[single signal, C(1)-$CH_3$] and no signal due to the other enantiomer could be detected; corresponding racemate[11] 2.70 [C(1)-$CH_3$, 1.5 H], 2.77 [C(1)-$CH_3$, 1.5 H]. Thus, the product was concluded to be enantiomerically pure within the sensitivity limits of 400-MHz NMR spectroscopy.

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**Supplementary Material Available:** $^1H$ NMR spectra for compounds **4e**, **7c**, **8**, **10**, and **11** (5 pages). Ordering information is given on any current masthead page.

# Lanthanide-Induced Shift Investigation of α-Alkoxy Aldehydes. A Spectroscopic Search for Evidence of Chelation in the Lewis Acid Catalyzed Hetero Diels–Alder Reaction

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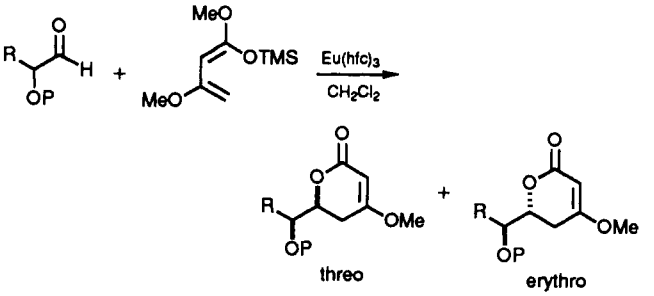
Lanthanide-induced shift studies were performed using a chiral lanthanide shift reagent Eu(hfc)$_3$. Simple ethers exhibited little complexation to the shift reagent. Simple aldehydes produced large lanthanide-induced shifts. The α-alkoxy aldehydes gave lanthanide-induced shifts consistent with contributions from a "chelated" species. The degree of chelation was dependent on the steric bulk of the alkyl side chain.

Lanthanide shift reagents (LSRs) have found extensive use in organic chemistry. Since the first reported use of lanthanide shift reagents,[1] the most common application has been in the area of structure determination through nuclear magnetic resonance spectroscopy.[2] Less common is the use of LSRs as a reagent in synthetic applications. Results from ours[3] and other laboratories[4] have demonstrated that LSRs will promote cycloaddition reactions of carbonyl compounds with activated dienes.

We have found that the chiral LSR tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) (Eu(hfc)$_3$) catalyzes the cycloadditions of α-alkoxy aldehydes with 1,3-dimethoxy-1-[(trimethylsilyl)oxy]-1,3-butadiene (Brassard's diene[5]). The degree of diastereoselectivity observed in the lactone products is dependent on the alkyl side chain and the protecting group of the alkoxy group (Table I).[6,7] Initially, the observed selectivity was rationalized by a "chelation-control" model of addition.[8] When this presumed chelation is diminished by the use of a bulky protecting group (TBDMS), there is little selectivity observed in the product.[9]

**Table I. Selectivity of Cycloaddition Reactions Catalyzed by Eu(hfc)$_3$**




| aldehyde | % yield | threo:erythro |
|---|---|---|
| 1a | 80 | 92:8 |
| 1b | 75 | 78:22 |
| 1c | 85 | 50:50 |

**Table II. Slopes[a] of the Observed LIS vs LSR/Substrate for Simple Aldehydes**

| aldehyde | Ha | Hb |
|---|---|---|
| 3a | 4.5 | 3.2 |
| 3b | 2.5 | 2.1 |
| 3c | 1.8 | 1.4 |

[a] Values are derived from the best fit (linear regression) line for a set of data; units are in ppm·mol % LSR$^{-1}$.

Of interest, however, was the fact that when protecting groups such as benzyl were used, the selectivity of cycloaddition was dependent on the size of the alkyl side chain. As the steric bulk of the side chain was increased from *n*-butyl to *tert*-butyl, the degree of diastereoselectivity decreased. This result was opposite of that predicted by a simple chelation-control model. In the chelation-control mode, an increase in size of the alkyl group should increase the facial selectivity by directing the diene to the least hindered face of the chelated complex. In an effort to better understand the mechanism of cycloaddition, we

(1) Hinckley, C. C. *J. Am. Chem. Soc.* **1969**, *91*, 5160.
(2) For a recent review, see: Wenzel, T. J. *NMR Shift Reagents*; CRC Press, Inc.: Boca Raton, FL, 1987.
(3) Midland, M. M.; Graham, R. S. *J. Am. Chem. Soc.* **1984**, *106*, 4294, Midland, M. M.; Afonso, M. M. *J. Am. Chem. Soc.* **1989**, *111*, 4368.
(4) Sims, J. J.; Castellino, S. *Tetrahedron Lett.* **1984**, *25*, 2307. Danishefsky, S.; Bednarsky, M. *J. Am. Chem. Soc.* **1983**, *105*, 3716. Danishefsky, S.; Bednarsky, M.; Maring, C. *Tetrahedron Lett.* **1983**, *24*, 3451. Jurczak, J.; Golebiowski, A.; Bauer, T. *Synthesis* **1985**, 928.
(5) Brassard, P.; Savard, J. *Tetrahedron Lett.* **1979**, 4911.
(6) Midland, M. M.; Koops, R. W. *J. Org. Chem.*, in press.
(7) Control experiments have indicated that no asymmetric induction is derived by catalysis with the chiral Lewis acid Eu(hfc)$_3$.
(8) Cram, D. J.; Elhafez, FA Abd *J. Am. Chem. Soc.* **1952**, *74*, 5828. Cram, D. J.; Kopecky, *J. Am. Chem. Soc.* **1959**, *81*, 2748. Cram, D. J.; Wilson, *J. Am. Chem. Soc.* **1963**, *85*, 1245.
(9) For effects of protecting groups on chelation control, see: Keck, G. E.; Henhre, W. J.; Kahn, S. D. *Tetrahedron Lett.* **1987**, *28*, 279. For spectroscopic investigations into chelation of β-alkoxy aldehydes, see: Keck, G. E.; Castellino, S.; Wiley, M. R. *J. Org. Chem.* **1986**, *51*, 5480. Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847.

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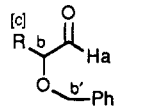
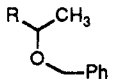
undertook a series of NMR lanthanide-induced shift (LIS) studies to obtain spectroscopic evidence for chelation.

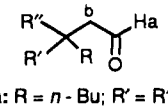
We chose as substrates the three benzyl protected α-alkoxy aldehydes (**1a–c**). In addition, the corresponding ethers and aldehydes (**2a–c**, **3a–c**, respectively)[10] were subjected to LIS studies. The solution of LSR was added in small increments to solutions of **1**, **2**, and **3**.



**1a**: *n*-butyl
**b**: isopropyl
**c**: *tert*-butyl



**2a**
**b**
**c**



**3a**: R = *n*-Bu; R′ = R″ = H
**b**: R = R′ = Me; R″ = H
**c**: R = R′ = R″ = Me

Virtually no complexation was observed with any of the ethers **2a–c**. No line broadening was observed, and the degree of LIS was barely measurable. The results are consistent with previous studies which indicate that ethers, as weaker Lewis bases, do not complex as well as other functional groups with LSRs.[11] In addition, the complexing ability of ethers is dependent on the steric environment of the ether. Typically, LIS have been observed on unhindered ethers such as cyclic ethers[12] and epoxides.[11,13] Although little LIS was observed in the ethers **2a–c**, the greatest degree of LIS was observed with *n*-butyl (**2a**) and least was *tert*-butyl (**2c**).[14]

When aldehydes **3a–c** were titrated with LSR, complexation with the LSR was more favorable as compared to the simple ethers **2a–c**. Large LIS was observed as well as significant line broadening. The results of these experiments are summarized in Table II.

Aldehydes have been reported to give strong complexes with LSRs.[15,16] In these cases it is generally believed that the complexation of the LSR occurs on the anti lone pair of the carbonyl oxygen.[15a-c,17,18] In each example (**3a–c**), the aldehydic proton (Ha) exhibited greater LIS than the α-methylene protons (Hb). The observed LIS for protons farther from the carbonyl was considerably less than for Ha and Hb. Qualitative analysis of the aldehyde substrates using the Wing dipolar field map[19] indicates that a bent geometry of the LSR–substrate complex would predict the observed results. Complexation of the LSR to the anti lone pair of the carbonyl oxygen is preferred. Many species may actually exist in the solution equilibria, making a strict analysis very difficult.

**Table III. Slopes[a] of the Observed LIS vs LSR/Substrate for α-Alkoxy Aldehydes**

| aldehyde | Ha | Hb | Hb′ | Hc |
|---|---|---|---|---|
| 1a | 0.42 | 1.27 | 0.90 | 0.5[b] |
| 1b | 0.85 | 1.21 | 0.97 | –[cd] |
| 1c | 1.22 | 0.95 | 0.42 | 0.32[e] |

[a] Values are derived from the best fit (linear regression) line for a set of data; units are ppm·mol % $LSR^{-1}$. [b] Hc are the protons at the β-position. [c] Signal (of isopropyl methine proton) is only partially observable during the course of titrations; the observed LIS was similar to Ha. [d] The isopropyl methyls gave an observed LIS much less in magnitude than Ha. [e] Hc represents the *tert*-butyl methyl protons.

The data in Table II also indicates that there is a dependence between the substrate structure and the association constant for the complex. As the steric bulk is increased, the observed LIS decreases, indicating a possible decrease in association constant. The relative LIS between Ha and Hb does not change, however, indicating still a preference for a complex with a bent geometry.

The LIS for each of the substrates **1a**, **1b**, and **1c** was then obtained. The degree of observed shift for each proton (aldehydic (Ha), carbinol (Hb), benzylic methylene (Hb′), and β-proton(s) (Hc)) was measured versus the substrate/LSR ratio. When multiplicity was observed, an average value was obtained and used for calculation of the shift ($\Delta\delta$). The initial increment was 5 mol % of LSR (equivalent to cycloaddition reaction concentrations). The results are summarized in Table III.

For **1a**, there is evidence of a chelated species as the predominant complex. Line broadening was observed in all of the observed protons.[20] There is significant LIS for the protons associated with the ether (Hb and Hb′). In comparison to the examples of the simple ether (**2a**), this increase in LIS for **1a** is considerable and would not be expected in the abscence of chelation. The ratio of the LIS between the aldehyde proton and carbinol (Ha/Hb) is quite low, approximately 0.3. The simple aldehyde **3a** showed reduced LIS of the protons vicinal (Hb and Hc) to the aldehyde proton (Ha) relative to the aldehyde proton (Ha) (a trend observed in **3b** and **3c**). In the α-alkoxy aldehyde (**1a**), these protons (Hb, Hb′, Hc) showed a greater degree of LIS.

Since the NMR spectrum could be an average of many complexed species in equilibrium (eq 1), consideration must be given to each association constant and the char-

(10) Aldehydes were obtained from Aldrich Chemical Co.

(11) Raber, D. J.; Johnson, M. D., Jr.; Campbell, C. M.; Guida, A.; Jackson, G. F., III; Janks, C. M.; Perry, J. W.; Propeck, G. J.; Raber, N. K.; Schwalke, M. A.; Sutton, P. M. *Monatsch. Chem.* **1980**, *111*, 43. de Boer, J. W. M.; Hilbers, C. W.; de Boer, E. *J. Magn. Reson.* **1977**, *25*, 437. Rackham, D. M. *Spectrosc. Lett.* **1981**, *14*, 117.

(12) Serve, P.; Rondeau, R. E.; Rosenberg, H. M. *J. Heterocycl. Chem.* **1972**, *9*, 721. Ribo, J. M.; Serra, X. *Org. Magn. Reson.* **1979**, *12*, 467.

(13) Wing, R. M.; Uebel, J. J.; Anderson, K. K. *J. Am. Chem. Soc.* **1973**, *95*, 6046. Manni, P. E.; Howie, G. A.; Katz, B.; Cassady, J. M. *J. Org. Chem.* **1972**, *37*, 2769. Vidal, J. P.; Girard, J. P.; Rossi, J. C.; Chapat, J. P.; Granger, R. *Org. Magn. Reson.* **1974**, *6*, 522. Caple, R.; Kuo, S. C. *Tetrahedron Lett.* **1971**, 4413.

(14) The observed LIS was extremely small but measurable. It may be unreliable within experimental error. The estimated association constant is $K \ll 1$.

(15) (a) Finocchiaro, P.; Recca, A.; Maravigna, P.; Montaudo, G. *Tetrahedron* **1974**, *30*, 4159. (b) Abraham, R. J.; Bergen, H. A.; Chadwick, D. J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1161. (c) Abraham, R. J.; Chadwick, D. J.; Sancassan, F. *Tetrahedron* **1982**, *38*, 1485. Abraham, R. J.; Chadwick, D. J.; Sancassan, F. *Tetrahedron Lett.* **1981**, *22*, 2139. Abraham, R. J.; Chadwick, D. J.; Sancassan, F. *J. Chem. Soc., Perkin Trans. 2* **1984**, *2*, 1037. Rackham, D. M. *Org. Magn. Reson.* **1979**, *12*, 388.

(16) Denmark has performed spectroscopic investigations into Lewis acid complexation with aldehydes in the Lewis acid promoted additions of allylstannanes. There is evidence for complete complexation with strong Lewis acids. See: Denmark, S. E.; Wilson, T.; Wilson, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 984. See also: Keck, G. E.; Andrus, M. B.; Castellino, S. *J. Am. Chem. Soc.* **1989**, *111*, 8136.

(17) Controversy exists over the nature of the LSR–carbonyl complex in ketones. There are reports of LIS studies favoring a two-site (bent) model, see: Pickering, R. A.; Roling, P. V. *J. Magn. Reson.* **1976**, *22*, 385. Chadwick, D. J. *Tetrahedron Lett.* **1974**, 2179. Reference 18a. Newman, R. H. *Tetrahedron* **1974**, *30*, 969. Servis, K. L.; Shue, F. F. *J. Magn. Reson.* **1980**, *40*, 293. Lienard, B. H. S.; Thomson, A. J. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1390. Evidence for a linear model has been reported, see: Raber, D. J.; Janks, C. M.; Johnston, M. D., Jr.; Raber, N. K. *J. Am. Chem. Soc.* **1980**, *102*, 6591. Hofer, O.; Foldesi, P. *Tetrahedron Lett.* **1980**, *21*, 2137. For additional discussion, see: Abraham, R. J.; Chadwick, D. J.; Sancassan, F. *Tetrahedron* **1982**, *38*, 3271 and references therein.

(18) More recent studies have suggested that the nature of the carbonyl–LSR complex is electrostatic. The orientation of the complex is governed by steric interactions between the LSR and substrate. See (a) Raber, D. J.; Janks, C. M.; Peters, J. A. *Tetrahedron* **1986**, *42*, 4354. (b) Raber, D. J.; Peters, J. A.; Niewenhuizen, M. S. *J. Chem. Soc., Perkin Trans. 2* **1986**, 853 (a and b were brought to the attention of the authors by one reviewer whose suggestions are gratefully acknowledged).

(19) Wing, R. M.; Early, T. A. *Tetrahedron Lett.* **1972**, 4153.

(20) Line broadening may result from both contact and pseudocontact contributions of complexation. LIS in proton NMR are usually pseudocontact in origin, contact shifts (observed typically in carbon-13 NMR) are usually considered negligible. See: (a) de Boer, J. W. M.; Sakkers, P. J. D.; Hilbers, C. W.; de Boer, E. *J. Magn. Reson.* **1977**, *26*, 253. (b) de Boer, J. W. M.; et. al. *Tetrahedron Lett.* **1971**, 4863.

acteristics of the intermediate(s) species. The association

$$\text{LSR} + \text{S} \overset{K_1}{\rightleftharpoons} \text{S–LSR} \overset{K_{ch}}{\rightleftharpoons} [\text{S–LSR}]_{ch} \qquad (1)$$

constant for the substrate–LSR (S–LSR) formation is relatively high (estimated $K > 10$ as opposed to an ether oxygen complex estimated $K \ll 1$). Previous studies have shown that chelation association constants are generally favorable (sometimes higher than S–LSR constants).[20a] It is difficult, however, to assess the association constants in these weakly binding systems.[21]

The data in Tables II and III allows for a qualitative estimate of the contributions of a chelated species in solution. The simple aldehyde (**3a**) complex with LSR exhibits relative LIS of the protons that is unlike that observed in **1a**. The dramatic increase in the observed LIS of the protons Hb and Hb′ (as well as Hc) relative to that observed for Ha seems to indicate a predominantly chelated species in the equilibrium mixture.[22]

Geometrical considerations are more difficult to establish in these substrates. It is clear that the LIS results for **1a** cannot be explained by a bent (anti) or linear geometry of a monocomplexed species when using the dipolar field map.[19] Applying the dipolar field map for the five-membered chelated species has its limitations. One limitation in the use of the dipolar field map is the necessity for planar complexation between the substrate and the LSR. In fact, the geometry of these chelated species may be more adequately described as an "envelope" conformation. Conformational mobility of the chelates would also make geometrical predictions difficult.

For **1b**, there is a very strong observed LIS for the proton (Hb). This, again, is quite different when comparing the simple ether case (**2b**). The ratio (LIS of Ha/Hb) of 0.7 is significantly higher than in the straight-chain example (0.3). The degree of the observed LIS for Hb and Hb′ is very similar to that observed in **1a**. The degree of the observed LIS for Ha has increased significantly over that observed for **1a**.

The changes that were observed upon going from **1a** to **1b** could be the result of a change in the geometry of the chelated species or a shift of equilibrium toward the monocomplexed aldehyde species. Changes in geometry of a chelated species are difficult to establish given the data. A change in the equilibrium governed by $K_{ch}$ (eq 1) is a more likely explanation. The increased steric bulk of the alkyl side chain could shift the equilibrium to favor the monocomplexed species (S–LSR). The result would be a greater contribution of observed LIS for the Ha of S–LSR (relative to Hb and Hb′). In the cycloaddition reaction, the observed result would be a decrease in chelation (or threo) selectivity.

A similar trend is observed in the observed LIS for **1c**. There is a dramatic increase in the degree of observed LIS for Ha compared to Hb and Hb′. The ratio of Ha/Hb is now 1.25.

Although contribution of a chelated species toward the total observed LIS cannot be discounted for **1c**, the profile of the observed LIS for all of the protons is very similar to that for a simple monocomplexed aldehyde (such as **3c**). Additional steric bulk of the alkyl side chain appears to shift the equilibrium governed by $K_{ch}$ (eq 1) in the reverse direction (toward S–LSR).

The evidence indicates that when a less bulky side chain such as *n*-butyl is used, the chelated species may be the preferred species in equilibrium. The result would be high diastereoselectivity of a chelated product in any subsequent Diels–Alder reaction. As the steric bulk of the side chain is increased (from isopropyl to *tert*-butyl), formation of the speculated chelated species becomes less favorable. Complexation to the aldehyde carbonyl is still favorable, however, and an increase in this species occurs in the equilibrium mixture. The predicted result experimentally would be a decrease in "chelated" product selectivity due to an increase in a nonchelated species. The experimental data follows a trend which is qualitatively in agreement with the above explanation (Table I).

To ensure that the diene bore no influence on the nature of the Lewis acid, Brassard's diene was subjected to identical LIS studies as described above. No observed LIS was produced upon titration of the diene with LSR solution. No line broadening or decomposition of the diene was observed. Additional studies are continuing on related systems to better understand the role of a chelating metal in the cycloaddition reactions of heterodienophiles.

## Experimental Section

Proton and carbon nuclear magnetic resonance spectra were obtained at 199.9 and 50.10 MHz, respectively. Silica gel was obtained from Fluka, Inc. Deuteriochloroform, hexanal, 3-methylbutanal, 2-methylpropanal, 2,2-dimethylpropanal, methylmagnesium chloride, benzyl chloride, sodium hydride, and $Eu(hfc)_3$ were obtained from Aldrich Chemical Co. Tetrahydrofuran (THF) from Fischer was distilled over potassium. Deuteriochloroform was dried over molecular sieves (type 4A). $Eu(hfc)_3$ was sublimed in vacuo and stored under argon as a solution in deuteriochloroform (typical concentration of 0.035 M). Analytical masses were determined on an Ainsworth analytical balance.

**General Preparation of Benzyl Ethers.** A suspension of sodium hydride (as a 60% dispersion in mineral oil, 1.2 equiv of hydride) in dry THF (to make a 1 M solution) was cooled (under argon) to 0 °C, and purified alcohol (1.0 equiv) was added dropwise. The suspension was stirred to room temperature over 30 min. Benzyl chloride (1.1 equiv) was added via syringe, and the suspension was heated to reflux for 20 h. The reaction was cooled in ice and 1 N aqueous HCl was added slowly until a homogeneous solution was observed. The solution was diluted with ether and extracted. The aqueous layer was extracted with ether (2×), and the combined ether layers were washed with brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to yield the crude ether. The ether was purified by column chromatography (silica gel, hexanes) to yield the pure benzyl ether. Typical yields were 80–90%.

**[(Hexyloxy)methyl]benzene (2a)**: $^1$H NMR ($CDCl_3$) δ 7.35 (m, 5-H), 4.69 (d, $J$ = 11.7 Hz, 1-H), 4.54 (d, $J$ = 11.7 Hz, 1-H), 3.50 (m, 1-H), 1.2-1.7 (m, 8-H), 1.18 (d, $J$ = 6.3 Hz, 3-H), 0.90 (t, 3-H); $^{13}$C NMR ($CDCl_3$) δ 128.3, 127.7, 127.4, 80.6, 70.0, 35.5, 31.8, 25.0, 24.3, 22.6, 14.1.

**[[(3-Methylbut-2-yl)oxy]methyl]benzene (2b)**: $^1$H NMR ($CDCl_3$) δ 7.35 (m, 5-H), 4.58 (d, $J$ = 11.7 Hz, 1-H), 4.54 (d, $J$ = 11.7 Hz, 1-H), 3.27 (m, 1-H), 1.8 (m, 1-H), 1.14 (d, $J$ = 6.4 Hz, 3-H), 0.92 (d, $J$ = 5.9 Hz, 3-H), 0.88 (d, $J$ = 5.9 Hz, 3-H); $^{13}$C NMR ($CDCl_3$) δ 128.5, 128.2, 127.6, 127.3, 86.0, 70.1, 32.6, 23.5, 18.7, 18.4.

**[[(3,3-Dimethylbut-2-yl)oxy]methyl]benzene (2c)**: $^1$H NMR ($CDCl_3$) δ 7.35 (m, 5-H), 4.55 (d, $J$ = 11.6 Hz, 1-H), 4.45 (d, $J$ = 11.6 Hz, 1-H), 3.25 (q, $J$ = 6.4 Hz, 1-H), 1.1 (d, $J$ = 6.4 Hz, 3-H), 1.0 (s, 9-H); $^{13}$C NMR ($CDCl_3$) δ 128.1, 127.5, 127.2, 88.6, 70.3, 34.6, 28.4, 26.2.

α-Alkoxy aldehydes were prepared previously: see ref 6.

**2-(Benzyloxy)hexanal (1a)**: $^1$H NMR ($CDCl_3$) δ 9.70 (d, $J$ = 2.0 Hz, 1-H), 7.40 (s, 5-H), 4.65 (q, 2-H), 3.80 (t(dd), $J$ = 2.0, 5.8 Hz, 1-H), 1.75 (m, 2-H), 1.40 (m, 4-H), 0.95 (t, 3-H); $^{13}$C NMR

(21) The observed LIS had not diminished at 2 equiv of LSR. The estimated association constant from this data is $K < 4$. For a review on association constants and bound shifts, see: Raber, D. J. The Nature Of The LSR-Substrate Complex. In *Methods In Stereochemical Analysis 5: Lanthanide Shift Reagents In Stereochemical Analysis*; Morill, T. C., Ed.; VCH Publishers: New York, 1986; p 55. See also: Bouquant, J.; Chuche, J. *Tetrahedron Lett.* **1972**, 2337. Rackham, D. M. *Org. Magn. Reson.* **1979**, *12*, 388.

(22) For a mathematical analysis of the equilibria involving LSRs and substrates, see: Johnston, M. D., Jr.; Shapiro, B. L. *J. Am. Chem. Soc.* **1972**, *94*, 8185.

($CDCl_3$) δ 203.9, 128.7, 128.5, 128.3, 127.96, 127.6, 83.45, 72.50, 29.69, 26.83, 22.45, 13.76; IR (neat, NaCl) 3000–3100, 2850–3000, 1745, 1510, 1475 $cm^{-1}$.

**2-(Benzyloxy)-3-methylbutanal (1b)**: $^1H$ NMR ($CDCl_3$) δ 9.60 (d, $J$ = 2.4 Hz, 1-H), 7.30 (s, 5-H), 4.67 (d, 1-H), 4.44 (d, 1-H), 3.43 (dd, $J$ = 2.4, 5.8 Hz,1-H), 2.03 (m, 1-H), 0.94 (dd, 6-H), $^{13}C$ NMR ($CDCl_3$) δ 204.4, 128.3, 127.8, 127.7, 127.5, 88.0, 72.7, 29.9, 18.3, 17.5; IR (neat, NaCl) 3000–3100, 2880–3000, 1740, 1605, 1595, 1500, 1455, 1375 $cm^{-1}$.

**2-(Benzyloxy)-3,3-dimethylbutanal (1c)**: $^1H$ NMR ($CDCl_3$) δ 9.68 (d, $J$ = 3.6 Hz, 1-H), 7.31 (s, 5-H), 4.60 (d, $J$ = 11.6 Hz, 1-H), 4.38 (d, $J$ = 11.6 Hz, 1-H); 3.24 (d, $J$ = 3.6 Hz, 1-H), 0.97 (s, 9-H), $^{13}C$ NMR ($CDCl_3$) δ 204.95, 128.3, 127.8, 90.4, 72.9, 35.3, 26.0; IR (neat, NaCl) 3000–3100, 2880–3000, 1735, 1605, 1595, 1505, 1460 $cm^{-1}$.

**Typical Procedure for the Lanthanide-Induced Shift Experiments.** The gradient method[20] was employed for all the substrates. An analytically prepared sample of substrate (typical concentration was 0.040–0.050 M) in $CDCl_3$ was titrated with a solution of $Eu(hfc)_3$ (typical concentration was 0.033–0.060 M in $CDCl_3$) via a Hamilton microliter syringe. The sample was allowed to equilibrate for 5 min before acquisition. The change in chemical shift (Δδ) for each increment was calculated and plotted versus the concentration of LSR/substrate to give the data depicted in Tables II and III.

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# Synthesis and Conformational Analysis of Epindolidione-Derived Peptide Models for β-Sheet Formation

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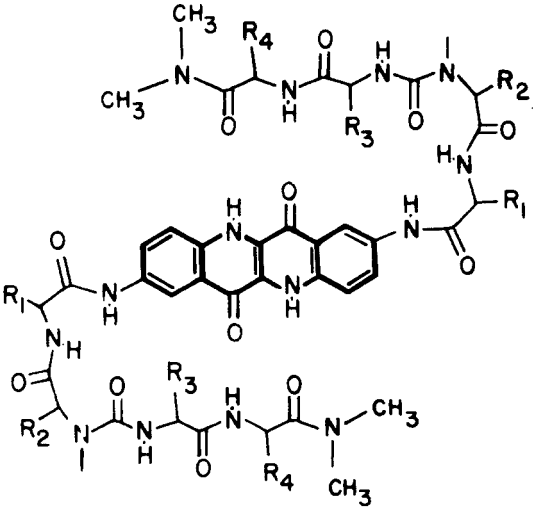
Synthesis of 2,8-diaminoepindolidione (2,8-diaminodibenzo[*b*,*g*][1,5]naphthyridine-6,12(5,11*H*)-dione) in 19% yield from *p*-nitroaniline is reported, as well as further conversion to 2,8-bis(Boc-L-Pro-Xxx)epindolidione (Xxx = Gly, D-Ala) and then to 2,8-bis(OC(Yyy-Zzz-$NMe_2$)-L-Pro-Xxx)epindolidione (Yyy = Gly, L-Ala, D-Ala; Zzz = Gly, L-Phe, D-Phe). The β-turn-forming tendencies of the series 2,8-bis(X-L-Pro-D-Ala)epindolidione, where X = Ac, Boc, and COGlyOEt, are assigned from $^1H$ NMR evidence.

The study of the secondary structures of polypeptides is impeded by the high cooperativity of the folding process for peptide chains, which ensures that most short linear peptides under normal conditions have no detectible conformational preferences,[1] although recently important exceptions have have reported.[2] In an effort to determine the role of hydrogen bonding in stabilizing secondary structure and to develop means of predictably enhancing the tendency of functionalized peptides to assume sheet or helical conformations, we have prepared conjugates of short peptides with rigid functionalities that mimic the hydrogen-bonding patterns of β-sheets[3] and α-helices[4] and that may therefore act as nucleation sites or templates for the folding of the linked peptide chain. Study of such template–peptide conjugates is expected to permit at least qualitative assignment of the relative importance of the factors that direct formation of secondary structure, to provide new, low molecular weight models for determining the individual and correlated biases of amino acids toward particular secondary structures, and ultimately to allow rational design of chimeric proteins in which the template structures are introduced in particular nucleation regions.

In preliminary reports[3] we have described synthesis and $^1H$ NMR study of antiparallel β-sheet formation with conjugates 1 of urea derivatives of short polypeptides and



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the epindolidione function, which was first synthesized by Robert Robinson as a structural isomer of indigo.[5] Doubtless owing to intermolecular hydrogen bonding within the crystalline phase, simple epindolidione derivatives are exceptionally insoluble substances and their

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