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A practical kinetic resolution of 4-acetyl[2.2]paracyclophane

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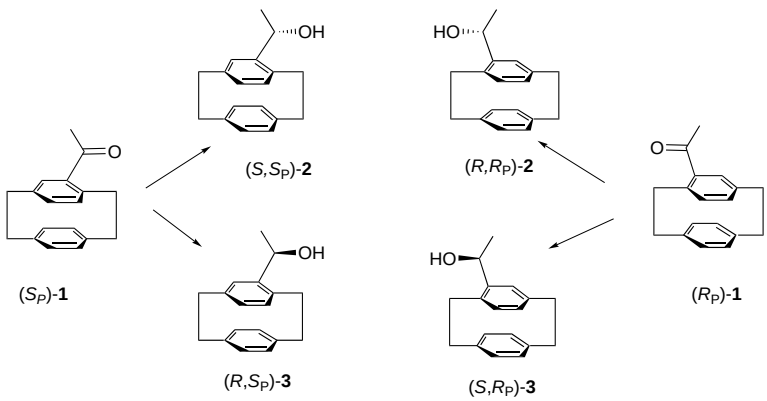
Abstract—The kinetic resolution of 4-acetyl[2.2]paracyclophane has been realized by borane reduction in the presence of a CBS catalyst. The structure of the two diastereomeric alcohol products has been established. The ketone was recovered in more than 99% e.e. at 69% conversion. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The [2.2]paracyclophane system can give rise to many chiral derivatives. The first known enantiopure compound was the [2.2]paracyclophane carboxylic acid, prepared in 1955 by Cram et al. by resolution.[1] The resolution was later improved by several groups.[2,3] In the last decade there has been a renewal of interest in enantiopure [2.2]paracyclophane derivatives, since they can be used for the preparation of chiral ligands for asymmetric catalysis[4–7] or as chiral auxiliaries in stoichiometric asymmetric synthesis.[8] The [2.2]paracyclophane skeleton may also be useful as a structural element of complex molecules, such as helicenophanes for example.[9] In that case, a good starting material is enantiopure 4-ethene[2.2]paracyclophane, itself obtained from 4-acetyl[2.2]paracyclophane **1**. A recent report[10] on the resolution of **1** by the SAMP-hydrazone method prompted us to describe herein an efficient kinetic resolution in the borane reduction of 4-acetyl[2.2]paracyclophane **1**.

Asymmetric reduction of (±)-**1** generates the diastereomeric alcohols **2** and **3** (Scheme 1). The partial conversion of racemic **1** can give rise to partially enantioenriched **1**, **2** and **3**. The relationships between the enantiomeric excesses of these three compounds ($e.e._1$, $e.e._2$ and $e.e._3$), the conversion (C) and the diastereomeric ratio (d.r. = 2/3) have been calculated.[11] These relationships allow the self-consistency of experi-



Scheme 1. Reduction of racemic 4-acetylparacyclophane **1**.

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mental data to be checked. The action of a chiral catalyst or reagent on a racemic substrate with creation of a new stereocenter may be highly diastereoselective but not necessarily enantioselective. This has been discussed by us in a general form.[11,12] It means that the formation of products such as **2** and **3** in high e.e. is not automatically associated with good kinetic resolution of the starting material **1**.

2. Kinetic resolution mediated by aminoindanol 4

It is known that some oxazaborolidines can mediate the asymmetric reduction of ketones by borane.[13] Aminoindanol **4** has been previously described to give excellent results (95% e.e. in the presence of 1 mol% of **4**) in the reduction of acetophenone.[14] Aminoindanol **4** has also been used catalytically.[15,16] The amino alcohol **4** generates an oxazaborolidine which mediates or catalyzes the asymmetric reduction. Asymmetric reduction of (±)-4-acetylparacyclophane **1** at 0°C in the presence of 1.25 mol% of **4** and an excess of borane (2.5 mol equiv.) gave a total conversion into an almost equimolar amount (53:47) of diastereomeric alcohols **2** and **3** in very high enantiomeric excess (89 and >99% e.e., respectively). The enantiomeric excesses of ketone **1** and alcohols **2** and **3** could be nicely analyzed by HPLC (Daicel Chiralcel OD-H, see Section 6). In order to be synthetically useful, this process must be catalytic with respect to the chiral auxiliary **4**. Unfortunately, by decreasing the amount of **4** (for example to 22 mol%) the two alcohols were recovered in near racemic form, presumably because of the competing uncatalyzed borane reduction. Furthermore, the recovered **1** at partial conversion is also close to racemic composition. For that reason we investigated the borane reduction catalyzed by other types of chiral oxazaborolidines.

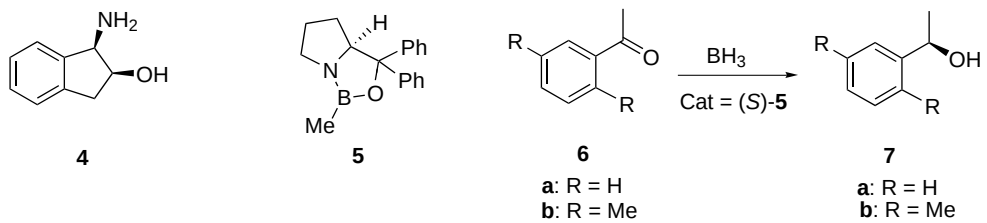
3. Kinetic resolution by CBS-catalyzed reduction

Chiral oxazaborolidines derived from proline and analogues are known to be good enantioselective catalysts in many reductions by borane (CBS catalysts).[17] For example, acetophenone **6a** (Scheme 2) has been transformed by borane into (*R*)-**7b** (96% e.e.) in the presence of catalytic amounts of (*S*)-**5**. Similarly, the dimethyl derivative **6b** provided (*R*)-**7b** (97% e.e.).

By using 15 mol% of (*S*)-**5** at 0°C we investigated the influence of the loading of borane (BH_3·THF or BH_3·Me_2S) on the conversion, the product distribution and the enantiomeric excesses of the various products. The results obtained in the reduction of (±)-**1** at the 0.2 g scale are listed in Table 1. In these experiments ketone **1** was added as a solid to a THF solution of BH_3 and catalyst.

Complete reduction of **1** provided a 2.4:1 mixture of diastereomeric alcohols **2** and **3** (35.9 and 89.3% e.e., respectively). The relationships between d.r. and e.e.s for 100% conversion is $\mathbf{2}/\mathbf{3} = e.e._3/e.e._2$, established by Guetté and Horeau.[18] This relationship is well satisfied, since $e.e._3/e.e._2 = 2.48$, against 2.4 measured. When the reaction was stopped before completion, the enantiomeric excess of the remaining ketone **1** increased with conversion (compare entries 4 and 3), as is usual in a kinetic resolution process.[19] Simultaneously the enantiomeric excess of the product **2** decreased.

In Table 2, the results for the addition of a THF solution of **1** (instead of addition of **1** as a solid) are shown. The optimal experimental conditions at a 0.2 g scale (entry 1, Table 2) with (*S*)-**5** as a catalyst are described in Section 6. Acetylparacyclophane **1** was recovered with 98.8% e.e. (*S*) and 33% isolated yield.



4 **5** **6** **7**

a: R = H
b: R = Me

Scheme 2.

Table 1. CBS reduction of (±)-4-acetyl[2.2]paracyclophane **1** (addition of **1** as a solid)

Entry	Cat. **5**[a,b] config.	BH_3·THF (mol equiv.)	Time[c] (min)	Conversion[d] (%)	Recovered **1** $e.e._1$ (%)	d.r.[e,d] **2**/**3**	$e.e._2$[d] (%)	$e.e._3$[d] (%)
1	(*R*)	0.90	80	100	–	2.4	35.9	89.3
2	(*S*)	0.60	100	85	95.1 (S_p)	2.1	64	>99
3	(*S*)	0.60	50	78	92.5 (S_p)	2.3	64.6	>99
4	(*S*)	0.30	50	30	31.3 (S_p)	17.2	90.1	>99

[a] **1** (0.2 g) added as a solid over 5 min to a mixture of catalyst **5** and BH_3·THF at 0°C.
[b] 15 mol%.
[c] Reaction time.
[d] Measured by HPLC.
[e] Diastereomeric ratio.

Table 2. (*S*)-CBS reduction of (±)-4-acetyl[2.2]paracyclophane **1** (addition of **1** dissolved in THF)

Entry	**1**[a,b] (g)	Addition time (min)	Time[c] (min)	Conversion[d] (%)	Recovered **1** e.e.$_1$ (%)	d.r.[e,d] **2**/**3**	s[f]	e.e.$_2$[d] (%)	e.e.$_3$[d] (%)
1	0.2	5	15	60	98.8 (S_p)	9.8	23	78.1	>99
2	1	5	15	59	99.1 (S_p)	9.4	27	74	>99
3	5	10	20	78.4	84 (S_p)	9.4	4	57.7	>99

[a] A solution of **1** in THF was added to a mixture of (*S*)-CBS and $BH_3{\cdot}Me_2S$ (0.6 mol equiv.) at 0°C.
[b] 15 mol%.
[c] Reaction time.
[d] Measured by HPLC.
[e] Diastereomeric ratio.
[f] Calculated by the formula: $s=k_{rel}=[\ln(1-c)(1-\text{e.e.}_1)]/[\ln(1-c)(1+\text{e.e.}_1)]$.[19]

The reaction has also been carried out successfully at the 1 g scale (entry 2, Table 2), with an isolated yield of 33% in **1** (99% e.e.). The mixture of diastereomeric alcohols is strongly enriched into **2** (d.r. = 9.4, 74% e.e.). An attempt to scale up the reaction to 5 g failed, since ketone **1** was recovered with only 84% e.e. for 78% conversion. This reflects the complexity of the reductions using CBS catalysts, needing a careful optimization for a given scale and a given substrate.[20] For that reason, we investigated the procedure described by Corey et al. with an inverse addition,[17] e.g. the addition of a THF solution of borane to the solution containing the ketone and the catalyst. Some representative results are indicated in Table 3. The procedure is very satisfactory with 10 mol% of catalyst at the 0.2 g, as well as at the 3 g scale (entry 3, Table 3). The synthetic usefulness of the process is well demonstrated by the optimization at the 3 g scale, leading to 23% of recovered (+)-(S_p)-**1** (>99% e.e.) and to 73% of a mixture of diastereomeric alcohols **2** and **3**, which on reoxidation using PCC,[21] gave (−)-(S_p)-**1** (54% e.e.) in 53% total yield. The final mass balance of the process was 23% of (S_p)-**1** (>98% e.e.) and 53% of (R_p)-**1** (54% e.e.).[22]

The intrinsic efficiency of the kinetic resolution of racemic **1** can be appreciated by the value of the stereoselectivity factor $s=k_{rel}$, using the formula $s=\ln[(1-C)(1-\text{e.e.}_1)/(1-C)(1+\text{e.e.}_1)]$ established for reactions which are first-order in substrate.[19] The reaction in entry 3 of Table 3 (69% conversion) gives $s=12$. The main source of error is the accuracy on the measurement of conversion. Conversion can be accurately calculated by the formula $C=\text{e.e.}_s/(\text{e.e.}_s+\text{e.e.}_p)$, where $\text{e.e.}_s=\text{e.e.}_1$ and e.e.$_p$ is the enantiomeric excess of the product. Here e.e.$_p$ is the e.e. of ketone **1** obtained through oxidation of the mixture of diastereomeric alcohols **2** and **3**. This second approach gives $C=0.65$ (65%) leading to $s=15.6$.

4. Assignment of stereochemistry to alcohols (−)-2 and (+)-3

The kinetic resolution of (±)-**1** provided recovered (S_p)-**1** when (*S*)-CBS catalyst **5** has been used. The major alcohol **2**, which was simultaneously produced in large excess (and in high e.e.) needs to be of (*R*)-configuration at the newly created stereogenic center. This hypothesis is based on the established rule in the CBS reduction that an arylmethylketone was consistently transformed into an excess of (*R*)-alcohol when (*S*)-**5** was the catalyst.[17] It means that the major alcohol (−)-**2** has the (R,R_p)-configuration. This was confirmed by oxidation of the crude mixture of (−)-**2** and (+)-**3** (9.8:1) (entry 1, Table 2), which generated (−)-(R_p)-acetylparacyclophane **1** in 80% e.e. The minor alcohol (+)-**3** necessarily has the alternate (S,R_p)- or (R,S_p)-configuration. The reoxidation of the minor diastereomer (+)-**3** (>99% e.e.) gave the ketone (+)-**1** of known (S_p)-absolute configuration.[2] The relative stereochemistry of (+)-**3** has been subsequently confirmed by X-ray crystal structural analysis. The molecular structure with (R,S_p) configuration is represented in Fig. 1. Owing to the lack of heavy atoms (Z>Si) the Flack parameter is unreliable and the absolute configuration could not be determined. The paracyclophane skeleton compares well with the related structure of racemic **1**.[23] Alcohol (+)-**3** was isolated after flash-chromatography of the products

Table 3. (*S*)-CBS reduction of (±)-4-acetyl[2.2]paracyclophane **1** (addition of borane to the ketone)

Entry	Cat. **5** (%)	**1**[a] (g)	Addition time (min)	Time[b] (min)	Conversion[c] (%)	Recovered **1** e.e.$_1$ (%)	d.r.[d,e] **2**/**3**	s[e]	e.e.$_2$[c] (%)	e.e.$_3$[c] (%)
1	15	0.2	5	25	53	98 (S_p)	6.3	13	88.8	>99
2	10	0.2	5	45	71	>99 (S_p)	3.4	11	80	>99
3	10	3	10	45	69	>99 (S_p)	2.6	12	60.8	76.8

[a] $BH_3{\cdot}Me_2S$ (0.6 mol equiv.) added in THF to a mixture of (*S*)-CBS and **1** at 0°C.
[b] Reaction time.
[c] Measured by HPLC.
[d] Diastereomeric ratio.
[e] Calculated by the formula: $s=k_{rel}=[\ln(1-c)(1-\text{e.e.}_1)]/[\ln(1-c)(1+\text{e.e.}_1)]$.[19]

in a kinetic resolution of racemic **1** catalyzed by (*S*)-**5**. Although being the minor product, the diastereomeric alcohol **3** ($[\alpha]_D = +40$ (CH_2Cl_2), >99% e.e.) was easily isolated. Its crystal structure shows a conformation where the hydroxyl group is away from the paracyclophane skeleton.

The epimeric alcohol **2** of (R,R_p)-configuration has not been isolated enantiomerically pure. A sample of 75.8% e.e. has a specific rotation of $[\alpha]_D = -110.4$ (c 1.35, CH_2Cl_2). It was then calculated that the enantiopure (R,R_p)-**2** must have a value of $[\alpha]_D = -145.6$ (CH_2Cl_2). The absolute configuration of (+)-4-acetyl[2.2]paracyclophane **1** ($[\alpha]_D = +65$ ($c = 0.8$, $CHCl_3$)) has been established as (S_p) by comparison with the literature value.[2] We use here the CIP nomenclature modified by Prelog and Helmchen[24](see also Ref. 25).

5. Conclusion

We have developed a simple way to resolve 4-acetyl[2.2]paracyclophane by a catalytic asymmetric reduction. This enantiopure compound is an interesting intermediate since it can be transformed into a wide variety of enantiopure paracyclophane derivatives such as 4-[2.2]paracyclophane carboxylic acid,[1] 4-ethene[2.2]-paracyclophane[10] or 4-bromo[2.2]paracyclophane.[26] Finally, the relative and absolute configuration of the diastereomeric alcohols **2** and **3** have been firmly established using chemical correlation and X-ray crystallography.

6. Experimental

6.1. General

^1H and ^{13}C NMR spectra were recorded at 250 and 63 MHz, respectively, with a Bruker AM 250 instrument. Chemical shifts are denoted in ppm (δ) relative to TMS (^1H and ^{13}C). Coupling constants are reported in Hz. Optical rotations: Perkin–Elmer 241 polarimeter (589 nm, 20°C). Concentrations (c) are reported in g/100 mL. High resolution mass spectra (HRMS) were performed with a GC/MS Finnigan-MAT-95-S. Analytical HPLC were recorded on a HPLC machine equipped with a Spectra Series P100 pump and a Spectra Series UV100 detector. The chiral stationary phase was a Daicel Chiralcel OD-H column. All reactions were carried out under argon in oven-dried glassware using standard vacuum-line techniques. All commercial reagents were used as received. Borane dimethyl sulfide and borane tetrahydrofuran complexes were purchased from Acros. (*S*)-CBS was purchased from Fluka.

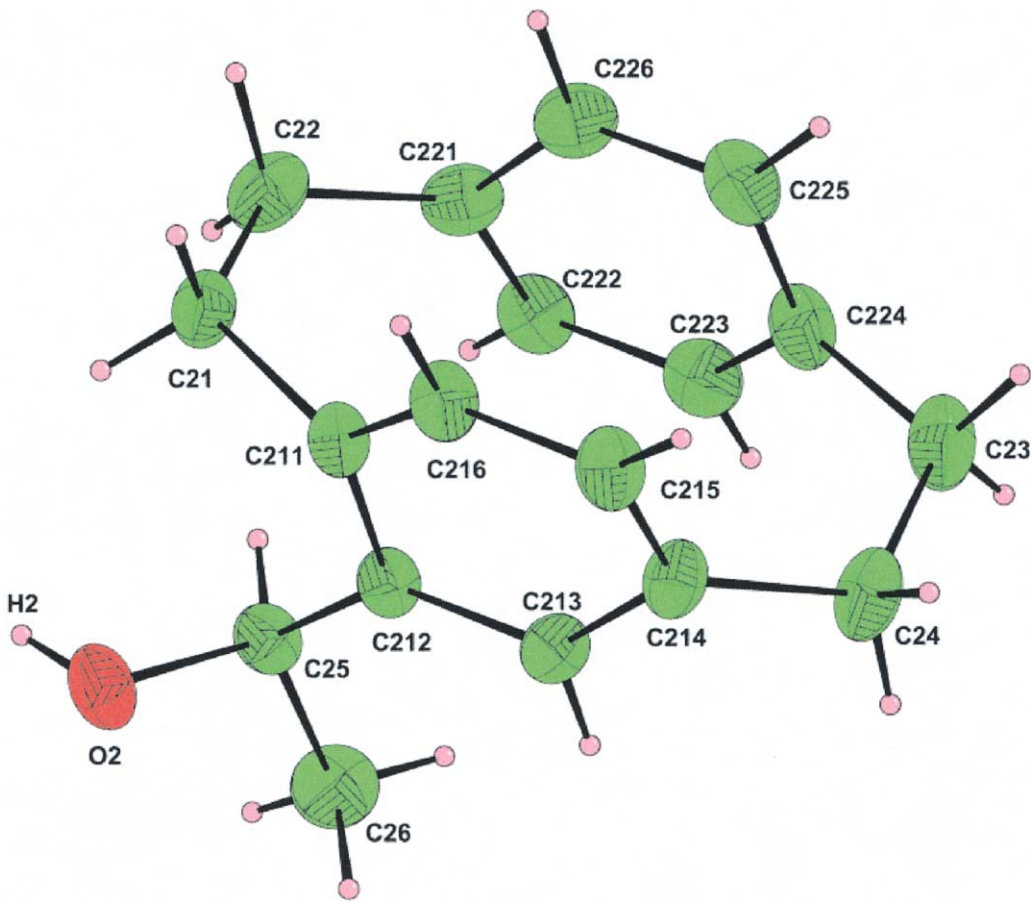


Figure 1. CAMERON view of the molecule **3** with atom labelling scheme. Ellipsoids are drawn at 50% probability.

6.2. Asymmetric reduction of racemic 1 using (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol 4

A 1 M solution of BH_3·THF (1 mL, 1 mmol) was added dropwise to a solution of **4** (80 mg, 0.5 mmol) at 0°C in THF (3 mL). After 2 h at 0°C, 4-acetylparacyclophane (0.1 g, 0.4 mmol) was added portionwise over 5 min and the mixture was stirred for 5 min. Then MeOH (0.5 mL) and a 2 M solution of HCl in EtOH (0.5 mL) were added. A white solid was filtered off and the solution was evaporated under reduced pressure. The crude mixture was analyzed by HPLC (OD-H Chiralcel, hexane/isopropanol: 98/2, 1 mL/min, 254 nm): see text. Purification by chromatography on silica gel (CH_2Cl_2/pentane/AcOEt: 5/5/1) afforded a mixture of alcohols **2** and **3** (75 mg).

6.3. Asymmetric reduction of racemic 1 using (*S*)-CBS 5

A solution of BH_3·THF (1 M, 0.24 mL, 0.24 mmol) was added to a solution of (*S*)-CBS (1 M, 0.06 mL, 0.06 mmol) at 0°C in THF (1 mL). After 2 h at 0°C, 4-acetylparacyclophane (0.1 g, 0.4 mmol) was added portionwise over 5 min and the mixture was stirred for 50 min. MeOH (0.1 mL) and a solution of HCl in EtOH (2 M, 60 μL) were added. A white solid was filtered off and the solution was evaporated under reduced pressure. The crude mixture was analyzed by HPLC (OD-H Chiralcel, hexane/isopropanol: 49/1). Results are collected in Table 1.

BH_3·SMe_2 (0.11 mL, 1.2 mmol) was added to a solution of (*S*)-CBS (1 M, 1.2 mL, 1.2 mmol) at 0°C in THF (40 mL). After 5 min at 0°C, 4-acetylparacyclophane (3 g, 12 mmol) was added and the mixture was stirred for 5 min. Then BH_3·SMe_2 (1.1 M, 0.57 mL, 6 mmol) in THF (10 mL) was added over 10 min and the mixture was stirred for 45 min. MeOH (3 mL) and a solution of HCl in EtOH (2 M, 1 mL) were subsequently added. A white solid was filtered off and the solution was evaporated under reduced pressure. The crude mixture was analyzed by HPLC (OD-H Chiralcel, hexane/isopropanol: 49/1). Purification by chromatography on silica gel (CH_2Cl_2/AcOEt: 98/2) afforded 0.7 g of ketone **1** and 1.85 g of a mixture of alcohols **2** and **3**. Diastereoisomers **2** and **3** can be cleanly separated on silica gel (CH_2Cl_2/pentane/AcOEt: 5/5/1) and pure alcohol **3** was recrystallized from ether. The results are collected in Tables 2 and 3.

6.3.1. 1-[4-[2.2]-Paracyclophanyl]-ethan-1-one 1. $[\alpha]_D^{25}$ +65 ($c=0.2$, $CHCl_3$) when e.e. >99%. HPLC (hex/*i*PrOH: 98/2, 1 mL/min, 254 nm) R_t (min): 18.84 (minor), 14.73 (major).

6.3.2. 1-[4-[2.2]-Paracyclophanyl]-ethan-1-ol 2. ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm) 1.27 (3H, d, $J=6.4$ Hz); 1.73 (1H, s large); 2.80–3.33 (8H, m); 4.92 (1H, q, $J=6.4$ Hz); 6.38–6.62 (7H, m). GC (200°C+10°C/min), Cpsil, 25 m, R_t (min): 2.49. HPLC (hex/*i*PrOH: 98/2, 1 mL/min, 254 nm) R_t (min): 20.93 (minor), 32.66 (major).

6.3.3. (R,S_p)-(+)-1-[4-[2.2]-Paracyclophanyl]-ethan-1-ol 3. ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm) 1.57 (3H, d, $J=7.6$ Hz,+1H, s large); 2.87–3.15 (7H, m); 3.58–3.65 (1H, m); 4.84 (1H, m); 6.31–6.51 (7H, m). ^{13}C NMR ($CDCl_3$, 62 MHz) δ (ppm): 25.7; 33.2; 34.4; 35.2; 35.3; 67.6; 128.2; 129.9; 131.6; 132.1; 133.0; 133.6; 134.9; 135.1; 139.3; 139.7; 140.4; 144.7. MS (EI) m/z: 252 (M^+, 23); 130 (93), 129 (100), 104 (75). HRMS calcd for $C_{18}H_{20}O$ 252.1514, found 252.1513. GC (200°C+10°C/min), Cpsil, 25 m, R_t (min): 2.56. HPLC (hex/*i*PrOH: 98/2, 1 mL/min, 254 nm) R_t (min): 43.89. >99% e.e., $[\alpha]_D^{25}$ +40 ($c=1.35$, CH_2Cl_2). Mp = 113°C (colorless crystals).

6.4. Oxidation of alcohol 3 into ketone 1

Alcohol **3** (2.2 g, 7.93 mmol) was dissolved in CH_2Cl_2 (12 mL). PCC (2.57 g, 11.9 mmol) was added and the mixture was stirred 2 h at room temperature. The black reaction mixture was diluted with five volumes of ether and filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was purified by flash chromatography to give ketone **1** as a white solid (1.6 g, 80%). Mp = 110–112°C.

6.5. X-Ray crystal structure of (R,S_p)-(+)-1-[4-[2.2]-paracyclophanyl]-ethan-1-ol 3

The crystal data were collected using a Stoe IPDS diffractometer operating at 180(2)° K. Intensities were collected with graphite monochromatized MoKα radiation ($\lambda=0.71073$) using a φ scan technique. Cell parameters were refined using 8000 selected reflections.

The structure was solved by direct methods (SIR-97[27]) and refined by least-squares procedures on F using the CRYSTALS[28] program. All H atoms attached to carbon were introduced in calculation in idealised positions [d(CH) = 0.96 Å] and treated as riding models. H atom of the hydroxyl group was isotropically refined. The drawing of the molecule was realized with the help of CAMERON.[29]

Crystal data for **3**: [$C_{18}H_{20}O$]; $M_r=252.35$; orthorhombic; space group $P2_12_12_1$; $a=8.0079(6)$, $b=13.0920(8)$, $c=26.739(2)$ Å, $V=2803.3(3)$ Å^3, $Z=8$, $\rho_{calcd}=1.196$ g cm^{-3}, $\mu=0.072$ cm^{-1}; $2\theta_{max}=48.4°$; reflections collected unique used, 15853, 4413 ($R_{int}=0.0276$) 3901 ($I>2\sigma(I)$); parameters refined, 352; $R/R_w=0.0311/0.0372$; GOF = 1.016; $\Delta/\sigma_{max}=0.042$; $[\Delta\rho]_{min}$ $[\Delta\rho]_{max}$, −0.22, 0.22 e Å^{-3}; Flack's parameter = not reliable.

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Center as supplementary publication N. CCDC 168418. Copies of the data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk

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