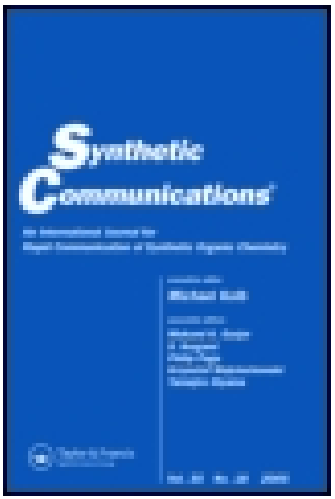

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A Practical Preparation of 4,4-Diphenylcyclohexanol: A Key Intermediate in the Synthesis of Ms-325

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A PRACTICAL PREPARATION OF 4,4-DIPHENYLCYCLOHEXANOL: A KEY INTERMEDIATE IN THE SYNTHESIS OF MS-325

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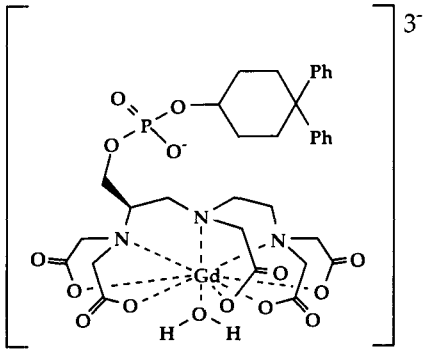
Abstract: A preparation of 4,4-diphenylcyclohexanol **2** is described from benzoin in five synthetic steps. The process uses readily available reagents and is suitable for manufacturing.

In our efforts to find a practical and efficient method toward a commercial synthesis of the gadolinium chelate **1** (MS-325)[1], an injectable vascular contrast agent, kilogram quantities of 4,4-diphenylcyclohexanol **2** were required.[2]



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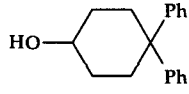

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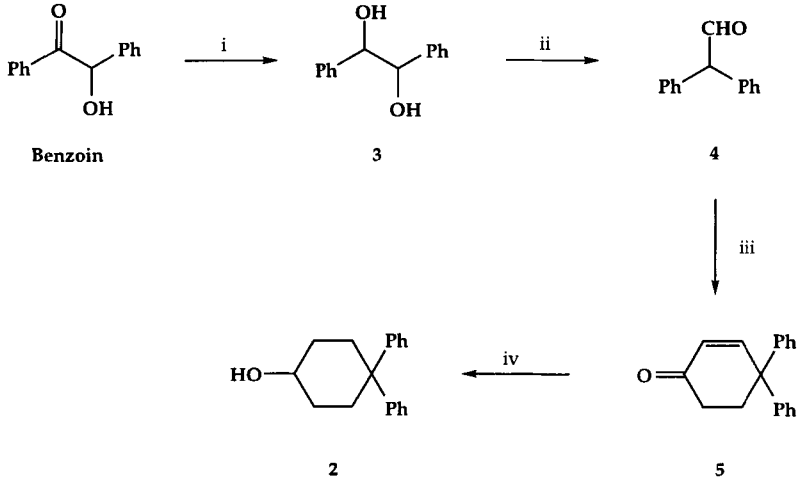
To this end, a modification of known chemistry was investigated. In this paper we describe an efficient preparation of 4,4-diphenylcyclohexanol **2**, along with improving the preparation of known chemical entities **3**, **4** and **5**. Our approach involves five synthetic transformations (Scheme I).[2]

Scheme I



i. Ethanol, $NaBH_4$, 1.0M aq. NaOH. ii. AcOH, conc. H_2SO_4. iii. Ethanolic KOH, methyl vinyl ketone. iv. H_2, Pd/C, THF; then $NaBH_4$, 0.1N aq. NaOH, THF

Although intermediates **3**, **4** and **5** are commercially available, their high cost and limited bulk supplies directed us toward an in-house synthesis.[3] Published procedures afforded satisfactory preparations of **3**, **4** and **5**, but had not been optimized for producing commercial quantities. Our objective was focused on the selection of appropriate reagents and solvents for commercial scale manufacture, refinements to reaction conditions that would lead to minimum process cycle times, and improvements in process work-ups that would minimize isolations and purifications while improving product quality.

The synthesis began with readily available benzoin, which was treated with sodium borohydride under basic conditions to provide hydrobenzoin **3**. Exposure of hydrobenzoin **3** to an acetic acid-sulfuric acid mixture resulted in a pinacol rearrangement, producing diphenylacetaldehyde **4**. Combining **4** with methyl vinyl ketone in ethanol, followed by the slow addition of a potassium hydroxide-ethanolic solution effected a Michael Addition/Aldol Condensation sequence giving enone **5**. Compound **2** was prepared by a hydrogenation-reduction of **5** in one pot. The overall yield of this process was 34%, requiring only one purification (**2**, recrystallization).

Step 1: Benzoin to Hydrobenzoin 3

Hydrobenzoin has been prepared from benzaldehyde by treatment with SmI_2/TMSCl/Mg,[4] $Sm(OTf)_3$/sec-BuLi,[5] $TiCl_4/Zn$[6] and sodium naphthalenide.[7] Furthermore, reduction of benzoin with $SmI_2/LiNH_2$,[8] Poly-η-(pyrazine)zinc borohydride,[9] and hydrogenation in the presence of $[RuCl(CO)_2Phpy]_2$ gave **3**.[10] Whereas these preparations produced **3** in high yield, drawbacks regarding raw material availability, safety issues and environmental concerns inspired us to investigate alternative conditions.

Using a modified literature procedure for the sodium borohydride reduction of benzil,[11] we adopted benzoin as the starting material. The bulk availability and cost rendered it most favorable. Table I summarizes the optimized conditions for the reduction.

Noteworthy is the addition of sodium borohydride as a solution in 1.0N aqueous sodium hydroxide, which significantly reduced handling complications. We observed spontaneous pinacol rearrangement when the diol was exposed to an

Table I Sodium Borohydride Reduction of Benzoin

Entry[a]	Equivalents of $NaBH_4$	pH of Mixture Before Product Isolation	Product Assay by GC[b] % 3 and 4
1	0.34	2.5	68.0 and 32.0
2	0.55	2.5	72.0 and 28.0
3	0.72	2.5	68.0 and 32.0
4	0.34	7.0	93.0 and <1.0%
5	0.34	7.0	95.0 and <1.0%
6	0.27	7.0	99.0 and <1.0%

a. All reactions were carried out using 0.47 moles of benzoin. b. GC of crude isolated product.

acidic media (entries 1-3). The quantity of sodium borohydride was optimized to 0.27 equivalents, and neutralization of the reaction media generated crude product stable for months.[12]

Step 2: Hydrobenzoin 3 to Diphenylacetaldehyde 4

A reasonable approach from **3** to **4** involves a pinacol rearrangement with p-TsOH in benzene.[11] These conditions required azeotropic removal of water and a reaction time of 3-5 days. On multi-gram quantities, this procedure provided aldehyde **4** in 30-50% yields. Anticipating scale-up issues, i.e. benzene as solvent, long reaction times, unacceptable distillation conditions and low yields, we focused on alternative reaction conditions. Table II highlights our findings.

Notable reaction variables addressed were acid catalyst, reaction time and temperature. We attempted to use water as the reaction solvent due to our observations in step 1 (see Table I, entries 1-3), but were unsuccessful (see Table

Table II Pinacol Rearrangement Conditions: Conversion of 3 to 4

Entry	Reaction Solvent	Acid Catalyst	Reaction Time/Temperature	GC assay of crude reaction mixture: % **4**
1	Benzene	p-TsOH	4.0 days/80 °C	60.0%
2	Toluene	p-TsOH	23.0 hrs/115 °C	20.0%[a]
3	Water	IR-120 resin	4.0 hrs/20 °C	No Reaction
4	Water	H_2SO_4	4.0 hrs/70 °C	No Reaction
5	Acetic Acid	none	4.0 hrs/20 °C	No Reaction
6	Acetic Acid	IR-120 resin	4.0 hrs/20 °C	No Reaction
7	Acetic Acid	HCl	4.0 hrs/70 °C	80.0%[b]
8	Acetic Acid	H_2SO_4	4.0 hrs/20 °C	20.0%[b]
9	Acetic Acid	H_2SO_4	4.0 hrs/70 °C	80.0%[b]
10	Acetic Acid	H_2SO_4	4.0 hrs/70 °C	83.0%[b]
11	Acetic Acid	H_2SO_4	1.5 hrs/104.0 °C	89.0%[b]

a. The major impurity was identified as 2-(1,1-diphenylmethyl)-4,5-diphenyl-1,3-dioxolane . b. The major impurity was identified as deoxybenzoin.

II, entries 3 and 4). The acetic acid/conc. sulfuric acid mixture (20:1) at 104 °C were optimal pinacol rearrangement conditions (entry 11, see also experimental section). Reaction times greater than 1.5 hours did not improve the purity of crude **4**. Major advantages are avoiding the purification (distillation), shorter reaction times and inexpensive raw materials. Crude **4** was found to be stable over one year at -5.0-0.0 °C.

Step 3: Diphenylacetaldehyde 4 to 4,4-Diphenylcyclohex-2-en-1-one 5

The Michael Addition/Aldol Condensation between diphenylacetaldehyde and methyl vinyl ketone has been reported.[14] Drawbacks of this procedure from a manufacturing perspective include the use of diethyl ether/95% ethanol (13.3:1) as a reaction solvent, benzene to dissolve "gummy" crude product for organic/aqueous extraction purposes. In addition, the reaction utilized purified diphenylacetaldehyde,

Table III Conversion of 4 to 5

Entry[a]	Purity of 4 (GC)	Purity of MVK (GC)	Purity of Crude 5 (HPLC)[b]
1	97.0%	98.0%	99.7%
2	69.4%	98.0%	91.3%
3	77.0%	94.0%	92.0%
4	84.0%	98.0%	94.0%
5	89.0%	98.0%	94.5%
6	89.0%	94.0%	93.0%

a. Diphenylacetaldehyde for entry 1 was purchased from Aldrich. Entries 2-6 used in-house material. b. The purity was based on an internal standard (purified **5**).

which is accomplished by high vacuum distillation. Our modification performs the reaction in 95% anhydrous ethanol alone.[15] The enone precipitates from the reaction mixture at 0-5 °C, which is collected by cold suction filtration. Crude product was an easily isolatable powder. The developed procedure generates enone **5** >91.0% purity from a wide range of diphenylacetaldehyde purities (69.0-97.0%). Furthermore, we found that a methyl vinyl ketone purity range of 95-99% was adequate. We were attracted to the less pure MVK due to cost.[16] Table III summarizes our results.

The Michael Addition/Aldol Condensation between diphenylacetaldehyde, purity 89.0% (GC) and methyl vinyl ketone, purity 94.0% (GC), were found most favorable (entry 6) for scale-up.

Step 4: 4,4-Diphenylcyclohex-2-en-1-one 5 to 4,4-Diphenylcyclohexanol 2

We selected a two-step operation for the hydrogentation-reduction of **5** to **4**.[17] Standard hydrogentation conditions were used to saturate **5** to the ketone,[18] which was isolated as a solution in THF. Removal of the catalyst by filtration and then addition of basic sodium borohyride facilitated reduction of **2**. Crude **2** was recrystallized in 95% anhydrous ethanol to provide desired compund in 95% purity (HPLC).

Conclusion

4,4-Diphenylcyclohexanol was prepared in five synthetic transformations from inexpensive, readily available starting materials. Our preparation addresses critical commercial manufacturing issues such as: unacceptable solvents, handling, cost, process cycle times, as well as work-ups that would minimize isolations and purifications. We improved either product quality and/or quantity of known chemical entities **3**, **4** and **5**. Alcohol **2** was produced in 35% overall yield from benzoin.

Experimental

Hydrobenzoin 3: To a solution of benzoin (50.0 g, 0.236 mol) in 95% ethanol (200 mL), under nitrogen, was added a solution consisting of sodium borohydride (2.4 g, 0.065 mol) and 1.0 M aqueous sodium hydroxide (7.5 mL) over a period of 35 minutes while maintaining an internal temperature of 2.4-5.6 °C. The reaction mixture was stirred for 2.0 hours at an internal temperature of 15-20 °C. Upon completion of reaction (in-process test by gas chromatography) a solution of 3N

aqueous hydrochloric acid (23 mL) was added over a period of 15 minutes while maintaining an internal temperature of 12.8-14.3 °C (pH 2.54). The mixture was stirred for 16 minutes and 5% aqueous sodium bicarbonate (25 mL) was added (pH 7.01) while maintaining a temperature of 12.4-14.1 °C. To the mixture was added water (200 mL) and cooled to an internal temperature of 7.0 °C over 15 minutes. The solids formed were collected by suction filtration and washed with water (50 mL) to obtain a white solid (70.0g, purity: 99.2% by gas chromatography).

Diphenylacetaldehyde 4: A solution of glacial acetic acid (100 mL) and hydrobenzoin **3** from above (67.0 g) was warmed to 49.0-51.0 °C. Concentrated sulfuric acid (5.0 mL) was added over a period of 30 minutes while maintaining an internal temperature of 49.0-51.0 °C. The mixture was warmed to 103.0-104.5 °C and stirred for 1.5 hours (in-process test by NMR). The mixture was cooled to 21.0-23 °C. Water (100 mL) and cyclohexane (100 mL) were added. The mixture was stirred for 5-10 minutes and the layers were separated. To the aqueous layer was added cyclohexane (100 mL). The mixture was stirred for 5-10 minutes and the layers were separated. The combined organic layers were washed with water (200 mL) and 5% aqueous sodium bicarbonate (2x100 mL, Caution: Foaming)(pH of aqueous layer after second wash equals 7.0). The organic layer was slurried with sodium sulfate (20 g) for 30 minutes, filtered and concentrated under vacuo to obtain an oil (36.4 g, Purity: 89.0% by gas chromatography).

4,4-Diphenylcyclohex-2-en-1-one 5: To a solution of diphenylacetaldehyde **4** from above (31.0 g), 95% anhydrous ethanol (112 mL) and methyl vinyl ketone (14 mL, 94% purity) under nitrogen was added a solution of potassium hydroxide (4.1 g) in ethanol (27 mL) over 55 minutes while maintaining an internal

temperature of 0.9-4.4 °C. The reaction mixture was stirred at -5.0 to 6.0 °C for 2 hours and 47 minutes (in process test by HPLC, gas chromatography and thin layer chromatography). The solids were collected by suction filtration (between 0.0-5.0 °C) and washed with pre-chilled (0.0-5.0 °C) ethanol (25 mL). The solids were dried (50-65 °C, 4-6 mm Hg) to a constant weight (15.0 hours) providing an off-white solid (23.4 g, Yield: 71.9 %, Purity: 93.0% by HPLC). For full characterization see reference 19.

4,4-Diphenylcyclohexanol 2: 4,4-Diphenylcyclohex-2-en-1-one **5** from above (50 g) in THF (250 mL) was placed in a hydrogenation flask. Under an inert atmosphere 2.0 g of 10% Pd/C catalyst was added. The mixture was subjected to 40-45 psi hydrogen for 8-24 hours. The flask was purged with nitrogen and the catalyst was filtered off over a bed of Celite 545. The filter bed was washed with THF (25-50 mL). $NaBH_4$ (2.5 g) was dissolved in 0.1N aqueous NaOH (25 mL) in a separate flask. The THF filtrate from the hydrogenation was placed in the reaction flask, which was equipped with a temperature control unit, addition funnel and nitrogen inlet. The mixture was chilled to 0.0 to 5.0 °C. The sodium borohydride/ aqueous NaOH solution was transferred to the addition funnel and added dropwise maintaining 0.0-10.0 °C (Caution: Exotherm). After the addition was complete the mixture was warmed to room temperature and stirred for 3.0 hours (in process test by thin layer chromatography). 3N aqueous HCl (25 mL) was added while maintaining an internal temperature of 15.0-25.0 °C (Caution: Exotherm and possible foaming), followed by pre-chilled (0.0-5.0 °C) H_2O (350 mL). The mixture was chilled to 0.0-5.0 °C and stirred 30 minutes. The solids were collected by suction filtration (Important!: Remove as much water as possible during the filtration). The solids were dissolved in warm (60.0 to 70.0 °C) ethanol (150 mL) and filtered to remove any insolubles. The filtrate was cooled to room

temperature over one hour, then chilled to 0 to 5 °C for 1.0 hour.. The solids were collected by suction filtration, dried between 25.0 -45.0 °C at 4-6 mm Hg to obtain a white solid (35.6 g, Purity: 99% (by area: HPLC); 95% (by weight, based on an internal standard: HPLC). ^{1}H NMR ($CDCl_3$, 300 mHz): δ 7.38-7.08 (10H), 3.80 (m, 1H), 2.62 (m, 2H), 1.89 (m, 2H), 1.55 (m, 2H), 1.45 (br. s, 1H): ^{13}C ($CDCl_3$, 75 mHz): 148.5, 146.0, 128.2, 127.2, 126.4, 125.5, 69.4, 45.4, 33.5, 31.4: MS (m/z): 235.0 (-OH).

Notes: a) Gas chromatography conditions for analysis of **3** and **4**: FID detector, split injection port, helium carrier gas, column: DB-1, 30 m x 0.32 mm, 0.5 micron film thickness, -60°C to 280°/300°C, J&W Scientific. Operating conditiions: Inlet temp.= -200 °C, FID temp.= 280 °C, split ratio = 50:1. Injection volume= 3 mcl., low rate (carrier gas)= 1.5 ml/min.b) HPLC conditions for analysis of **5** and **2**: UV detector, Column: Inertsil C4, 250x4.6 mm, MetaChem Technologies, Inc, sample loading: 1.0 mg/mL in 20:80 in Buffer:ACN, Detector parameters wavelength: 254 nm, Flow rate: 1.0 mL/min., Injection volume: 20 µL, Column temp.: ambient, Run time: 40 minutes (buffer: triethylamine/acetic acid/water (1.4/1.0/285.7), pH=4.8).

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14. From reference 13: It was not reported if the 95% ethanol was anhydrous.

15. The remaining 5% is isopropanol.

16. The cost of 99.0% MVK was twice that for the 94.0% material (Aldrich Chemical).

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