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Synthesis and structure of 4-*R*,5-*R*-[5-(hydroxy-diphenyl-methyl)-2, 2-dimethyl-[1,3]dioxolan-4-yl]-phenyl-methanone, a chiral ligand building block

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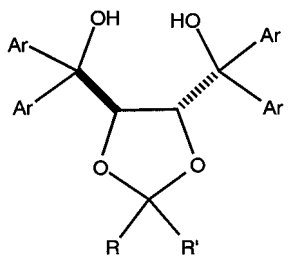
A triphenyl analog of taddol, 4-*R*,5-*R*-[5-(hydroxy-diphenyl-methyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-phenyl-methanone, has been synthesized and structurally characterized. This molecule could act as a chiral ligand building block in the creation of tuned taddol analogs. Structural analysis of the title compound reveals that the hydroxyl group is involved in an intramolecular hydrogen bond and does not take part in any intermolecular interaction. Crystal packing is influenced by C—H · · · O hydrogen bonding and phenyl · · · phenyl interactions. Crystal data: Triclinic, $P1$ (No. 1), $a = 5.9343(4)$ Å, $b = 8.2367(17)$ Å, $c = 10.987(2)$ Å, $\alpha = 88.290(6)^\circ$, $\beta = 75.442(4)^\circ$, $\gamma = 80.655(6)^\circ$, $V = 512.86(15)$ Å^3, $Z = 1$, $D_{calc} = 1.258$ mg/m^3. Final residual values were $R_1 = 0.0407$ for 3022 observed data ($I > 2s(I)$) and $wR_2 = 0.0941$ for all 3524 unique data.

KEY WORDS: Taddol; chiral; ligand; precursor; triphenyl.

Introduction

Chiral diols based on the tetraaryl-1,3-dioxolane-4,5-dimethanol structure, "taddol," developed by Seebach and coworkers have been remarkably useful as ligands in a wide variety of asymmetric reactions, including enantioselective alkylations, reductions and Diels-Alder reactions,[1] as well as in the formation of chiral clathrate inclusion complexes.[2] These compounds have been particularly useful because they can be readily synthesized in enantiomerically pure form using naturally available tartaric acid.



Basic Taddol Structure

The original taddol ligands were C_2 symmetric, a geometry that was thought to be valuable in asymmetric catalysis because it made both sites on the molecule yield the same enantiomeric

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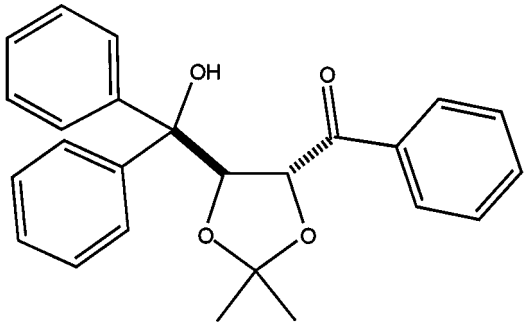
selectivity. Seebach has shown that selectivity can actually be improved by breaking the symmetry in the backbone of the ligand by moving to a less symmetric structure that could adopt a more favorable conformation for catalysis. Recent studies of chiral ligand systems have pointed out the value of slight steric modifications in a chiral ligand to tune it to a particular substrate.[3]

An approach to tuning the ligand system would be by modification or replacement of the aryl groups. This type of system could be accessed from intermediates in which addition of the aryl groups was incomplete. By synthesizing and isolating an intermediate containing only three aryl groups, a precursor could be made for systematic modification of the ligand system. Toward this goal, a triphenyl analog to taddol, 4-*R*,5-*R*- [5-(hydroxy-diphenyl-methyl)-2,2-dimethyl-[1,3] dioxolan-4-yl]-phenyl-methanone, was synthesized. This molecule could act as a chiral ligand building block in the creation of tuned taddol analogs.



1

Experimental

*Synthesis of 4-R,5-R-[5-(hydroxy-diphenyl-methyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-phenyl-methanone (**1**)*

A 105 g (512 mmol) portion of diethyl tartrate and a 64 g (615 mmol) portion of dimethoxypropane were added to 50 mL of toluene containing 0.5 g of *p*-toluene sulfonic acid. The solution was refluxed for 7 h during which time a methanol-toluene azeotrope was slowly removed by distillation. The solution was quenched with 0.5 g of $NaHCO_3$. The product was concentrated on a rotary and distilled under vacuum to yield 80.9 g (329 mmol, 64.2%) yield of the acetal. A 10 g (40.1 mmol) portion of this product was then dissolved 50 mL diethyl ether. To this solution was added 128 mL phenylmagnesium bromide (1.0 M in diethyl ether) slowly via an addition funnel. The reactants were stirred for 3 h and then quenched with a saturated NH_4Cl solution. Two products, **1** and the tetrarylated compound, were separated via recrystallization from methanol to yield 5.65 g (16.0 mmol, 40%) of the desired crystalline product as white needles. m.p. 186–188°C. $[\alpha]_D = -21.0$ ($c = 7.76$, acetone). ^{1}H NMR: (300 MHz): 7–8 (m, 15 aromatic H): 5.96 (d, $j = 6$ Hz, 1C2HO): 5.24 (d, $j =$ 6 Hz, 1C2HO): 0.6 (s, 3H): 0.5 (s, 3H). ^{13}C APT NMR (300 MHz) 197.145 [C(O)(CH5)2]: 145.581 [C(C)(OH)(CH5)2], 142.743, 135.822, 133.621, 129.409, 128.559, 128.385, 127.687, 127.535, 127.406, 126.131 (phenyl): 112.517 [C(O)2(CH3)2]: 80.971, 76.964 [C(C)(H)(O)]: 27.259, 26.364 (CH3).

X-ray crystallography

Intensity data for **1** was measured at 20 ± 1°C with graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) on a Rigaku AFC78 diffractometer with a Mercury CCD area detector. The data were collected to a maximum 2θ value of 53.3° in 0.5° oscillations (in ω) with two 15.0-s exposures (to identify detector anomalies). The data were corrected for Lorentz and polarization effects, and an absorption correction[4] was applied to the data. The structure was solved by direct methods and refined by using full-matrix least-squares techniques (on F^2). All non-hydrogen atoms were refined anisotropically; hydrogen atoms were refined isotropically. Data processing was performed with Crystal Clear,[5] and structure solution, refinement and the calculation of

Table 1. Crystal Data for **1**

Compound	Compound **1**
CCDC no.	201733
Color/shape	Colorless/prism
Dimensions, mm	$0.096 \times 0.192 \times 0.312$
Chemical formula	$C_{25}H_{24}O_4$
Formula weight, g mol^{-1}	388.44
Crystal system, space group	Triclinic, $P1$ (No. 1)
Unit cell dimensions, reflections used	2903 (all with $I > 5\sigma(I)$)
	$a = 5.9343(4)$ Å
	$b = 8.2367(17)$ Å
	$c = 10.987(2)$ Å
	$\alpha = 88.290(6)^\circ$
	$\beta = 75.442(4)^\circ$
	$\gamma = 80.655(6)^\circ$
Volume, Å^3	512.86(15)
Z	1
Density (calculated), mg/m^3	1.258
Absorption coefficient, mm^{-1}, Trans. range	0.084, 0.72–1.00
Extinction coefficient	0.081(9)
Scan type, frame width (time/frame)	ω, 0.5° frames (15 s)
θ range, deg	2.51–26.65
Reflections measured	4917
Independent reflections, R_{merge}	3524, 0.022
Observed reflections, $[I > 2\sigma(I)]$	3022
S	1.13
R_1[a]	0.0407 (0.0523)
wR_2[b]	0.0900 (0.0941)

[a] $R_1 = \sum \|F_o| - |F_c\| / \sum |F_o|$ for observed data ($I > 2\sigma(I)$); number in parentheses is for all data.
[b] $wR_2 = \{\sum[w(F_o^2 - F_c^2)^2] / \sum[w(F_o^2)^2]\}^{1/2}$ for observed data ($I > 2\sigma(I)$); number in parentheses is for all data.

Table 2. Atomic Coordinates (10^4) and equivalent Isotropic Displacement Coefficients (10^3 Å^2) for **1**

	x	y	z	U_{eq}[a]
O(1)	1485(3)	4027(2)	6011(2)	51(1)
O(2)	6063(3)	2429(2)	5151(2)	58(1)
O(3)	5474(3)	3397(2)	3290(2)	56(1)
O(4)	8546(5)	6282(3)	3896(2)	102(1)
C(1)	3375(4)	4617(3)	6368(2)	42(1)
C(2)	5623(4)	4191(3)	5309(2)	43(1)
C(3)	5336(5)	4838(3)	4016(2)	47(1)
C(4)	6664(5)	2033(3)	3848(2)	53(1)
C(5)	9289(6)	1811(6)	3320(4)	82(1)
C(6)	5614(7)	523(4)	3690(4)	75(1)
C(7)	7170(5)	5884(3)	3360(2)	54(1)
C(8)	7190(4)	6474(3)	2070(2)	48(1)
C(9)	5521(5)	6177(3)	1451(2)	58(1)
C(10)	5568(6)	6804(4)	251(3)	73(1)
C(11)	7265(6)	7736(4)	−308(3)	75(1)
C(12)	8933(6)	8027(4)	285(3)	71(1)
C(13)	8901(5)	7395(3)	1473(3)	59(1)
C(14)	3595(4)	3851(3)	7635(2)	42(1)
C(15)	1564(5)	3913(3)	8598(2)	55(1)
C(16)	1633(6)	3253(4)	9765(3)	67(1)
C(17)	3756(6)	2524(4)	9983(3)	67(1)
C(18)	5793(5)	2454(4)	9036(3)	62(1)
C(19)	5718(5)	3124(3)	7869(2)	52(1)
C(20)	2699(4)	6487(3)	6534(2)	41(1)
C(21)	4042(4)	7356(3)	7064(2)	50(1)
C(22)	3426(5)	9036(3)	7255(3)	58(1)
C(23)	1450(5)	9871(3)	6945(3)	58(1)
C(24)	135(5)	9026(3)	6387(3)	59(1)
C(25)	752(4)	7335(3)	6183(2)	50(1)

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

derived results were performed with SHELXTL-Plus.[6] Neutral atom scattering factors were those of Cromer and Waber,[7] and the real and imaginary anomalous dispersion corrections were those of Cromer.[8] Relevant crystallographic data is given in Table 1 and atomic coordinates are given in Table 2.

Results and discussion

Compound **1** was synthesized from diethyl tartrate by acetonide protection of the diol, followed by the slow addition of 3.2 equiv. of phenylmagnesium bromide in diethyl ether. The tetraarylated species was also isolated; however, careful control of the amount and rate of addition of the Grignard reagent allowed for maximization of the yield.

Bond distances and angles for **1** are listed in Table 3. Figure 1 is a thermal ellipsoid plot showing the molecular structure of **1** with thermal ellipsoids represented at the 50% probability level. Crystal packing down the a-axis is illustrated in Fig. 2.

The bonding distances and angles for **1** are all within expected ranges for a hydrocarbon structure. The five-membered heterocyclic ring has an envelope conformation, with the four-atom segment (O2—C2—C3—O3) planar (rms deviation of 0.018(4) Å) and one atom (C4) displaced by 0.425(4) Å from the plane. The phenyl rings are all

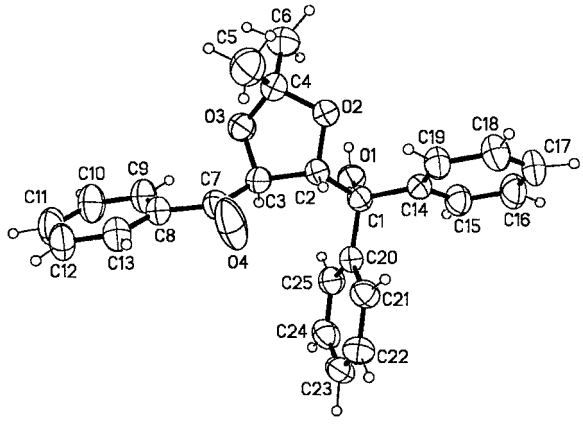


Fig. 1. Molecular structure of **1**. Thermal ellipsoids are shown at the 50% probability level.

planar (maximum deviation of 0.016(2) Å). The molecule is reported with the expected absolute configuration based on the starting material, and the refined Flack parameter of −0.1(11) confirms the assignment.

Surprisingly, the strongest hydrogen-bonding donor (O1—H1) interacts in an intramolecular fashion (H1 · · · O2 = 2.27(4) Å; O1 · · · O2 = 2.762(3) Å; O1—H1 · · · O2 = 119(3)°) and is not directly involved in any intermolecular interactions. Reasonably strong C—H · · · O hydrogen bonding from a phenyl C—H to the methanone oxygen atom links molecules related by translation along the *a*-axis (H24 · · · O4′ = 2.43(3) Å; C25 · · · O4′ = 3.306(3) Å; C25—H24 · · · O4′ = 147(2)°). Packing of the resulting chains is dominated by phenyl · · · phenyl interactions with centroid–centroid distances ranging from 4.715(3) to 5.102(3) Å and dihedral angles of 44.71(9) to 89.44(9)° (see Fig. 2).

The structural data can be used to predict the geometry of the product of nucleophilic attack at the ketone. Based on this structure, the most important geometric feature around the ketone is the dioxolane ring, which should be conformationally rigidified by the presence of the intramolecular hydrogen bond. This ring should hinder the approach of a nucleophile to the *Si* face of the carbonyl, and thereby promoting selective attack at the *Re* face. The hydrogen-bonding would suggest that a monometallated intermediate (with a main

Table 3. Important Bond Distances (Å) and Angles (deg) for **1**

Distances			
O(1)—C(1)	1.435(3)	O(2)—C(4)	1.420(3)
O(2)—C(2)	1.440(3)	O(3)—C(3)	1.430(3)
O(3)—C(4)	1.434(3)	O(4)—C(7)	1.209(3)
C(1)—C(20)	1.531(3)	C(1)—C(2)	1.532(3)
C(1)—C(14)	1.538(3)	C(2)—C(3)	1.542(3)
C(3)—C(7)	1.523(3)	C(4)—C(5)	1.502(4)
C(4)—C(6)	1.511(4)	C(7)—C(8)	1.482(3)
Angles			
C(4)—O(2)—C(2)	109.18(17)	C(3)—O(3)—C(4)	107.77(18)
O(1)—C(1)—C(20)	107.25(18)	O(1)—C(1)—C(2)	108.40(18)
C(20)—C(1)—C(2)	110.13(16)	O(1)—C(1)—C(14)	108.47(17)
C(20)—C(1)—C(14)	109.11(17)	C(2)—C(1)—C(14)	113.29(18)
O(2)—C(2)—C(1)	107.06(17)	O(2)—C(2)—C(3)	103.94(17)
C(1)—C(2)—C(3)	113.25(18)	O(3)—C(3)—C(7)	111.1(2)
O(3)—C(3)—C(2)	104.99(18)	C(7)—C(3)—C(2)	114.2(2)
O(2)—C(4)—O(3)	104.77(19)	O(2)—C(4)—C(5)	110.7(3)
O(3)—C(4)—C(5)	111.8(2)	O(2)—C(4)—C(6)	107.8(2)
O(3)—C(4)—C(6)	108.2(2)	C(5)—C(4)—C(6)	113.1(3)
O(4)—C(7)—C(8)	120.0(2)	O(4)—C(7)—C(3)	120.7(2)
C(8)—C(7)—C(3)	119.3(2)	C(13)—C(8)—C(9)	118.8(2)
C(13)—C(8)—C(7)	118.7(2)	C(9)—C(8)—C(7)	122.5(2)
C(15)—C(14)—C(1)	118.1(2)	C(19)—C(14)—C(1)	123.56(19)

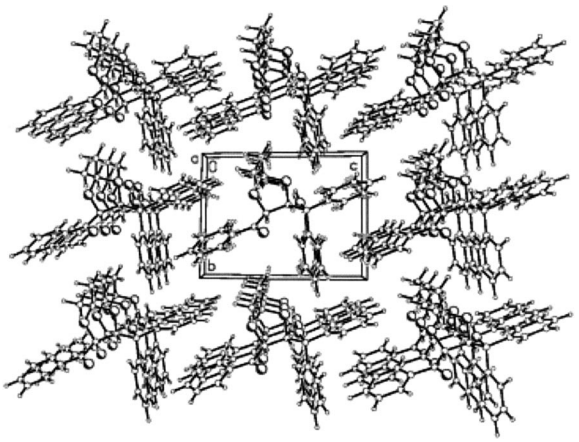


Fig. 2. Crystal packing viewed down the *a*-axis.

group metal replacing the proton) could form a chelate that would favor attack of an alkyl metal nucleophile on the *Re* face preferentially. This selectivity is likely to be dependent on the metal, the alkyl group, and the solvent.

Conclusion

A triphenyl analog of taddol, 4-*R*,5-*R*-[5-(hydroxy-diphenyl-methyl)-2,2-dimethyl-[1,3] dioxolan-4-yl]-phenyl-methanone, has been synthesized and structurally characterized. Structure analysis of the title compound reveals that the hydroxyl group is involved in an intramolecular hydrogen bond and does not take part in any intermolecular interaction. The structural data has been used to predict the selectivity of nucleophilic attack at the ketone. In future work, we hope to examine this selectivity and test these new compounds as ligands for enantioselective catalysis.

Acknowledgments

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