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SYNTHESIS AND X-RAY STRUCTURE OF A NOVEL CHIRAL TRINUCLEAR TITANIUM-TETRAOL COMPLEX

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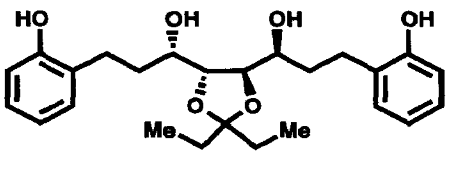
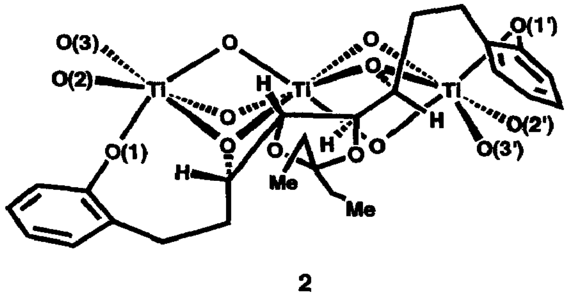
Summary: *This paper describes the synthesis of the chiral tetraol* **1**, *and its conversion with Ti(IV) 1,1,1,3,3,3-hexafluoroisopropoxide to the novel linear trinuclear titanium complex* **8** *whose structure has been determined by spectroscopic and X-ray crystallographic analysis.*

Recently there has been great interest in metal complexes with chiral ligands as promoters of enantioselective reactions.[1] For example, research in these laboratories has dealt with catalytic systems for reactions such as Diels-Alder addition, which incorporate π-donor-acceptor interactions as a key stereocontrolling element.[2] Although several chiral titanium complexes have been utilized as effective asymmetric catalysts, relatively few of these have been titanates.[3] The potential of titanates as chiral Lewis acids has been demonstrated by Seebach and Yamamoto, who have employed them as catalysts for the addition of diethylzinc to aldehydes and for Diels-Alder reactions respectively.[4,5] This paper describes the synthesis of an interesting new chiral ligand, the tetraol **1**, and its conversion to a novel trinuclear Ti(IV) compound with the complex Ti-O core system shown in **2** (two ligands corresponding to **1** have been omitted for clarity).

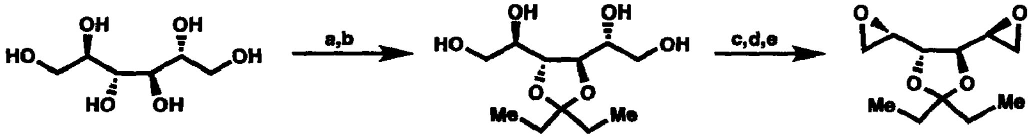


1



2

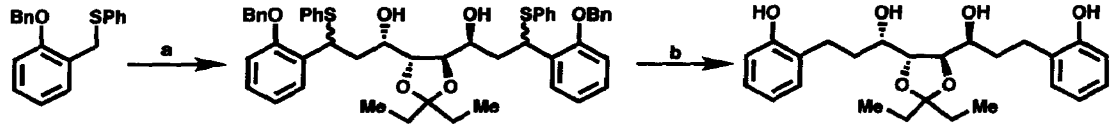
The synthesis of tetraol **1** was accomplished in seven steps from D-mannitol (**3**). Treatment of D-mannitol with 3-pentanone in the presence of H_2SO_4 afforded the triketal which was converted selectively to the 3,4-monoketal **4**.[6] Inversion of the two secondary alcohol stereocenters of **4** was accomplished by selective formation of the primary dibenzoate followed by conversion of the secondary alcohols to the ditosylate and



3 4 5

(a) 3-pentanone, H_2SO_4, 23%; (b) AcOH, 45 °C, 82%; (c) BzCl, pyr., CH_2Cl_2, -78 °C, 99%; (d) TsCl, Et_3N, DMAP; (e) K_2CO_3, MeOH, CH_2Cl_2, then MeONa, 41% for the two steps.

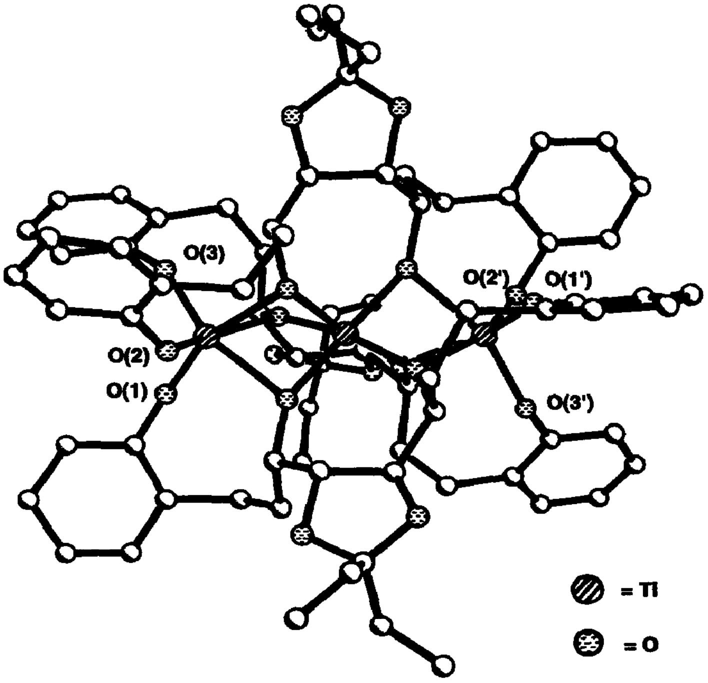
methanolysis with concomitant base induced oxirane formation gave **5** with the L-*ido* configuration. Although there are some reports of *o*-alkoxybenzylorganometallics in the literature,[7] initial experiments to form a suitable organometallic reagent for epoxide opening were not promising. Reactions including Grignard formation with a benzyl halide, transmetallation of tributyltin and phenyltelluride derivatives, metal halogen exchange or directed lithiation all led to poor yields of the organometallic reagent due mainly to side reactions involving homo- and heterocoupling. The α-lithio derivative of phenylsulfide **6**,[8] however, proved to be a superior benzyl anion equivalent. Treatment of **6** with *s*-BuLi in Et_2O at -25 °C followed by the addition of bis epoxide **5** afforded a mixture of diastereomeric alcohols **7** in 76% yield after silica gel chromatography. The tetraol ligand **1** was obtained, by desulfurization and debenzylation with hydrogen in the presence of Raney nickel, in 88% yield after silica gel chromatography.[9]



6 7 1

(a) *s*-BuLi, Et_2O, -25 °C, 3 h then **5**, 15 h, 76%; (b) Raney Ni (W-2), EtOH, H_2, 88%.

Initial attempts to form a monomeric catalyst from **1** with 1 eq. Ti(IV) 1,1,1,3,3,3-hexafluoroisopropoxide[10] under controlled low temperature conditions (0 °C, toluene, 30 min) led to formation of a species which displayed NMR spectra not consistent with a symmetric monomeric 1:1 complex with all four oxygens bonded to a single titanium. However, when the reaction was performed at higher temperature or for longer periods a new species was formed which appeared to have C_2-symmetry as would be required for the 1:1 monomer complex. Attempts to alter the relative amounts of these titanium complexes led to the finding that upon heating, the dissymmetric complex is gradually converted to the symmetric complex **8** in good yield.[11] Although the ^1H, ^{13}C NMR and IR spectra were consistent with a monomeric species, the mass spectrum showed a molecular ion of 1422 (triple the expected value) and indicated a trimeric structure with a high level of symmetry. The complex also displayed some interesting properties such as stability to air and toward satd. aq. $NaHCO_3$ solution, which indicated a coordinatively saturated compound, and an extremely high optical rotation ($[\alpha]_D^{23}$ = -854° (c = 0.2, CH_2Cl_2)). Purification of **8** by reverse phase chromatography and slow recrystallization from CH_2Cl_2–pentane bilayer at ambient temperature afforded orange crystals. An orange prism (0.5 x 0.25 x 0.3 mm), monoclinic, space group $P2_1$, two molecules per unit cell, was subjected to X-ray diffraction analysis and yielded the D_3-symmetric structure of complex described by **8**.[12] The structure contains a unique core of three linear titanium atoms to which are attached bridging alkoxides and terminal phenoxides.[13] The ligands tie together the three hexacoordinate titanium atoms in a helical fashion, as is shown in the simplified structure **2**; the terminal phenoxy oxygens have been labeled in order to show the connectivity of the remaining two ligands. As expected, the titanium-oxygen bonds are shortest for the terminal oxygens (≈1.8 Å) while the μ-bridging oxygens have length of ≈2.1 Å and ≈1.9 Å for the titanium-oxygen bonds to the terminal and internal titaniums respectively. The crystal structure lacks the D_3-symmetry of the solution structure due to incorporation of one equivalent of CH_2Cl_2 in the crystal lattice.



X-ray Crystal Structure of 8

The unique structure, chemical stability, color and high optical rotation of complex **2** suggest that this compound may be of some interest with regard to electro-optical behavior. Attempts to synthesize the zirconium and hafnium analogues have led so far to formation of alternative complexes with different physical properties.[14]

References and Notes

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4. von dem Bussche-Hünnefeld, J. L.; Seebach, D. *Tetrahedron* **1992**, *48*, 5719-5730.
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8. Prepared in 86% yield from the known *o*-benzyloxy benzyl chloride (Ono, K.; Katsube, J. *Chem. Pharm. Bull.* **1983**, *31*, 1267-1276) by treatment with PhSK in DMF and recrystallization from hexane.
9. Spectral data for **1**; mp 54-56 °C; $[\alpha]_D^{23}$ = -18 (c = 0.25 in CH_2Cl_2); IR (neat/ NaCl) 3356, 2973, 2939, 2882, 1457, 1239, 1081 cm^{-1}; ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 130.7, 127.7, 127.1, 120.8, 116.3, 112.9, 79.3, 68.7, 34.8, 30.2, 25.5, 8.1; ^1H NMR (500 MHz, $CDCl_3$) δ 7.13-7.08 (m, 4H), 6.87 (t, *J* = 7.4, 2H), 6.82 (d, *J* = 7.8, 2H), 6.80 (s, 2H), 3.86 (s, 2H), 3.48-3.44 (m, 2H), 2.81 (ddd, *J* = 14.0, 10.0, 6.0, 2H), 2.71 (dt, *J* = 14.0, 5.7, 2H), 2.63 (d, *J* = 8.5, 2H), 1.96-1.88 (m, 2H), 1.76-1.70 (m, 2H), 1.64 (q, *J* = 7.5, 4H), 0.90 (t, *J* = 7.5, 6H); MS (FAB) *m/z* 453 (M+Na); HRMS (FAB) (M+Na) calcd. for $C_{25}H_{34}O_6Na$: 453.2253. Found 453.2275.
10. Corey, E. J.; Ishihara, K.; Roper, T. D.; Sarakinos, G. *in preparation.*
11. Complex **8** was prepared in the following way. The dry tetraol **1** (41.8 mg, 97.1 μmol) was dissolved in toluene (5 mL). To the solution was added $Ti(OCH(CF_3)_2)_4$[10] (39.6 μL, 97.0 μmol) and the mixture was stirred for 40 min. The solvent was removed *in vacuo* and the flask was then heated with kugelrohr apparatus (ot = 250 °C at 1 mm Hg) for 6 h. The residue was purified by reverse phase chromatography (C18, CH_3CN->15%CH_2Cl_2–CH_3CN) to yield the pure complex **8** (30 mg, 65%). X-ray quality crystals were obtained by recrystallization from CH_2Cl_2–pentane (0.3 mL/10 mL) bilayer in a 16 x 100 mm tube, sealed with a septum, at room temperature for 18 h; mp 295 °C dec; $[\alpha]_D^{23}$ = -854° (c = 0.2, CH_2Cl_2); UV (λ max) 338, 250; IR ($CDCl_3$ solution) 2972, 2931, 2885, 1596, 1575, 1239, 1047 cm^{-1}; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 129.8, 128.6, 127.7, 122.6, 117.8, 112.3, 82.9, 76.0, 32.4, 30.0, 26.0, 8.0; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.0, 6H), 7.21 (skewed t, *J* = 7.7, 6H), 7.10 (d, *J* = 7.3, 6H), 6.89 (app t, *J* = 7.2, 6H), 4.93 (br d, *J* = 11.2, 6H), 4.66 (s, 6H), 3.31 (br t, *J* = 12.5, 6H), 2.58 (d, *J* = 12.1, 6H), 2.12 (br t, *J* = 12.6, 6H), 2.04 (br t, *J* = 13.1, 6H), 1.47 (q, *J* = 7.2, 12H), 0.77 (t, *J* = 7.2, 18H); MS (FAB) *m/z* 1423 (M+H); HRMS (FAB) (M+H) calcd. for $C_{75}H_{91}O_{18}Ti_3$: 1423.4643. Found 1423.4657.
12. The assistance of Mr. Sepehr Sarshar in obtaining this X-ray crystal structure is gratefully acknowleged. Detailed X-ray crystallographic data are available from Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K. Empirical formula $C_{76}H_{92}Cl_2O_{18}Ti_3$ (complex+ CH_2Cl_2); monoclinic, space group $P2_1$, a = 12.240 (3) Å, b = 19.881 (2) Å, c = 15.997 (2) Å, β = 108.913 (14), V = 3682.7 (14), Z = 2, d = 1.360; Mo-K_α radiation (23 °C); reflections collected 6299, unique reflections 5918, observed reflections 3551 ($F>4.0\sigma(F_o)$), R-index 0.0958, GOF = 1.15.
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14. This research was assisted financially by the grants from National Science Foundation and Merck, Sharp and Dohme.

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