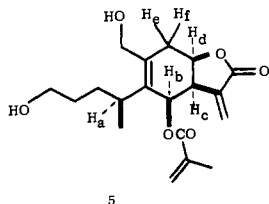
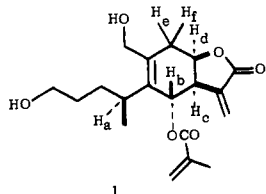


coupling constant of  $J = 1.8$  Hz which is in complete agreement with the predicted value of 1.6–1.8 Hz.<sup>9</sup>

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- (16) (a) The desired opening of epoxide **18** was accompanied by cleavage of the silyl ether and conversion of the resultant alcohol into its formyl ester. (b) Attempted hydrolysis of the two formate esters with anhydrous potassium carbonate in methanol at varying temperatures gave, in addition to hydrolysis of the two formyl groups, the product derived from Michael addition of methanol to the  $\alpha$ -methylene- $\gamma$ -butyrolactone moiety. The methacrylate unit appeared not to suffer 1,4 addition.
- (17) ( $\pm$ )-Eriolanin: IR (CHCl<sub>3</sub>) 3440, 1758, 1710, 1660, 1635 cm<sup>-1</sup>; NMR (250 MHz)  $\delta$  (CDCl<sub>3</sub>) 6.45 (d, 1 H,  $J = 2.5$  Hz), 6.08 (s, 1 H), 6.05 (d, 1 H,  $J_{bc} =$



- 3 Hz), 5.61 (s, 1 H), 5.27 (d, 1 H,  $J = 2.5$  Hz), 5.05 (dt, 1 H,  $J_{cd} = 8$  Hz,  $J_{de} = 2.5$  Hz,  $J_{ef} = 3$  Hz), 4.23 (AB q, 2 H,  $\Delta\nu_{AB} = 21.2$  Hz,  $J = 12$  Hz, CH<sub>2</sub>OH), 3.4–3.6 (m, 3 H, -CH<sub>2</sub>CH<sub>2</sub>OH, H<sub>c</sub>), 2.80 (AM portion of an AMX system, 2 H,  $\Delta\nu_{AM} = 80.4$  Hz,  $J_{de} = 2.5$  Hz,  $J_{df} = 3$  Hz), 2.77 (m, 1 H, H<sub>a</sub>), 1.93 (s, 3 H), 1.0–1.4 (m, 4 H, -CH<sub>2</sub>CH<sub>2</sub>-), 0.90 (d, 3 H,  $J = 7$  Hz).
- (18) After the submission of this manuscript, alcohol **19** was converted in two steps (1, angelic anhydride, <sup>19</sup>Et<sub>3</sub>N, THF, 4-dimethylaminopyridine, room temperature, 23 h; 2, Dowex 1X-8 (OH<sup>-</sup> form), methanol, 0 °C, 1.5 h) into ( $\pm$ )-eriolangin (**2**), mp 90–91 °C, which was shown to be identical in all respects with an authentic sample of natural eriolangin.
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- (20) The NMR spectrum<sup>21</sup> of compound **5** at 250 MHz revealed that it was not identical with the NMR spectrum of natural eriolangin; however, it was obvious that all functional groups were present. Unfortunately, NMR analysis did not permit assignment of structure **5** to racemic 6-epieriolanin.
- (21) ( $\pm$ )-6-Epieriolanin: IR (CHCl<sub>3</sub>) 3620, 3450, 1762, 1712, 1665, 1640 cm<sup>-1</sup>; NMR (250 MHz)  $\delta$  (CDCl<sub>3</sub>) 6.36 (d, 1 H,  $J = 2$  Hz), 6.00 (s, 1 H), 5.97 (d, 1 H,  $J_{bc} = 5$  Hz), 5.77 (d, 1 H,  $J = 2$  Hz), 5.56 (s, 1 H), 4.85 (q, 1 H,  $J_{cd} = J_{de} = J_{ef} = 8$  Hz), 4.22 (AB q, 2 H,  $\Delta\nu_{AB} = 18.4$  Hz,  $J = 12$  Hz, -CH<sub>2</sub>OH), 3.51 (t, 2 H, -CH<sub>2</sub>CH<sub>2</sub>OH), 3.25 (m, 1 H, H<sub>a</sub>), 2.88 (m, 1 H, H<sub>c</sub>), 2.86 (AM portion of an AMX system, 2 H,  $\Delta\nu_{AM} = 55.7$  Hz,  $J_{de} = 16$  Hz,  $J_{df} = 8$  Hz,  $J_{ef} = 8$  Hz), 1.87 (s, 3 H), 1.2–1.5 (m, 4 H, -CH<sub>2</sub>CH<sub>2</sub>-), 1.07 (d, 3 H,  $J = 7$  Hz).



- (22) Crystals of racemic 6-epieriolanin are monoclinic, space group  $P2_1/c$ , with cell constants  $a = 9.4729$  (6),  $b = 12.064$  (1),  $c = 16.426$  (2) Å;  $\beta = 97.60$  (1)°;  $V = 1860.7$  Å<sup>3</sup>;  $\rho_0 = 1.257$  g cm<sup>-3</sup>,  $\rho_c = 1.26$  g cm<sup>-3</sup> (for  $Z = 4$ ). A total of 3804 reflections were measured, of which 2229 are considered observable ( $I > 2\sigma$ ). The structure was determined by routine multiscan direct methods<sup>23</sup> and refined to a current residual of  $R = 0.067$ .
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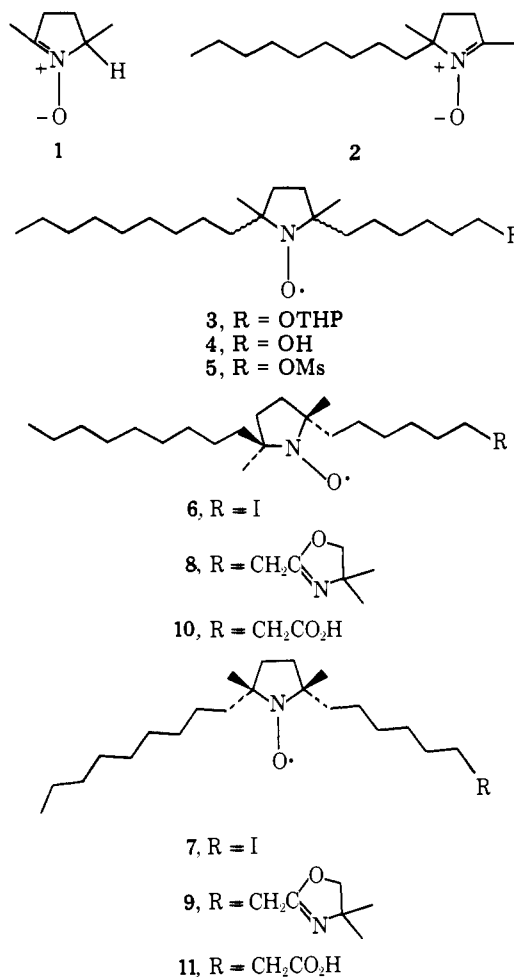
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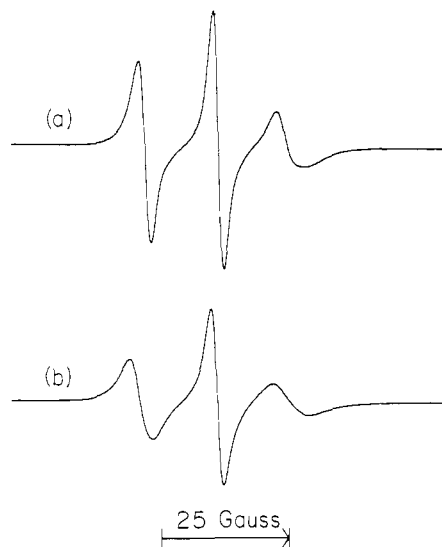
## A New Series of Minimum Steric Perturbation Nitroxide Lipid Spin Labels

Sir:

A continuing concern in the study of biological and other systems by the nitroxide spin-labeling technique has been the extent to which the system is perturbed by the steric bulk of the nitroxide moiety.<sup>1</sup> We describe herein a new series of "minimum steric perturbation" nitroxide lipid spin labels which we term azethoxyl nitroxides.<sup>2</sup> The nitroxyl nitrogen atom and two of the pyrrolidine ring carbon atoms of the azethoxyl nitroxides are integrated into the lipid chain. Additionally, both bent and straight chain structures can be prepared corresponding to cis (e.g., **11**) and trans (e.g., **10**) isomers about the pyrrolidine ring. Since the cis azethoxyl nitroxides appear from molecular models to resemble quite well the geometry about a cis carbon-carbon double bond, one has in effect a near-ideal ESR probe for the motion and environment experienced by a cis double bond in lipids. On the other hand, models suggest that the trans azethoxyl nitroxides are a reasonably good analogue of a saturated chain.

The synthesis of representative trans and cis azethoxyl fatty acid derivatives **10** and **11** closely parallels our recent synthesis of proxyl nitroxides.<sup>3</sup> Reaction of nitrene **14** with 2 equiv of nonylmagnesium bromide in ether followed by an aqueous workup and Cu<sup>2+</sup> catalyzed air oxidation<sup>3,5</sup> of the *N*-hydroxy intermediate gave nitrene **2** (45%, bp 100–109 °C (0.005 mm); *m/e* 239.223). Reaction of **2** with the Grignard reagent derived from 1-tetrahydropyranyloxy-6-chlorohexane and subsequent Cu<sup>2+</sup>-catalyzed air oxidation of the product gave after silica gel chromatography nitroxide **3** (22%, *m/e* 424.380) as a mixture of cis-trans isomers. Hydrolysis (0.1 M HCl in MeOH) of **3** gave alcohols **4** (76%, *m/e* 340.321) which were





**Figure 1.** The 9.5-gHz spectra of (a) trans isomer **10** and (b) cis isomer **11** ( $1 \times 10^{-4}$  M) in egg lecithin vesicles (60 mg/ml in 10 mM Tris buffer, pH 7.4) at 25 °C, scaled to the same total double integral.

converted into the mesylates **5**<sup>6</sup> and thence into iodides **6** (74%, *m/e* 450.221) and **7** (16%, *m/e* 450.223) which were separable by silica gel chromatography (elution with  $\text{CHCl}_3$ ). Following the procedure of Meyers,<sup>8</sup> **6** and **7** separately were converted into oxazolines **8** and **9** and thence by quaternization and base hydrolysis<sup>8</sup> into azethoxyl acids **10** (60%, *m/e* 382.332) and **11** (35%, *m/e* 382.332).

Evidence for the smaller steric size of an azethoxyl nitroxide as compared with a doxyl<sup>9</sup> or proxyl nitroxide<sup>3</sup> of similar chain length was obtained by trapping **10** in the cavity of a thiourea inclusion crystal.<sup>10</sup> Neither the doxyl nor the proxyl nitroxides could be included in the thiourea crystals under similar conditions, presumably because they are sterically too large to fit into the cavity.

While the solution ESR spectra of **10**<sup>11</sup> and **11** were virtually identical, significant differences (over a temperature range of 25–45 °C) were observed in the spectra of the two isomers when diffused into egg lecithin vesicles (Figure 1). Computer simulation<sup>12</sup> of the ESR spectra led to an estimate of  $50 \pm 3^\circ$  and  $57 \pm 3^\circ$  for the angle between the nitroxide *Z* axis and the long axis of rotation of **10** and **11**, respectively. Simulations also revealed that the rotational motion experienced by cis isomer **11** was less than that of the trans isomer **10**.

A preliminary study of the relative rates of reduction of 12-doxylstearic acid, 14-proxylstearic acid<sup>13</sup> and azethoxyl acid **10** indicate that the azethoxyl nitroxide is the most resistant toward reduction. In one series of experiments the nitroxides ( $1.1 \times 10^{-4}$  M) were dissolved in 0.1 M phosphate buffer, pH 7.5, containing sucrose (0.25 M), EDTA ( $10^{-3}$  M), and sodium ascorbate (0.011 M).<sup>14</sup> After 20 min only 3% of the original signal intensity remained for the doxyl nitroxide, whereas 90% remained for the proxyl nitroxide and 94% remained for the azethoxyl nitroxide.

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## References and Notes

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- (11) Isotropic *A* and *g* values for  $2 \times 10^{-4}$  M solutions of **10** are *A* = 14.1 G, *g* = 2.0062 in hexane and *A* = 16.3 G, *g* = 2.0054 in 0.1 M phosphate buffer (pH 7.5). The corresponding values for 14-proxylstearic acid are *A* = 14.5 G, *g* = 2.0058 (hexane) and *A* = 16.3 G, *g* = 2.0055 ( $\text{H}_2\text{O}$ ); and for 12-doxylstearic acid *A* = 14.4 G, *g* = 2.0062 (hexane) and *A* = 16.0 G, *g* = 2.0056 ( $\text{H}_2\text{O}$ ). Experimental errors are estimated to be  $\pm 0.1$  G for *A* and  $\pm 0.0002$  for *g*.
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## Detection and Measurement of the Rate of 1,3 Iron Shift in Cycloheptatrieneiron Tricarbonyl

Sir:

Many fluxional organometallic systems are known in which a transition metal is bound to a fragment of a totally conjugated cyclic polyenyl or polyene system.<sup>1</sup> Examples include complexes containing the  $(\eta^3\text{-C}_7\text{H}_7)\text{M}$ ,<sup>2</sup>  $(\eta^5\text{-C}_7\text{H}_7)\text{M}$ ,<sup>3</sup>  $(\eta^4\text{-C}_8\text{H}_8)\text{M}$ ,<sup>4</sup>  $(\eta^6\text{-C}_8\text{H}_8)\text{M}$ ,<sup>5</sup> and  $(\eta^4\text{-C}_6\text{R}_6)\text{M}$ <sup>6</sup> moieties. In almost every case where the fluxional mechanism has been determined, the metal migrates around the ring via a series of 1,2 shifts with concomitant  $\pi$ -bond migration.<sup>1–8</sup>

In similar cyclic polyene complexes, such as cycloheptatrieneiron tricarbonyl (I), cyclooctatrieneiron tricarbonyl (II), and cyclononatetraeneiron tricarbonyl (III) where the cyclic conjugation of the polyene system has been interrupted by a  $(\text{-CH}_2\text{-})_n$  group, the facile 1,2 metal migration is precluded and the complex displays no fluxional behavior at moderate temperatures. For example, the <sup>1</sup>H NMR spectrum of I shows no line broadening up to temperatures of  $\sim 100$  °C, where initial decomposition begins.<sup>9</sup>

Although 1,2 metal shifts are ruled out for complexes such as I, II, and III, degenerate isomerization by net 1,3 metal shifts is possible. Such formal 1,3 iron shifts have been observed by Takats and Li Shing Man for  $(7\text{-exo-MMe}_3\text{C}_7\text{H}_7)\text{Fe}(\text{CO})_3$  (*M* = Si or Ge).<sup>10</sup> In an effort to determine the activation energy for the 1,3 metal shift in the simplest unsubstituted non-conjugated polyene system and to contrast this with the energetics of 1,2 metal shifts, we have examined cycloheptatrieneiron tricarbonyl using the Forsén and Hoffmann technique of spin saturation transfer.<sup>11</sup>

In the spin saturation transfer (SST) experiment, the rate constant for exchange, *k*, in a two-site, equal-population system,  $\text{A} \rightleftharpoons \text{B}$ , is given by<sup>12</sup>

$$k = \frac{1}{T_{1A}} \left[ \frac{M(0)}{M(\infty)} - 1 \right] \quad (1)$$