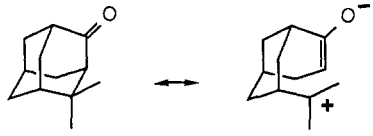
carbonyl C2 and all β carbon atoms (C4, C8, C9, C10) become significantly deshielded (see Figure 2, bottom).

For comparison we have also measured the ^{13}C NMR spectra of 4,4-dimethyladamantan-2-one (**4**)[17] and its complex **4**·$SbCl_5$. The predominance of resonance formula **4'** (tertiary cationic center at C4!) is expressed by the strong downfield shift of C4 by ca. 6 ppm upon complexation.



4 **4'** (3)

It seems reasonable to conclude that hyperconjugation can lead to different π electron distributions on the two faces of a carbonyl group.

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Supplementary Material Available: Lists of fractional coordinates, thermal parameters, bond lengths, bond angles, and torsion angles of **3**·$SbCl_5$, data of the symmetrized structure, and ^{13}C NMR data (15 pages). Ordering information is given on any current masthead page.

(16) All ^{13}C NMR spectra (75 MHz) were measured in CD_2Cl_2 between −80 and −95 °C. The complexes were synthesized in 2-g scales, in some cases recrystallized, and then redissolved in CD_2Cl_2.

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A Sulfur-Mediated Total Synthesis of *d,l*-Methynolide

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We report a total synthesis of *d,l*-methynolide (**1**) based on organosulfur ring expansion methodology.[1] Remote stereocontrol over a chain of 10 carbons is demonstrated in medium-sized ring intermediates by using a combination of local conformer preferences and stereoelectronic effects to define relative stereochemistry.

The starting point for the current study was the eight-membered sulfide **2**, prepared by highly stereospecific ring expansion as described earlier.[2,3] Reduction at the C-4,C-5 double bond (methynolide numbering) of **3** (prepared from **2** + *i*-Bu_2AlH) was necessary at this stage. The route had been designed with the expectation that local conformer preferences of allylic substituents for the pseudoequatorial geometry[4] would ensure that diimide reduction of **3** would occur via transition state **4**, similar to the favored local geometry of **3** with diimide approaching the less hindered olefin face. Unusual conditions proved necessary.[5] No reduction occurred below ca. 120 °C, but syringe pump addition of excess $TsNHNH_2$ to **3** in diglyme–ethylene glycol–Et_3N at 180 °C gave 64% conversion and, eventually, 84% of isolated **5** after several recycles. No diastereomers could be detected. Swern oxidation, Wittig olefination, and protection steps (Scheme I) then gave the alkenes **6** (62% overall) to set the stage for introduction of the remaining carbons.

The alkene sulfide **6** was S-alkylated with triflate **7**[6] and treated with 2,6-lutidine to induce ylide ring expansion. Surprisingly, a *kinetic* 16:1 ratio of isomers identified as **10** and **11** was obtained (76%) even though **6** was a 1:1 diastereomer mixture due to equilibration at the Wittig stage. Control experiments proved that each purified diastereomer **6a** or **6b** gave a different major sulfonium salt but the same major 2,3-sigmatropic shift product **10**. These results are most readily explained if local geometry preferences of the eight-membered ring favor S-alkylation from below, regardless of α-vinyl stereochemistry. Ring expansion via the transoid vinyl rotamers of ylides **8** or **9** then accounts for the formation of **10**. This is important because the C-10 stereochemistry α to sulfur has been controlled relative to the remote asymmetric centers at C-2,C-6 and can now be used to control the C-11 center.

Reduction of **10** with $LiEt_3BH$ (−78 °C) gave **12** (94%), **13** (4%), and 1–1.5% of a third isomer. Since **13** was formed as the major product from **11** (generated in situ via enolization of **10**), reduction selectivity of **10** according to the Felkin–Anh[7] mode was >60:1, presumably due to the presence of an α-sulfur substituent. Felkin–Anh selectivity was established specifically for the conversion of **11** to **13** by an X-ray structure determination of the crystalline product, and the stereochemistry for **12** (noncrystalline) was assigned by analogy. The X-ray study proved that all of the other stereocenters had been introduced correctly.

After alcohol protection and sulfur oxidation, **14** was subjected to an oxidative activation sequence which had been developed earlier for conversion of cyclic sulfides into lactones.[8,9] Quenching the sulfoxide anion of **14** with chlorodiphenylphosphine, followed by iodine catalyzed S to P oxygen transfer, gave **15** (60% overall). Horner–Bestmann oxygenation of phosphine oxide **15** then produced the desired thiolactone **16** together with recovered **15** (70% efficiency after recycle; 50% conversion). After silyl ether cleavage ($HF/H_2O/CH_3CN$), thiolactone **17** was subjected to camphorsulfonic acid catalysis in benzene (70 °C) to effect S to O acyl transfer (63%). This step converts the cyclic sulfur intermediate into the macrolide without resorting to high dilution conditions.[9]

Final removal of sulfur could be achieved by exploiting the photochemistry of phenacyl sulfides as previously reported.[10] Sunlamp irradiation of phenacyl sulfide **19** (obtained from **18** and phenacyl triflate[6]) in the presence of the *tert*-butyldimethylsilyl nitronate ester of nitroethane[11] as thio ketone trap, followed by fluoride-induced cleavage of the resulting cycloadducts,[10] generated **20** (74%) without affecting the α,β-unsaturation or the adjacent asymmetric center.

Next, it was necessary to introduce the correct oxidation pattern at C-7,C-10. Epoxidation of **20** with MCPBA gave a single epoxide diastereomer **21** (80%). The stereochemistry assignment is based on control by the local conformer effect of allylic C-6 methyl.[4] Upon treatment with DBU, keto epoxide **21** gave enone **22** in 70% yield (Scheme II). The last (C-10 methyl) carbon of methynolide could now be attached by organometallic addition, but CH_3Li in THF attacked the least hindered face of the ketone carbonyl[12] and formed largely the unnatural C-10 alcohol (3:1

(1) Vedejs, E. *Acc. Chem. Res.* **1984**, *106*, 358. Vedejs, E.; Hagen, J. P. *J. Am. Chem. Soc.* **1975**, *97*, 6878.

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(3) Modifications in the original scheme were studied by Dr. J. Schaffhausen and will be described in the full paper.

(4) Vedejs, E.; Gapinski, D. M. *J. Am. Chem. Soc.* **1983**, *105*, 5058. Vedejs, E.; Dent, W. H., III; Gapinski, D. M.; McClure, C. K. *J. Am. Chem. Soc.* **1987**, *109*, 0000.

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(8) Vedejs, E.; Meier, G. P.; Powell, D. W.; Mastalerz, H. *J. Org. Chem.* **1981**, *46*, 5253.

(9) Vedejs, E.; Powell, D. W. *J. Am. Chem. Soc.* **1982**, *104*, 2046. Vedejs, E.; Buchanan, R. A. *J. Org. Chem.* **1984**, *49*, 1840.

(10) Vedejs, E.; Perry, D. A. *J. Org. Chem.* **1984**, *49*, 573.

(11) Calvin, E. W.; Beck, A. K.; Bastani, B.; Seebach, D.; Kai, Y.; Dunitz, J. D. *Helv. Chim. Acta* **1980**, *63*, 697.

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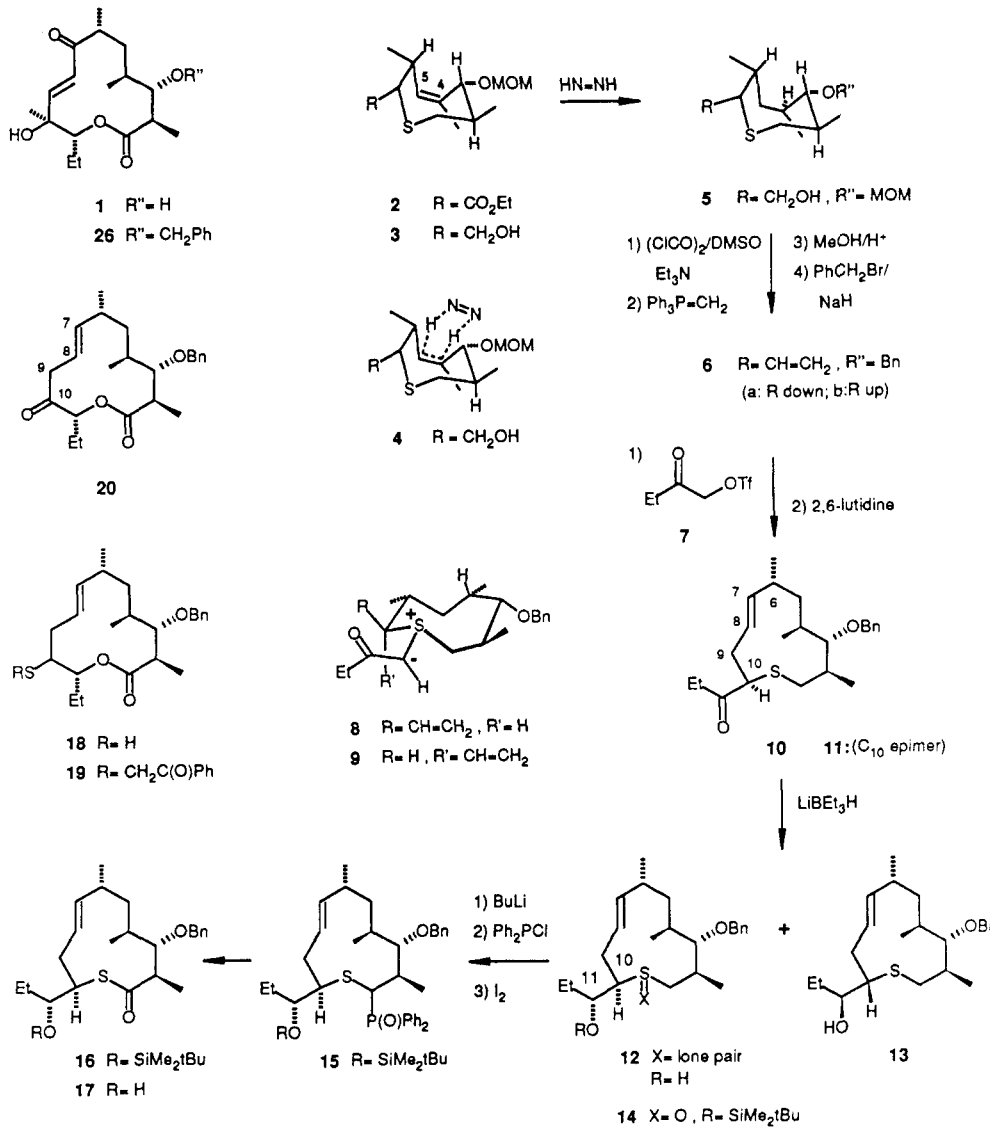
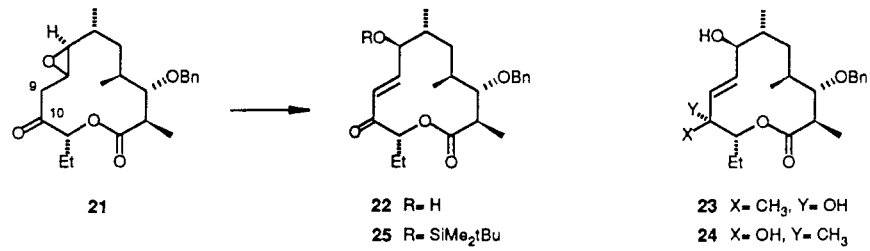
Scheme I



Scheme II



23:**24**). However, CH_3MgI in toluene gave predominantly the natural isomer **24** (48%), together with **23** (7%). A much better yield of the mixture was obtained by using trimethylaluminum (91%), but this reagent was nonselective (1:1.2). Protection of the C-7 hydroxyl (*tert*-butyldimethylsilyl triflate/2,6-lutidine) completely reversed the selectivity of Grignard addition, thus implicating a directive effect of the magnesium alkoxide derived from **22**. The specific nature of this effect is not known, but the most likely possibilities are (1) a conformational change or (2) intramolecular delivery of methyl via some sort of alkoxide–Grignard aggregate.

Oxidation of the allylic C-7 alcohol with pyridinium chlorochromate produced enone **26**, and, finally, cleavage of the benzyl ether (DDQ)[13] gave **1**[14] (60%). Since *d,l*-methynolide has not been prepared previously, the identity of **1** was established by high field NMR comparisons. All chemical shifts were within 0.003 ppm of the signals of natural methynolide. For further confirmation, **23** was similarly converted into *d,l*-10-*epi*-methynolide. Chemical shifts differed by as much as 0.1 ppm relative to the natural isomer, and there were clear differences in splitting patterns.

Previous syntheses of methynolide or related naturally occurring macrolides have achieved stereocontrol by the coupling of optically pure segments.[15] Approaches to macrolides that rely totally upon

(12) Assuming a transoid lactone and adjacent pseudoequatorial C-11 ethyl and C-2 methyl groups.

(13) Oikawa, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1985**, *26*, 1541.

(14) Characterization data for **1** and other key structures: see Supplementary Material.

control of *relative* stereochemistry are rare.[16]

Acknowledgment. This work was supported by the National Science Foundation (CHE-8306121) and by NIH for the AM-500 spectrometer (RRO 2388-01). We also thank Prof. O. Yonemitsu for spectra of methynolide.

Supplementary Material Available: Experimental data for **5**, **10**, **11**, **12**, **17**, **18**, **20**, *d,l*-methynolide, and *d,l*-10-*epi*-methynolide (4 pages). Ordering information can be found on any current masthead page.

(15) Masamune, S.; Kim, C. V.; Wilson, K. E.; Spessard, G. O.; Georghiou, P. E.; Bates, G. S. *J. Am. Chem. Soc.* **1975**, *97*, 3512. Masamune, S.; Ouchida, S.; Inoue, K.; Nakano, A.; Okukado, N.; Yamaguchi, M.; *Chem. Lett.* **1979**, 1021. Oikawa, Y.; Tanaka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1986**, *27*, 3647.

(16) Recent examples: Still, W. C.; Novack, V. J. *J. Am. Chem. Soc.* **1984**, *106*, 1148. Still, W. C.; Romero, A. G. *J. Am. Chem. Soc.* **1986**, *108*, 2105. Schreiber, S. L.; Sammekia, T.; Hulin, B.; Schulte, G. *J. Am. Chem. Soc.* **1986**, *108*, 2106.

Helical Ferric Ion Binders

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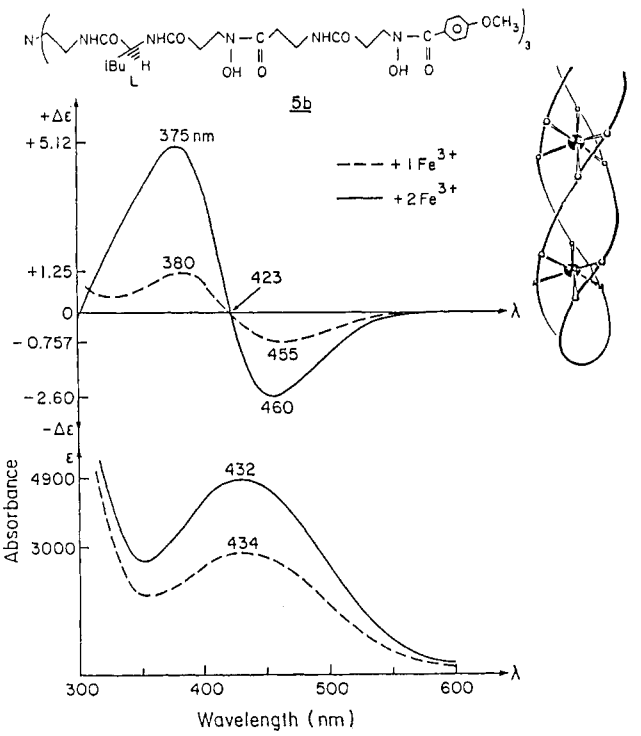
Ditopic metal ion binders[1,2] are of interest for the study of cooperative and allosteric effects that are crucial in enzyme regulation and related processes.[3,4] It occurred to us that triple-stranded helices could be promising structures for such studies as they may accommodate binding cavities of varying proximity in their inner space, are extendable, and may exhibit chiral recognition.[5] However, in order to generate helical conformations in tripodlike molecules, random coiling of the chains has to be avoided, possibly by noncovalent interstrand linkages.[6] In this communication we describe the first triple-stranded helices that incorporate two metal ions and are stabilized by interstrand hydrogen bonds (H bonds). These H bonds may be modulated to generate diastereomeric helices of either right- or left-handedness. The molecules are assembled from tris(2-aminoethyl)amine as an anchor, extended by L-leucine, and elongated by an alternating sequence of hydroxamate and amide groups as ligands and H bonding units, respectively. When loaded with Fe^{3+} ions, the presence of chiral amino acids and hydroxamate chromophores as probes allows the determination of the absolute configuration around each metal ion and thereby the helicity of the overall structure.

The syntheses of the monotopic binder **3** and of the ditopic binders **5** and **7** were achieved by Scheme I outlined below.[7] First, the conformation and ion-binding properties of the monotopic binder **3** were examined. The IR of **3a** shows bonded NH centered around 3310 cm^{-1} (1.8 mM, $CDCl_3$), and its NMR spectrum reveals nonequivalence of the diastereotopic NCH_2CH_2NH protons in $CDCl_3$ ($\Delta\delta$ = 0.53 ppm) and to a smaller extent in CD_3OD ($\Delta\delta$ = 0.17 ppm). The single stranded *n*-PrNHCOCH(*i*-Bu)NHCOCH$_2$CH$_2$N(OBz)COC$_6$H$_4$OCH$_3$ shows free NH absorptions at 3430 cm^{-1} in the IR and minor nonequivalence of its diastereotopic protons in $CDCl_3$ ($\Delta\delta$ < 0.05 ppm) that collapsed in CD_3OD. This establishes restricted conformational freedom in **3a** caused by interchain H bonds.[8] The IR of the Fe^{3+} complex, **3b-Fe**,[9] shows similarly bonded NH (3285 cm^{-1} in 4 mM $CDCl_3$),



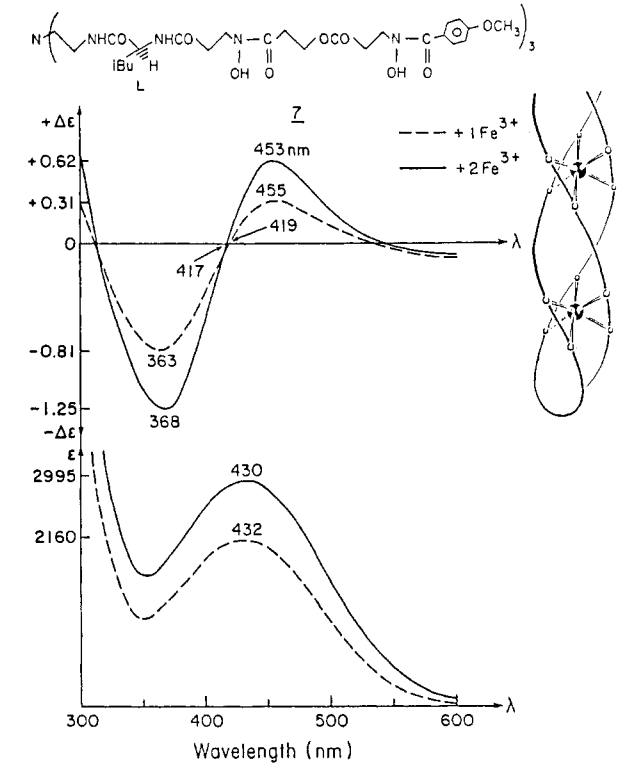


Figure 1. CD and UV spectra of **5b-Fe** (0.16 mM), **5b-2Fe** (0.16 mM), **7-Fe** (0.15 mM), and **7-2Fe** (0.15 mM) in $CDCl_3$.

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(3) Koshland, D. E., Jr.; Neet, K. E. *Annu. Rev. Biochem.* **1968**, *37*, 359-410.
(4) Hammes, G. G; Wu, C.-W. *Annu. Rev. Biophys. Bioen.* **1974**, *3*, 1-33.
(5) Meurer, K. P.; Voegtle, F. *Top. Curr. Chem.* **1985**, *127*, 1-76.
(6) Tor, Y.; Libman, J.; Shanzer, A. Felder, C. E.; Lifson, S. *J. Chem. Soc., Chem. Commun.* **1987**, 749-750.
(7) The linear carboxylates **2**, **4**, and **3** were prepared by a series of condensation reactions involving 2-(hydroxylamino)propionic acid, 2-aminopropionic acid, and 4-methoxybenzoic acid. The detailed reaction procedures will be given in a full account of this work.
(8) The reliability of spectrometric IR/NMR analyses in identifying such interchain H bonds has recently bee described (ref 6).
(9) All spectroscopic data for the Fe^{3+} complexes in $CDCl_3$ were obtained with isolated, TLC purified complexes.

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