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Resolution of (±)-[2.2]paracyclophane-4,12-dicarboxylic acid

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Abstract—The resolution of (±)-[2.2]paracyclophane-4,12-dicarboxylic acid (±)-**1** has been realized through the diastereomeric esters of (1*S*)-hydroxymethyl-4,7,7-trimethyl-2-oxabicyclo-[2.2.1]heptan-3-one, simply separated by flash chromatography and hydrolyzed with ^{t}BuOK/H_2O. (*R*)-(−)-**1** and (*S*)-(+)-**1** were obtained in high enantiomeric excesses (>97%) while the determinations of the absolute configurations of (*R*)-**1** and (*S*)-**1** were carried out by X-ray diffraction.
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1. Introduction

Chiral ligands play an important role in asymmetric synthesis. In comparison with tetrahedrally chiral compounds, axially chiral binaphthyl derivatives,[1] planar chiral ferrocene derivatives[2] and arene metal complexes,[3] less attention has been paid to the planar chiral [2.2]paracyclophane derivatives,[4] although they have been used in some asymmetric catalytic reactions.

[2.2]Paracyclophane-4-carboxylic acid proved to be the first representative of optically active derivatives.[5] Using the monosubstituted [2.2]paracyclophane as the starting material, more mono- and disubstituented planar chiral paracyclophanes were obtained and used as chiral ligands in asymmetric catalytic reactions.[6]

Phanephos [4,12-bis(diphenylphosphino)[2.2]-paracyclophane], one of the excellent ligands used in the asymmetric catalytic reactions, has been developed by Pye recently.[7] It was used in asymmetric hydrogenation[7–10] and kinetic resolution.[11] [2.2]Paracyclophane and 1,1′-binaphthyl, the respective stereocontrolling skeleton of phanephos and BINAP, express similar stereoselectivity in asymmetric catalytic reactions. Although phanephos has been succeeded in asymmetric catalytic reactions, the shortage of optically pure paracyclophane derivatives limited its application in this field, especially the 4,12-disubstituented paracyclophane derivatives. In addition, (±)-[2.2]paracyclophane-4,12-dicarboxylic acid derivatives are supposed to act in a similar role in asymmetric catalytic reactions as 2,2′-dicarboxylic acid-1,1′-binaphthyl derivatives,[12] an excellent ligand for asymmetric epoxidation of olefins.

The preparation of racemic (±)-[2.2]paracyclophane-4,12-dicarboxylic acid (±)-**1** was first reported by Rezenberg in 1997.[13] However, to the best of our knowledge, the resolved enantiomers of **1** have never been reported. As part of our study of chiral paracyclophanes in asymmetric reactions, here we report the resolution of (±)-**1** using a camphanyl template, (1*S*)-hydroxymethyl-4,7,7-trimethyl-2-oxabicyclo-[2.2.1]-heptan-3-one.[14]

2. Results and discussion

Compound (±)-**1** was synthesized according to literature.[13] Initially, we tried to resolve (±)-**1** using methods commonly used for diacids,[15] [2.2]paracyclophane-4-carboxylic acids,[5,16] or [2.2]paracyclophane-4,7-dicarboxylic acids.[17] Compound (±)-**1** was subjected to the treatment of chiral amines such as (*S*)-α-phenylethylamine, but the result was unsatisfactory. Then we turned our attention to a chiral auxiliary reagent. Hence, (±)-**1** was converted to (±)-[2.2]paracyclophane-4,12-dicarboxylic acid dichloride followed by the addition of L-borneol and pyridine to give a mixture of diastereomeric esters, which were inseparable by recrystallization or flash chromatography.

Recently, we developed a simple and efficient method for the resolution of (±)-PHANOL in excellent yield

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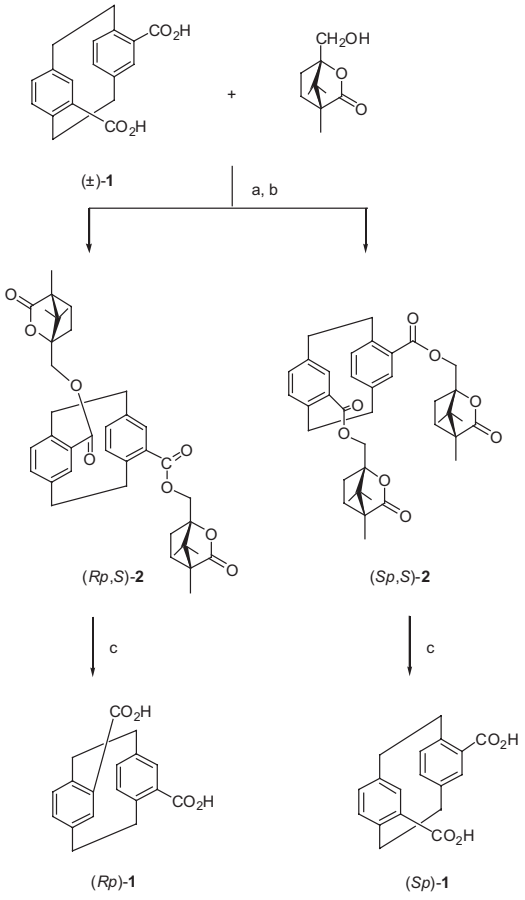
with high enantiomeric excess through the diastereoisomeric esters of (1*S*)-(−)-camphanic acid.[18] We were then encouraged to resolve the (±)-[2.2]paracyclophane-4,12-dicarboxylic acid using the same method by a pair of diastereomeric esters, which have both the paracyclophane skeleton and camphanyl template. Although the camphanic acid was used as an efficient chiral resolution reagent, its derivatives, (1*S*)-hydroxymethyl-4,7,7-trimethyl-2-oxabicyclo-[2.2.1]heptan-3-one, has never been reported as a chiral resolution reagent.

Finally, the resolution was achieved by treating (±)-[2.2]paracyclophane-4,12-dicarboxylic acid dichloride with (1*S*)-hydroxymethyl-4,7,7-trimethyl-2-oxabicyclo-[2.2.1]heptan-3-one and pyridine. The diastereoisomers were readily separated by flash chromatography on silica gel. The lower polarity portion (*Rρ*,*S*)-**2** {37% yield, >99% de determined by ^{1}H NMR, $[\alpha]_D^{20} = -39.6$ (*c* 3.25, $CHCl_3$)} and the higher polarity portion (*Sρ*,*S*)-**2** {36% yield, >99% de, $[\alpha]_D^{20} = +81.3$ (*c* 1.00, $CHCl_3$)} were hydrolyzed with ^{t}BuOK/H_2O to produce (*R*)-(−)-**1** (94% yield, 97% ee) and (*S*)-(+)-**1** (96% yield, 99% ee), respectively (Scheme 1). The absolute configuration of (*R*)-(−)-**1** and (*S*)-(+)-**1** were determined by X-ray diffraction analysis of (*Rρ*,*S*)-**2**. The results are shown in Figure 1.



Scheme 1. Reagents and conditions: (a) $SOCl_2$, reflux; (b) pyridine, flash chromatography; (c) ^{t}BuOK/H_2O/THF, 25 °C.

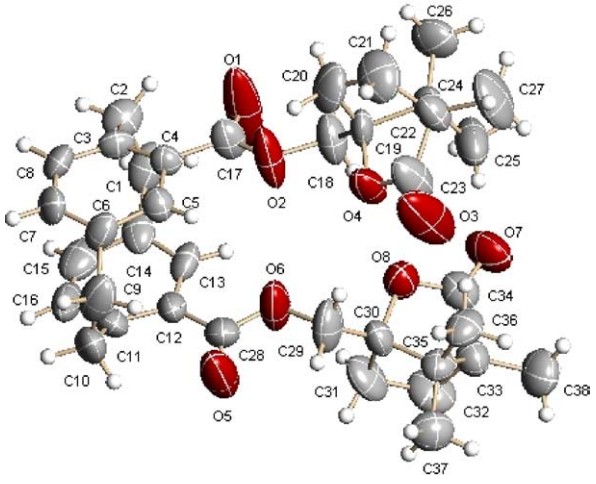


Figure 1. X-ray structures of (*Rρ*,*S*)-**2**.

3. Conclusion

In conclusion we have developed a new method of resolution of (±)-[2.2]paracyclophane-4,12-dicarboxylic acid. (1*S*)-Hydroxymethyl-4,7,7-trimethyl-2-oxabicyclo-[2.2.1]heptan-3-one was first used as chiral resolution reagent. Further extension of the use of these enantiomerically pure enantiomers in the generation of ligands for asymmetric catalytic reaction is currently being explored and will be reported separately.

4. Experimental

4.1. General

Melting points were measured on a WR*S*-1A digital melting point apparatus and are uncorrected. Optical rotations were recorded on Perkin–Elmer 341MC instrument. Infrared (IR) spectra were determined with a Shimadzu I*R*-440 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX-300. The chemical shifts were expressed in ppm and coupling constants given in Hz. Low- and high-resolution mass spectra were obtained, respectively, on a Finnigan 4021 GC MS/DC and Bruker APEXIII 7.0 TESLA FTMS. Chiral HPLC analysis was performed on a Chiralcel® OD Analytical Column using EtOH–hexane–TFA = 90:10:0.1 as an eluent (0.7 mL/min) detecting at 254 nm. Flash chromatography was performed using silica gel H (10–40 μm). Standard reagents and solvents were purified according to known procedures.[19] (±)-[2.2]Paracyclophane-4,12-dicarboxylic acid[13] and (1*S*)-hydroxymethyl-4,7,7-trimethyl-2-oxabicyclo-[2.2.1]heptan-3-one[14] were synthesized according to the literature.

4.2. (*Rρ*,*S*)-2 and (*Sρ*,*S*)-2

A mixture of (±)-[2.2]paracyclophane-4,12-dicarboxylic acid (90 mg, 0.3 mmol) and thionyl chloride (0.6 mL) was heated under reflux for 3 h. Excess thionyl chloride was distilled off and the remaining traces removed under vacuum to give the corresponding acid chloride.

(1*S*)-Hydroxymethyl-4,7,7-trimethyl-2-oxabicyclo-[2.2.1]-heptan-3-one (120 mg, 0.65 mmol) and anhydrous pyridine (2 mL) were added to the acid chloride at room temperature. The progress of the reaction was monitored by TLC. The reaction mixture was diluted with CH_2Cl_2 and washed successively with 2 M HCl, water and saturated $NaHCO_3$ aqueous. The organic solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain a mixture of diastereomeric esters **2**. They were purified by flash chromatography on silica gel using petroleum ether–ethyl acetate (6:1) as the eluent.

(*Rρ*,*S*)-**2**, TLC $R_f = 0.50$ (petroleum ether–ethyl acetate 3:1), eluted first; 52 mg (28% yield); mp 184 °C; $[\alpha]_D^{20} = -39.6$ (*c* 3.25, $CHCl_3$); IR (cm^{-1}) 1784, 1716; ^1H NMR ($CDCl_3$ 300 MHz) δ 0.99 (s, 6H); 1.01 (s, 6H); 1.10 (s, 6H); 1.61–1.69 (m, 2H); 1.77–1.87 (m, 2H); 1.90–2.07 (m, 4H); 2.81–2.91 (m, 2H); 3.14–3.22 (m, 4H); 4.09–4.17 (m, 2H); 4.45–4.85 (m, 4H); 6.58 (d, $J = 7.8$ Hz; 2H), 6.75 (dd, $J = 7.8$ and 1.8 Hz, 2H); 7.18 (d, $J = 1.8$ Hz, 2H), ^{13}C NMR ($CDCl_3$ 75 MHz) δ 9.55, 16.40, 16.62, 28.41, 28.84, 34.04, 35.69, 51.27, 54.18, 62.13, 92.20, 129.73, 133.48, 136.04, 136.64, 140.36, 142.78, 166.04, 179.59, MS (EI) *m*/*z* 628 [M^+] (4); HRMS (ESI) calcd for $C_{38}H_{44}O_8Na$ 651.29283, found 651.29330.

(*Sρ*,*S*)-**2**, TLC $R_f = 0.36$ (petroleum ether–ethyl acetate 3:1), eluted next; 51 mg (27% yield); mp 185 °C; $[\alpha]_D^{20} = +77.6$ (*c* 1.68, $CHCl_3$); IR (cm^{-1}) 1780, 1716; ^1H NMR ($CDCl_3$ 300 MHz) δ 1.00 (s, 6H); 1.02, (s, 6H); 1.12 (s, 6H); 1.66–1.75 (m, 2H); 1.80–1.90 (m, 2H); 1.99–2.11 (m, 4H); 2.80–2.90 (m, 2H); 3.08–3.27 (m, 4H); 4.04–4.11 (m, 2H); 4.55–4.65 (m, 4H); 6.59 (d, $J = 7.8$ Hz, 2H), 6.75 (dd, $J = 1.8$ and 7.8 Hz; 2H), 7.14 (dd, $J = 1.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$ 75 MHz) δ 9.64, 16.53, 16.73, 28.51, 29.09, 34.33, 36.15, 51.35, 54.30, 62.13, 91.72, 129.67, 133.84, 136.07, 136.61, 140.38, 142.41, 166.46, 179.51, MS (EI) *m*/*z* 628 [M^+] (1); HRMS (ESI) calcd for $C_{38}H_{44}O_8Na$ 651.29283, found 651.29252.

4.3. (*R*)-(−)-[2.2]Paracyclophane-4,12-dicarboxylic acid

A mixture of potassium *tert*-butoxide (684 mg, 6 mmol), THF (40 mL) and water (108 mg, 6 mmol) was stirred at room temperature for 5 min,, then (*Rρ*,*S*)-**2** (314 mg, 0.5 mmol) added and the mixture stirred for 12 h at room temperature. HCl solution (2 M) was added to the reaction mixture and the white precipitate formed, collected by filtration, washed with water and dried at reduced pressure to yield 140 mg of (*R*)-(−)-[2.2]paracyclophane-4,12-dicarboxylic acid (94%), 97% ee by HPLC analysis ($t_R = 10.16$, $t_S = 12.18$). $[\alpha]_D^{20} = -156$ (*c* 0.25, EtOH).

4.4. (*S*)-(+)-[2.2]Paracyclophane-4,12-dicarboxylic acid

(*S*)-(+)-[2.2]Paracyclophane-4,12-dicarboxylic acid was obtained by the same method from (*Sρ*,*S*)-2 in 96% yield; 99% ee by HPLC analysis. $[\alpha]_D^{20} = +150$ (*c* 0.09, EtOH).

4.5. Crystallographic analysis of (*Rρ*,*S*)-2

Colourless, needle-like crystals were grown from hexane–CH_2Cl_2 (10:1), $C_{38}H_{44}O_8$, $M = 628.73$, $a = 12.5622$ (17) Å, $b = 14.2117$ (17) Å, $c = 19.240$ (3) Å, $v = 3434.9$ (8) $Å^3$, $T = 293$ (2) K, $Z = 4$, $D_{calcd} = 1.216$ mg/m^3. Final *R* indices [$I > 2\sigma(I)$], $R1 = 0.0508$, $wR2 = 0.0574$; *R* indices (all data), $R1 = 0.2821$, $wR2 = 0.0895$.

Crystallographic data (excluding structure factors) for (*Rρ*,*S*)-**2** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 243418. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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References

1. See, for example, (a) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169–2178; (b) Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712–4713; (c) Majima, K.; Takita, R.; Okada, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 15837–15845; (d) Matsunaga, S.; Kinoshita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7559–7570; (e) Gnanadesikan, V.; Horiuchi, Y.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7782–7783.
2. See, for example, (a) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850–14851; (b) Mermerian, A.; Fu, G. *J. Am. Chem. Soc.* **2003**, *125*, 4050–4051; (c) Matsumura, S.; Maeda, Y.; Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **2003**, *125*, 8862–8869; (d) Dai, L. X.; Tu, T.; You, S. L.; Deng, W. P.; Hou, X. L. *Acc. Chem. Res.* **2003**, *36*, 659–667, and references cited therein.
3. See, for example, Gibson, S. E.; Ibrahim, H. *Chem. Commun.* **2002**, *21*, 2465–2473, and references cited therein.
4. See, for example, Gibson, S. E.; Knight, J. D. *Org. Biomol. Chem.* **2003**, *1*, 1256–1269, and references cited therein.
5. Cram, D. J.; Allinger, N. L. *J. Am. Chem. Soc.* **1955**, *77*, 6289–6294.
6. See, for example, (a) Hou, X. L.; Wu, X. W.; Dai, L. X.; Cao, X. B.; Sun, J.; Cram, D. J. *Chem. Commun.* **2000**, *19*, 1195–1196; (b) Marchard, A.; Maxwell, A.; Mootoo, B.; Pelter, A.; Reid, A. *Tetrahedron* **2000**, *56*, 7331–7338; (c) Wu, X. W.; Hou, X. L.; Dai, L. X.; Tao, J.; Sun, J. *Tetrahedron: Asymmetry* **2001**, *12*, 529–532; (d) Bolm, C.; Wenz, K.; Raabe, G. *J. Organomet. Chem.* **2002**, *662*, 23–33; (e) Wu, X. W.; Yuan, K.; Sun, W.; Zhang, M. J.; Hou, X. L. *Tetrahedron: Asymmetry* **2003**, *14*, 107–112.
7. (a) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *125*, 6207–6208; (b) Pye, P. J.; Rossen, K. *Tetrahedron: Asymmetry* **1998**, *9*, 539–541.

8. When, P. M.; Bois, J. D. *J. Am. Chem. Soc.* **2002**, *124*, 12950–12951.
9. Pye, P. J.; Rossen, K.; Reamer, R. A.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 4441–4444.
10. Burk, M. J.; Hems, W.; Herzberg, D.; Malan, C.; Zanotti-Gerosa, A. *Org. Lett.* **2000**, *2*, 4173–4176.
11. Rossen, K.; Pye, P. J.; Maliakal, A.; Volante, R. P. *J. Org. Chem.* **1997**, *62*, 6462–6463.
12. (a) Yang, D.; Yip, Y. C.; Tang, M. W.; Wong, M. K.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1996**, *118*, 491–492; (b) Yang, D.; Wang, X. C.; Wong, M. K.; Yip, Y. C.; Tang, Ma. W. *J. Am. Chem. Soc.* **1996**, *118*, 11311–11312; (c) Yang, D.; Wong, M. K.; Yip, Y. C.; Wang, X. C.; Tang, M. W.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1998**, *120*, 5943–5952.
13. Antonov, D. Y.; Sergeeva, E. V.; Vorontsov, E. V.; Rezenberg, V. I. *Russ. Chem. Bull.* **1997**, *46*, 1897–1900.
14. Kokotos, G.; Noula, C. *J. Org. Chem.* **1996**, *61*, 6994–6996.
15. See, for example, (a) Itoh, T.; Chika, J. I. *J. Org. Chem.* **1995**, *60*, 4968–4969; (b) Seki, M.; Yamada, S. I.; Kuroda, T.; Imashiro, R.; Shimizu, T. *Synthesis* **2000**, *12*, 1677–1680.
16. (a) Falk, H.; Reich-Rohrwig, P.; Schlögl, K. *Tetrahedron* **1970**, *26*, 511–527; (b) Rozenberg, V.; Dubrovina, N.; Sergeeva, E.; Antonov, D.; Belokon, Y. *Tetrahedron: Asymmetry* **1998**, *9*, 653–656.
17. Popova, E. L.; Rozenberg, V. I.; Starikova, Z. A.; Keukerbaumann, S.; Kitzerow, H. S.; Hopf, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3411–3414.
18. Jiang, B.; Zhao, X. L. *Tetrahedron: Asymmetry* **2004**, *15*, 1141–1143.
19. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: Oxford, 1988.