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Lanthanide-Induced Chemical Shifts and the Relative Stereochemistry of Multistriatin, 2,4-Dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane

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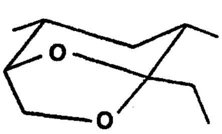
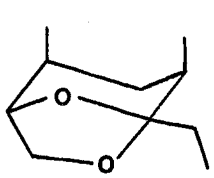
The ^{1}H NMR spectra of the four diastereomers of multistriatin, 2,4-dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane (**1**α–δ), and of frontalin, 1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane (**2**), were recorded in the presence of the europium paramagnetic shift reagent d_{27}-tris(2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedionato)europium(III) [(Eu(fod)$_3$]. The binding of Eu(fod)$_3$ to each substrate was investigated by comparing observed shift ratios with those calculated for lanthanide atom positions about each of the oxygen atoms in **1**α–δ and in **2**. The calculations indicated that for each of these dioxabicyclo[3.2.1]octanes, substrate binding occurred preferentially at one oxygen atom, and that the location of the lanthanide atom was related to steric hindrance about the two potential binding sites. Comparisons of the observed shift ratios for each isomer of **1** with the calculated shift ratios of all isomers of **1** verified the relative stereochemical assignments for these isomers. A correlation between the shift reagent binding site and the biological activity of **1**α–δ was observed.

α-Multistriatin (**1**α), a component of the aggregating pheromone of the European elm bark beetle, *Scolytus multistriatus,* was identified as 2,4-dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane by spectrometric and synthetic methods.[2] The previously reported synthesis yielded the four possible diastereomers (**1**α–δ), and these isomers were separated by GLC and were characterized by NMR, ir, and MS.[3] The spectrometric data in combination with a stereospecific synthesis provided evidence for the assignment of the relative stereochemistry of each of the four diastereomers.


1α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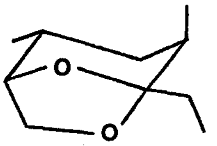
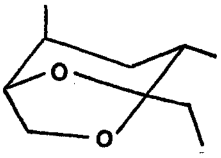

1γ


1δ

Lanthanide-induced shift (LIS) experiments represented a potential and possibly unique method for testing structural assignments for **1**α–δ. The objective of this study was to first evaluate the binding of the shift reagent to **1**α–δ and to 1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane, frontalin (**2**), and then to compare any definitive evidence relating the structure of the 6,8-dioxabicyclo[3.2.1]octanes to the previous stereochemical assignments for **1**α–δ.

The use of LIS data to test proposed configurations or conformations has been recently reviewed.[4–7] In the case of monofunctional substrates, bonding occurs between donor atom (X) on the substrate (S) and the lanthanide metal atom (L), and a set of equilibria exists for L, S, LS, LS$_2$, and perhaps additional species. This bonding situation is essentially the same for a multifunctional substrate if L binds preferentially to one functional group.

Competitive complexing with multiple donor atoms on the substrate molecule has also been reviewed[8] and is of particular importance in this study of bicyclic ketal structures. Similar donor atoms with identical environments should experience identical L–X bonding, and this expectation has been verified by experiment. However, the lanthanide bonding properties of like functional groups with dissimilar environments can differ. Functional groups usually bond preferentially (OH > ketones ≥ esters > ethers); however, this bonding trend can be altered as a consequence of steric hindrance. Such was the case in a computer-assisted LIS study by Farid et al., who described preferential bonding of tris(2,2,6,6-tetramethyl-3,5-heptanedionato)europium(III) to an unhindered ether in the presence of a hindered alcohol group.[9] Selective binding in substrates that contain two dissimilar ether groups has also been reported.[8]

The lanthanide-induced change in chemical shift for proton H$_n$ ($\Delta\delta_n$) can be calculated from the pseudocontact term of the McConnell–Robertson equation[10]

$$\Delta\delta_n = K\,(3\cos^2\theta_n - 1)r_n^{-3} \tag{1}$$

where θ_n is the XLH$_n$ angle and r is the LH$_n$ distance.[5–7] Direct application of this equation to the evaluation of the paramagnetic shifts assumes the absence of a contact contribution to the observed chemical shifts and that the LS complex has effective axial symmetry about the L–X bond. Both

Table I. LIS Data for Frontalin (2)

Shift ratios[a]	Frontalin
$\Delta\delta_1/\Delta\delta_2$	0.45
$\Delta\delta_1/\Delta\delta_3$	0.28
$\Delta\delta_1/\Delta\delta_4$	0.27

[a] [L] = 0.016, [S] = 0.70.

assumptions have been shown to apply, particularly in the case of proton shift studies.[11-13]

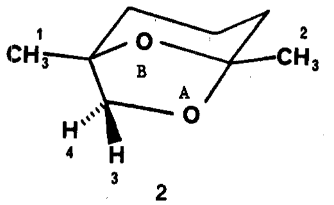
The $\Delta\delta_n$ values can be measured from the δ_n' for a single shifted spectrum and δ_n for an unshifted spectrum ($\Delta\delta_n = \delta_n' - \delta_n$); however, spectra are usually recorded at several [L]/[S] ratios.[7] One $\Delta\delta_i$ value is selected as the reference value, and the remaining $\Delta\delta_n$ are related to $\Delta\delta_i$ as the shift ratio $\Delta\delta_i/\Delta\delta_n$ (calcd) for protons j through n for which observed shift values are available.

$$R = \left[\frac{\Sigma_{n \neq i} w_n \{(\Delta\delta_i/\Delta\delta_n)\text{obsd} - (\Delta\delta_i/\Delta\delta_n)\text{calcd}\}^2}{\Sigma_{n \neq i} w_n (\Delta\delta_i/\Delta\delta_n)\text{obsd}^2}\right]^{1/2} \qquad (2)$$

The agreement factor R is used to compare the calculated shift ratios and the corresponding observed shift ratios for several different locations of L. This process is continued, usually as a computer operation, and L is moved through all space surrounding X. A minimum R value is associated with those positions of L which give the best agreement. The calculation is described as being "relatively insensitive (0.2–0.3 Å) to assumed lanthanide position or to error in model coordinates, but sensitive to signal assignments and to substrate stereochemistry".[5]

Results and Discussion

The binding of tris(2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedionato)europium(III), Eu(fod)$_3$, to the bifunctional dioxabicyclo[3.2.1]octane ring system was initially investigated with a known compound, frontalin (2),[14] for which four observable proton signals could be unambiguously assigned. The $\Delta\delta_n$ values for protons 1, 2, 3, and 4 were measured, and the $\Delta\delta_i/\Delta\delta_n$ obsd values are given in Table I.



2

Two separate Cartesian coordinate systems were calculated (for details see Experimental Section) for the atoms in 2 with OA and OB at the origins in systems A and B, respectively. These coordinate systems, depicting the calculated position of the Eu atom, are diagrammed in Figure 1.

The location of L with respect to substrate atoms H_i–H_n was defined with respect to the donor atom (the origin), as shown by the right-handed coordinate system in Figure 2. The L–O bond was the assumed magnetic axis for the lanthanide–substrate complex, and the length of the L–O bond was $\bar{R}$. The angle Ω is the C_2–O–L bond angle and Φ the dihedral angle between the C_2–C_3 and the L–O bonds.

The lanthanide SHIFT program executed the calculations for a given test structure. The Eu atom was moved by increments through all possible angles of Ω and Φ for reasonable $\bar{R}$ values (2.6–4.0 Å for 2) for both coordinate systems. The calculation was thus constrained such that the search for minimum R values was limited to a sphere about the donor atom with a radius equal to the upper limit of the Eu–O bond length.[5] A set of shift ratios were calculated at each Eu position, and the calculated values were compared to the observed shift ratios. A maximum limit C_x for $\Delta\delta_i/\Delta\delta_n$ calcd − $\Delta\delta_i/\Delta\delta_n$ obsd was set, and if C_x exceeded the limit, the comparison for that Eu position was discarded. When this condition was satisfied, the agreement factor R was calculated.

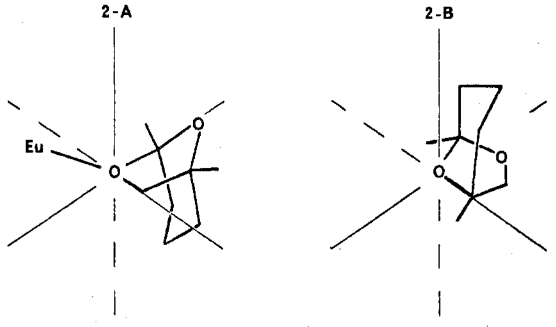


Figure 1. Frontalin (2) in coordinate systems A and B depicting the optimum calculated position of the Eu atom.

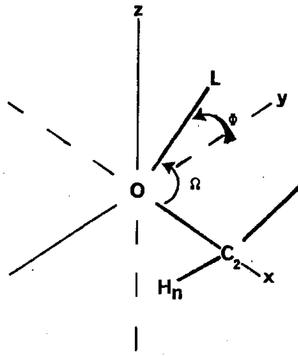


Figure 2. Location of the lanthanide atom with respect to the substrate atoms.

The R values in combination with the position of the Eu atom relative to the substrate molecule provided a basis for the evaluation of a test structure. Minimum R values were regarded as indicators of relatively good agreement particularly where relatively small values were found for a cluster of Eu positions. The location of the Eu atom was examined, and any positions coincident with other atoms in the substrate were eliminated. The possibility of chance agreement cannot be completely eliminated, particularly when a limited number of proton signals can be observed; however, as our data will demonstrate, these criteria provided a basis for consistent interpretation of the data.

No agreement between calculated and observed shift ratios was obtained for 2 in coordinate system B over the range of R, Ω, and Φ searched, but good agreement ($R < 0.06$) was obtained for coordinate system A with $C_x = 0.05$. Test calculations indicated that, where good agreement was possible, R values were found for several Eu positions (usually clustered about one point) when C_x was set equal to 0.2. The reduction of C_x to 0.05 yielded the Eu positions with the lowest R values. As shown in Table II, the lanthanide positions which gave low R values are clustered about Ω = 114–120°, Φ = 160°, and $\bar{R}$ = 3.5–3.9 Å.

This result indicated that Eu(fod)$_3$ was bound to OA rather than OB on the exo surface of the five-membered ring, as shown in Figure 1. In this case, preferential bonding was observed in a molecule with endocyclic oxygen atoms. Although the electronic and steric effects related to Eu–O bonding in 2 are difficult to evaluate quantitatively, increased steric hindrance at the OB binding site can be a factor in the preferential bonding of Eu to OA. OA is adjacent to a tertiary and

Table II. Agreement between LIS Data and 6,8-Dioxabicyclo[3.2.1]octane Structures

Test structure and coordinate system	Obsd compd		Eu location		
		Ω, deg	Φ, deg	$\bar{R}$, Å	*R*
Frontalin (2)					
A	(2)	114–120	160	3.5–3.9	0.06
B	(2)		No agreement[a]		
Multistriatin					
1α-A	1α	72–78	0–20	4.4–4.8	0.09
1α-B	1α	108–112	220	2.0–2.4	0.08
1β-A	1β	114–126	180–240	2.6–4.4	0.05
1β-B	1β	66–72	20	4.4–5.8	0.10
1γ-A	1γ	96–102	200–240	2.8–4.0	0.07
1γ-B	1γ	60–72	20	4.4–4.6	0.10
1δ-A	1δ	108–150	80–120	3.2–4.4	0.05
1δ-B	1δ	78	20	5.8	0.10

[a] For all possible angles of Ω and Φ for $\bar{R}$ values of 2.6–4.0 Å.

Table III. LIS Data for Multistriatin-d_3 Isomers, 1α–δ

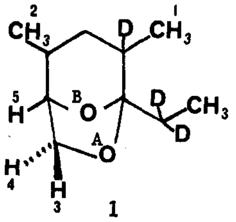
Shift ratios	1α[a]	1β[b]	1γ[c]	1δ[d]
$\Delta\delta_1/\Delta\delta_2$	3.02	1.15	2.48	1.96
$\Delta\delta_1/\Delta\delta_3$	0.45	0.27	0.29	0.41
$\Delta\delta_1/\Delta\delta_4$	0.50	0.24	0.27	0.49
$\Delta\delta_1/\Delta\delta_5$	0.57	0.53	0.50	0.89

[a] [L] = 0.006, [S] = 0.046. [b] [L] = 0.003, [S] = 0.020. [c] [L] = 0.006, [S] = 0.045. [d] [L] = 0.006, [S] = 0.052.

a primary carbon atom while OB is flanked by two tertiary centers, and the approach of the bulky Eu(fod)$_3$ complex to OB should be less favorable than the approach to OA.

This initial experiment demonstrated that selective binding was possible and that good agreement values can be obtained with a monofunctional binding model. Although we would not a priori expect Eu to bind to all 6,8-dioxabicyclo[3.2.1]octanes in the same manner, we were encouraged to apply the LIS calculation to the data obtained from the multistriatin isomers, 1.

The LIS data were collected for a series of [L]/[S] values for each of the multistriatin isomers, and the data used in the calculation are given in Table III. The $\Delta\delta_i/\Delta\delta_n$ obsd values for a given compound were constant for [L]/[S] values between 0.1 and 0.5, with only minor variability observed for small $\Delta\delta_n$ values (1–3 Hz). The chemical shift assignments and the preparation of 4,11,11-trideuteriomultistriatin (1α-δ-d_3) have been reported.[3] Methyl groups 1 and 2 appeared as two doublets with similar chemical shifts in 1, but in 1-d_3, methyl group 1 appeared as a singlet. Since methyl groups 1 and 2 could be readily distinguished in the D-labeled isomers, 1α–δ-d_3 were used in the LIS experiments. Since signals for the three protons at C$_2$ and C$_3$ were not clearly resolved, they were not used in the LIS calculation. The ethyl group at C$_5$ probably exhibits an undetermined degree of hindered rotation. Thus, the coordinates for these CH$_3$ protons could not be assigned with confidence, and this resonance was also excluded from the calculation.



1

The LIS data obtained for 1α–δ were analyzed in a similar manner to that described for compound 2. As before, both coordinate systems A and B were treated and structures for the Eu(fod)$_3$–multistriatin complexes which gave the best agreement and the most reasonable Eu–O bond length are shown in Figure 3. In the initial calculation, the $\Delta\delta_i/\Delta\delta_n$ obsd values for **1α** were compared to the $\Delta\delta_i/\Delta\delta_n$ calcd values for **1α-A** and **1α-B.** In like manner, structures **1β, 1γ,** and **1δ** in coordinate systems A and B were compared to their respective LIS data. Agreement factor *R* was printed for $C_x = 0.2$ in all cases except for **1α**. In this case, the observed $\Delta\delta_2$ value was very small, thus introducing greater uncertainty in the ratio $\Delta\delta_i/\Delta\delta_2$ obsd, and it was necessary to increase the value of C_1 ($\Delta\delta_1/\Delta\delta_2$ obsd − $\Delta\delta_1/\Delta\delta_2$ calcd) to 1.5. Angles Ω and Φ were varied over all space for $\bar{R}$ values from 2.0 to 5.8 Å. Good agreement could be obtained between the $\Delta\delta_i/\Delta\delta_n$ obsd values for 1α–δ and the corresponding $\Delta\delta_i/\Delta\delta_n$ calcd values for the assigned structures (Table II). Similar agreement factors were obtained with both coordinate systems A and B; however, the

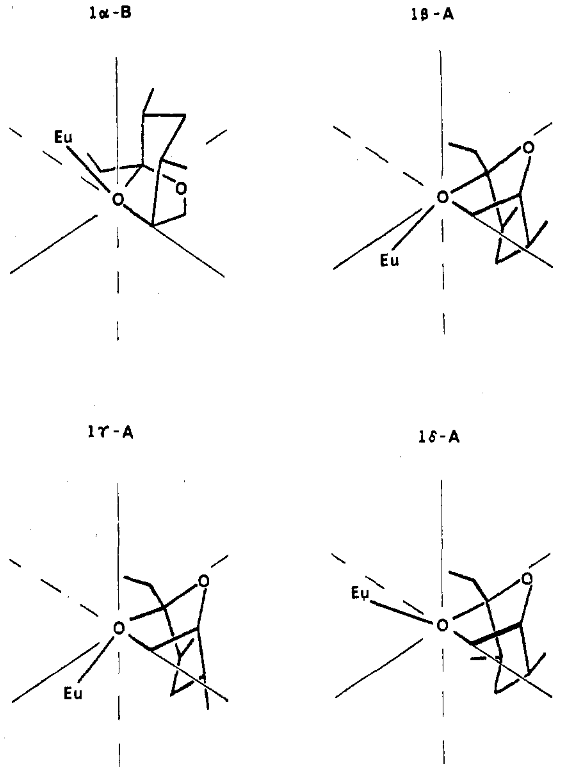


Figure 3. Structures for the Eu(fod)$_3$–multistriatin complexes depicting the optimum position of the Eu atom as determined by the LIS calculation.

Table IV. Comparisons of 1α–δ LIS Data with Structures 1α–δ[a,b]

Structure, coordinate system	Source of LIS data 1α	 1β	 1γ	 1δ
1α-B	+	0	0	0
1β-A	0	+	0	0
1γ-A	0	0	+	0
1δ-A	0	+	0	+

[a] + = agreement; 0 = no agreement. [b] Lanthanide positions were varied over all values of Ω and Φ and $\bar{R}$ values from 2.6 to 4.6 Å. Agreements were based on minimum R values for reasonable structures of the Eu(fod)$_3$–substrate complex.

location of the Eu atom and the R values suggested that Eu(fod)$_3$ bonded preferentially to one of the oxygen atoms (vide infra).

In the case of **1α**, a consideration of the $\bar{R}$, θ, and Φ values for those Eu positions which gave the best agreement between observed and calculated shift ratios indicated that Eu was coordinated to OB. As shown in Figure 3 and Table II, the Eu positions which gave minimum R values were clustered about one point which was over the exo surface of the six-membered ring. The location of the Eu atom was supported by the calculation for coordinate system A, since low R values were obtained for Eu positions coinciding with those obtained for the B system. The Eu–OA bond is nearly collinear with the assumed magnetic axis defined by the Eu–OB bond. Thus, the θ_n and r_n values (eq 1) in coordinate systems A and B were nearly equal, and these values would give rise to similar calculated shift ratios. In view of the equivalent location of the Eu atom with respect to donor atoms OA and OB, the "more reasonable" $\bar{R}$, θ, and Φ values associated with system B suggested that the coordination of Eu(fod)$_3$ to **1α** occurred primarily to OB.

The results obtained for **1β** and **1γ** provided an interesting reversal of the **1α** bonding situation. Consideration of R values and the Eu–O bond distance ($\bar{R}$) indicated that Eu(fod)$_3$ bonded preferentially to OA in both **1β** and **1γ** (Table II) with the Eu atom located on the endo surface of the five-membered ring (Figure 3). As in the **1α** case, the Eu–OA and the Eu–OB bonds were nearly collinear, and low R values were obtained in both coordinate systems with the Eu position in B corresponding exactly to those in A. Calculations for the **1δ** isomer gave low R values for a cluster of Eu positions on the exo surface of the five-membered ring in system A, as shown in Table II and Figure 3. For this isomer, however, the Eu–OA and Eu–OB bonds did not coincide and relatively poor agreement and unreasonable $\bar{R}$ values were found in system B. The single Eu position for B was on the exo surface of the five-membered ring, with a relatively long (5.8 Å) Eu–OB bond length. These results suggested that in **1δ**, like **1β** and **1γ**, OA was the primary bonding site for the Eu atom.

In a second series of calculations the agreement between the calculated shift ratios for structures **1α–δ** and the "wrong" LIS data was tested. The best agreement for the **1α** data and the **1α** structure was obtained with a coordinate system B. Consequently, the calculated shift ratios for **1α-B** were compared to the LIS data for **1β**, **1γ**, and **1δ**, and, as shown in Table IV, no reasonable agreement values were obtained. For **1β**, **1γ**, and **1δ**, coordinate systems A gave the best agreement with the **1β**, **1γ**, and **1δ** LIS data, respectively. Calculated shift ratios for **1β-A** were therefore compared to the observed shift ratios for **1α**, **1γ**, and **1δ**, and likewise structures **1γ-A** and **1δ-A** were compared to the observed shift ratios for **1α**, **1β**, and **1δ**, and for **1α**, **1β**, and **1γ**, respectively. The comparisons of the calculated **1δ-A** shift ratios and the observed **1β** values gave low R values for $\Omega = 114$–$156°$, $\Phi = 140$–$200°$, and $\bar{R} = 2.6$–4.4 Å. However, equally good agreement values were obtained for comparison of the observed and calculated shift ratios for **1β** and for **1δ** and agreement was not found for the comparison of the calculated **1β-A** shift ratios and the observed **1δ** data. Furthermore, low R values for a cluster of reasonable Eu positions were not found for any of the remaining wrong data comparisons. Thus we conclude that the low R values for the **1δ-A** vs. **1β** (observed data) comparison represented a coincidental agreement which is not unexpected in view of the statistical nature of the calculation.

The structures assigned to **1α–δ** based on the LIS data are in accord with those determined by other means,[3] and in each isomer the location of the Eu atom was consistent with the relative stereochemistry of the structure. Only in **1α** are methyl groups 1 and 2 both endo and this configuration leaves the exo surface of the six-membered ring relatively unhindered. This unique situation was reflected in the binding of Eu to OB. In the three remaining isomers, at least one methyl group was exo, thus hindering the approach of Eu(fod)$_3$ to OB. This steric hindrance was apparently sufficient to make OA the preferred binding site for Eu(fod)$_3$ in **1β**, **1γ**, and **1δ**. In **1β** and **1γ**, methyl group 1 was exo and the calculated position of the Eu atom was on the endo surface of the five-membered ring. This situation was altered in **1δ** where methyl group 1 was endo, and Eu(fod)$_3$ occupied a position on the exo surface of the five-membered ring. This result further indicated that stereochemical features of the substrate were reflected in the calculated position of the Eu atom.

Conclusions

We have successfully utilized LIS data to verify the structures of a series of diastereomeric 6,8-dioxabicyclo[3.2.1]octanes. The calculation was selective in relating each set of experimental data with a single structure. The calculated location of the Eu atom was in each case consistent with the structural features of the compound and indicated that Eu–substrate bonding occurred primarily at one site. These results reflected the importance of steric factors in the bonding of Eu(fod)$_3$ to these bifunctional substrate molecules.

An additional feature of this study was the correlation that was observed between the calculated Eu bonding site and the biological activity of **1α–δ**. Isomers **1α–δ** had been tested as one component of the aggregating pheromone for *S. multistriatus*, and naturally occurring **1α** was the only isomer that exhibited biological activity.[15] Molecular geometry and electrostatic effects of odorant molecules are important factors in determining olfactory responses, and current theories of olfaction have related the unique olfactory response elicited by an odorant to the fit of the odorant molecules on receptor sites.[16–18] Our finding that the fit of **1α** on the Eu(fod)$_3$ complex differed from that of **1β**, **1γ**, and **1δ** paralleled the observation that **1α** exhibited unique biological activity. This single comparison of Eu(fod)$_3$ bonding and olfactory responses does not prove a relationship; however, these results indicate that Eu(fod)$_3$ could be mimicking some steric and/or electronic features of the olfactory receptor site.

Experimental Section

Lanthanide Shift Experiments. The NMR spectra were recorded for **1α–δ** in carbon tetrachloride solution in the presence of freshly sublimed d_{27}-tris(2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedionato)europium (III), Eu(fod)$_3$. The carbon tetrachloride was dried over 4 Å molecular sieves, and all transfers were performed in an inert atmosphere. Samples containing 0.1–1 mg of substrate in 50 μl of solvent were filtered into the inner cell of a coaxial cell (Wilmad, 520-2), and benzene-d_6 (100% D)–Me$_4$Si solution was placed in the outer cell. Spectra for **2** were recorded in CDCl$_3$ solution. All spectra were recorded in the Fourier transform mode with a Varian XL-100

NMR spectrometer. Spectra were recorded at four [L]/[S] values for each substrate compound, and δ_n values were obtained from the spectra. The $\Delta\delta_i/\Delta\delta_n$ obsd values were constant within the experimental accuracy of the measurements. The values for **2** and for **1α–δ**, which were used in the calculations, are given in Tables I and III, respectively.

Calculations. The coordinates for each atom in each of the substrate structures were calculated with the COORD program.[7] Two coordinate systems were calculated for each molecule. The origins for systems A and B were OA and OB, respectively. The agreement between the observed shift ratios for a given substrate were calculated with the SHIFT program.[7]

Preparation of 4,11,11-Trideuteriomultistriatin Isomers (1α–δ). A sample of multistriatin (1) was refluxed in 1 M D_3PO_4–tetrahydrofuran solution and worked up according to the previously described method.[3]

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Registry No.—1α, 54815-06-4; 1β, 54832-20-1; 1γ, 54832-21-2; 1δ, 54832-22-3; 2, 28401-39-0.

References and Notes

(1) (a) Lederle Laboratories, Pearl River, N.Y. 10965. (b) This work was supported in part by the U.S. Forest Service, the Elm Research Institute, the Rockefeller Foundation, and the College of Environmental Science and Forestry. (c) *Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.*

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Synthesis of Samandarine-Type Alkaloids and Analogues[1,2]

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Facile stereoselective syntheses of samandarine and its regioisomers are described.

European salamanders, *Salamandra maculosa taeniata* and *S. maculosa maculosa,* are known to secrete alkaloidal venoms from the glands located on the skin, probably for defensive purposes. The chemical structures of these alkaloids had been vigorously investigated by Schöpf and Habermehl's group over a number of years, and the structure of the major alkaloid, samandarine (1), was first established by X-ray crystallography in 1961.[3]

A group of alkaloids represented by samandarine are characterized by the presence of a peculiar 6-aza-8-oxabicyclo[3.2.1]octane ring system in the A ring of steroidal nuclei.

Owing to this peculiar bridged system and the reported neurotoxicity of these naturally scarce substances, the synthesis of samandarine and its analogues has been pursued by several groups. A multistep synthesis of samandarine was first reported by a Japanese group.[4] A few other attempts to synthesize samandarine and the ring system have also been reported.[5]

Since there are several established ways to introduce an oxygen function at C-16, the major problem inherent in the synthesis of these alkaloids is in the construction of the bridged oxazolidine system with the correct stereochemistry.

In this paper, the author reports a general procedure for the preparation of the bridged oxazolidines from α,β-unsaturated cyclic ketones and a facile, stereoselective formal synthesis of samandarine (1).