3 gives diagnostic NOE enhancements at the 8-CH_3, H-11β, H-2β, H-6β and the ethyl methylene and methyl signals; (B) irradiation of H-9α reveals NOE enhancements at H-5α and H-14α; (C) irradiation of the 4.34 ppm C-14 methylene reveals enhancements at the 4.19 ppm C-14 methylene, H-7β and the acetyl group. (D) Normal 1D spectrum.

one of the exocyclic C-13 methylene protons (4.87 ppm) and the acetyl group (2.02 ppm). Irradiation of the 4.34 ppm C-14 methylene proton showed only an enhancement of the first C-14 methylene proton (4.19 ppm), H-7β and the acetyl group [Fig. 5(C)].

The assignments of the α-configuration to the epoxy group at C-13 and the β-configuration to the C-14 hydroxymethylene in **9** were based on the following NOE results: irradiation of the 8-CH_3 (0.91 ppm) showed enhancement of one of the diastereotopic protons of the epoxide (3.21 ppm) and one of the hydroxymethylene protons (4.34 ppm). While irradiation of the 3.21 ppm epoxy proton showed enhancements of the 8-CH_3 (0.91 ppm), one hydroxymethylene (4.34 ppm), one epoxy (2.72 ppm) and the OH (3.01 ppm), irradiation of the epoxy proton at 2.72 ppm showed only an enhancement of the epoxy proton at 3.21 ppm and the C-12 equatorial proton at 1.42 ppm.

Overall, the NMR data indicate (1) the 4-CH_2 group in **5** and **5a–c** and the 19-CH_2 group in **3** to be axial and β, (2) the 4-CH_3 group in **5** and **5a–c**, **8** and **9** and the 18-CH_3 group in **3** to be equatorial and α, (3) the 10-CH_3 group in **5** and **5a–c**, **8** and **9** and the 20-CH_3 group in **3** to be axial and β and (4) the 8-CH_3 group in **5** and **5a–c**, **8** and **9** and the 17-CH_3 group in **3** to be axial and β. These are precisely the substituent orientations sought after in spongian intermediates and analogs.

CONCLUSION

The intramolecular oxidative free radical synthetic strategy[3–5] is shown to lead to the stereoselective construction of spongian furanoditerpenes and intermediates with the desired configurations at the stereogenic centers. Long-range COSY correlations are found to be diagnostic for the NMR analyses of the spongian intermediates and analogs. Synthetic *d,l*-isospongiadiol is seen to have identical carbon and similar proton NMR spectral properties to those previously reported for natural isospongiadiol.

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