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Enantiomerically enriched cryptone by lipase catalysed kinetic resolution

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Abstract—Thiophenol was added to racemic cryptone (4-isopropyl-2-cyclohexene-1-one) and the resulting 1,4-addition products, *cis*- and *trans*-4-isopropyl-3-(phenylsulfanyl)cyclohexanone were separated and the latter reduced to *rac*-1,3-*cis*-1,4-*trans*-4-isopropyl-3-(phenylsulfanyl)cyclohexanol, which was subjected to lipase catalysed resolution by acylation catalysed by CAL-B (*Candida antarctica* lipase B). The alcohol enantiomers obtained were oxidised. The remaining alcohol was separated from the produced acetate, which was hydrolysed to the alcohol. The initial products, probably sulfoxidoketones spontaneously decomposed to furnish enantiomerically enriched (*R*)- and (*S*)-cryptone with up to 76% and 98% ee, respectively.

1. Introduction

The enantiomers of the nor-monoterpene cryptone (4-isopropyl-2-cyclohexene-1-one, **1**, Scheme 1) are of interest as starting materials for the synthesis of natural products.[1–3] Several synthetic approaches to enantiomerically enriched cryptone have been described.[1,4–8] The resulting enantiomeric excesses (ees) range from 66% to 95%.

In the last 10 years, some marine natural products with a cadinene-type skeleton have attracted considerable interest among biochemists as well as synthetic chemists due to their antifouling properties.[9,10] Enantiomerically pure (*R*)- and (*S*)-cryptone (*R*)- and (*S*)-**1** could be suitable starting materials for the enantioselective synthesis of such biologically active compounds. Racemic cryptone **1** can easily be obtained from the readily available β-pinene[11] (regardless of the initial enantiomeric purity of the β-pinene, the cryptone product is virtually racemic). Lipase catalysed acylation reactions were looked at as a means to resolve *rac*-cryptone **1** into (*R*)- and (*S*)-**1**.

Highly enantioselective transesterification reactions of enol esters with secondary alcohols can be catalysed by lipases.[12] Regio- and stereoselective reduction of *rac*-cryptone **1** could furnish a secondary allylic alcohol, which when subjected to lipase-catalysed resolution and subsequent oxidation to the ketone would potentially provide both enantiomers of cryptone **1** in high ee. For a secondary alcohol to be resolved by a lipase it is important that the lipase can differentiate between the two enantiomers. The hydroxylated carbon must, in addition to the hydroxyl group, be linked to two groups which differ considerably in size.[13] Simple racemic cyclo-2-hexenols are notoriously difficult to resolve by lipase catalysed acylation.[14,15] Similar resolutions of *rac*-2- and/or 3-substituted cyclo-2-hexene-1-ols or similarly substituted cyclohexanols are, however, usually successful.[14–16] As reported by Morgan et al.[17] it is possible to temporarily attach a large and removable group by 1,4-addition to a cyclohexenone and in this way create the size difference required for a successful resolution of the corresponding alcohol.[17] Inspired by this work, we hoped that thiophenol could be added diastereoselectively to *rac*-cryptone **1** and that the product would after reduction provide one diastereomer of alcohol **3** which would be resolvable by lipase catalysed acylation (steps a and b in Scheme 1). Oxidation of the enantiopure alcohol and oxidative elimination of thiophenol would then provide the desired enantiomer of cryptone [(*R*)- or (*S*)-**1**].

2. Results and discussion

Bakuzis et al.[18] have shown that Michael addition of thiophenol to α,β-unsaturated cyclic ketones can be

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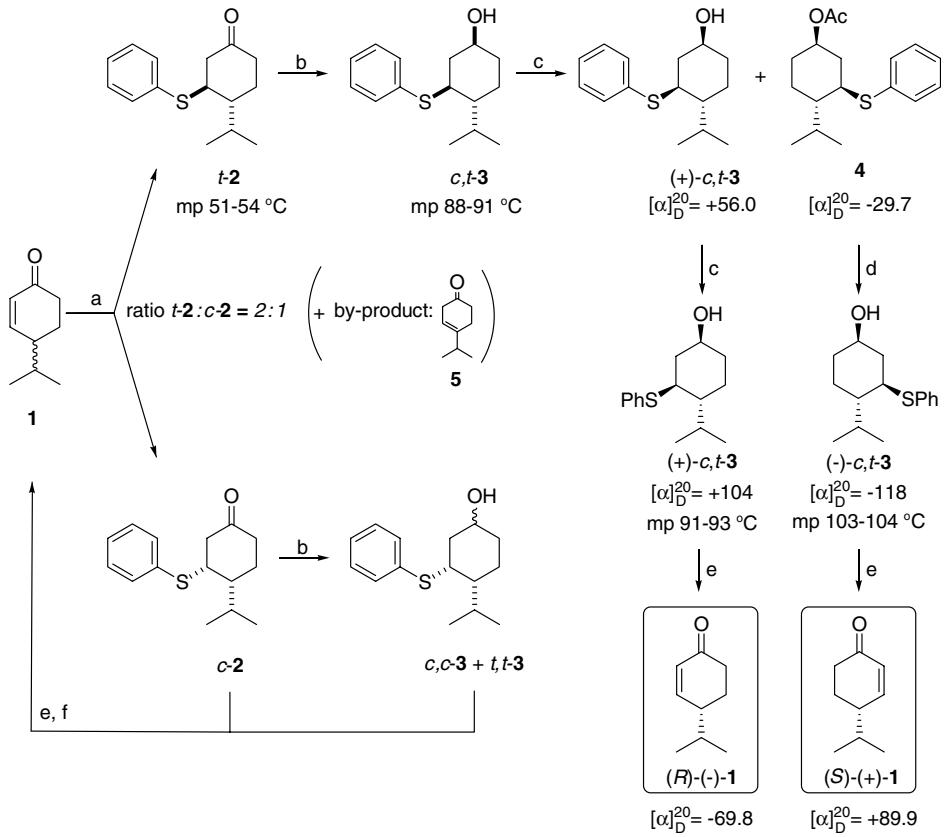

Scheme 1. Reagents and conditions: (a) thiophenol (1 equiv), Et_3N (0.05 equiv) in dichloromethane 0 °C, 36% (isolated yield of *t*-**2** calculated from **1**); (b) $NaBH_4$ (1 equiv), $CeCl_3{\cdot}7H_2O$ (1 equiv) in methanol 66% (isolated yield of *c*,*t*-**3** calculated from *t*-**2**); (c) CAL-B, vinylacetate (5 equiv) in diisopropylether; (d) 1 M NaOH in methanol, reflux (82% from **4**); (e) (i) Jones reagent in acetone, (ii) $NaHCO_3$ (aq) (86% yield from **3**); (f) Et_3N in THF/H_2O.

performed successfully. We found that the addition of thiophenol to cryptone **1** (step a in Scheme 1) was accompanied by the formation of substantial amounts of a side-product, 4-isopropyl-3-cyclohexenone **5**. By using a catalytic amount of base and lowering the temperature to −15 to 0 °C, we suppressed the formation of **5**. Thus, two diastereomeric products were formed in a 2:1 ratio. Relative to the isopropyl group, the major product, *t*-**2**, had the phenylsulfanyl group *trans*, whereas the minor one, *c*-**2**, was *cis*. The diastereomeric products *t*-**2** and *c*-**2** were separated by flash column chromatography. The low energy conformations of *t*-**2** and *c*-**2** are shown in Figure 1 (calculated by using Chem3D®). The relative configuration of the proposed major product *t*-**2** was confirmed by its ^1H NMR and H,H-COSY spectrum. The proton at carbon 3 coupled to three protons, two at carbon 2 and one at carbon 4 with one small (4.6 Hz) and two large coupling constants. The latter were large enough to indicate an axial–axial–axial relationship between the protons at carbons 2, 3 and 4 and were equal in size (≈9.5 Hz). Thus, the signal for the proton at carbon 3 in *t*-**2** appeared as a doublet of triplets thus confirming the proposed structure (Fig. 1). On the other hand, in the ^1H NMR spectrum of *c*-**2**, the signal for the proton at carbon 3 was a non-resolved multiplet due to three smaller coupling constants compared to those observed in the spectrum of the *trans*-product *t*-**2**.

When subjected to Luche reduction ($NaBH_4$, $CeCl_3$), cyclic ketones can be stereoselectively reduced.[19,20] Thus, such a reduction of the major PhSH addition product *t*-**2** gave a single crystalline product, the 1,3-*cis*-1,4-*trans*-cyclohexanol *c*,*t*-**3**. In contrast, the minor Michael addition product *c*-**2** furnished two diastereomeric cyclohexanols, the 1,3-*cis*-1,4-*cis*- and the 1,3-*trans*-1,4-*trans* ones, *c*,*c*-**3** and *t*,*t*-**3**, respectively (in a 1:1 ratio). We were unable to separate the two products *c*,*c*-**3** and *t*,*t*-**3**. As a result, the lipase catalysed resolution of the cyclohexanol *c*,*t*-**3** only was studied. The relative configuration of *c*,*t*-**3** was determined by ^1H NMR and H,H-COSY. The signal from the axial proton at carbon 2 (H_a^2) was an apparent quartet due to three couplings of similar size, two axial and one vicinal ($J_{H_a^2-H_a^3} \approx J_{H_a^1-H_a^2} \approx J_{H_a^2-H_e^2} \approx$ 11.2–12 Hz). The signal for H_a^3 in *c*,*t*-**3** appeared as in *t*-**2** as a doublet of triplets, confirming that there was still an axial relationship between the protons at the 2-, 3- and 4-positions. If the coupling constants $J_{H_a^1-H_a^2}$ had been smaller and the signal for the axial proton 2 would have appeared as a doublet of triplets, the diastereomeric alcohol could have been the product. The large coupling between the protons at carbons 1 and 2 and the apparent quartet for H_a^2 shows that H^1

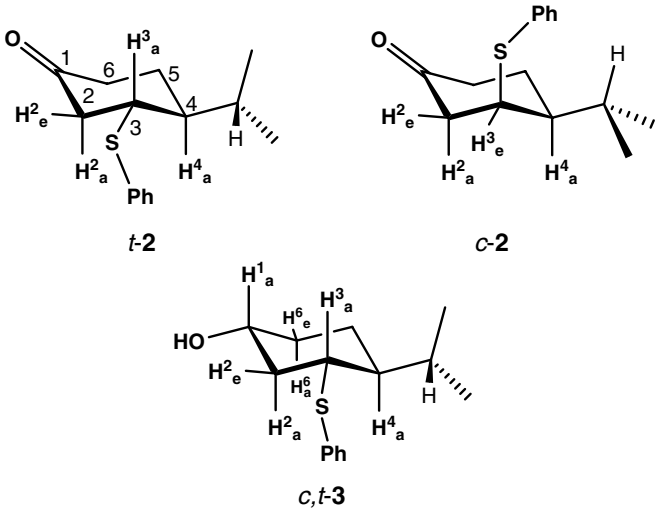

Figure 1. Relative stereochemistry of the products *t*-**2**, *c*-**2** and *c*,*t*-**3** determined by NMR.

has to be axial, thus proving the proposed structure of *c*,*t*-**3**.

With the masked cryptone in hand as its derivative *c*,*t*-**3**, we turned our attention to the possibility of resolving it using a lipase catalysed acylation with vinyl acetate. Three different lipases were tested: CAL-B, Lipase PS and PPL. Only CAL-B catalysed the acylation of the alcohol. Hence, immobilised CAL-B was added to a solution of vinyl acetate and the cyclohexanol *c*,*t*-**3** and the conversion was monitored by GC. When it reached 40%, the reaction was stopped by filtration, which removed the immobilised CAL-B. Ester **4** and alcohol (+)-*c*,*t*-**3** were separated by chromatography. In order to increase the enantiomeric purity of the remaining substrate, alcohol (+)-*c*,*t*-**3**, was treated a second time with vinyl acetate and CAL-B. The reaction was very slow and after 25% conversion, it seemed to stop spontaneously, indicating that most of the (−)-*c*,*t*-**3** was consumed. The remaining substrate after the second esterification, alcohol (+)-*c*,*t*-**3** was purified by chromatography. Although the conversion in the CAL-B catalysed resolution was determined relatively easy by GC, we were unable to obtain good enantioseparations for either the produced acetates or the remaining alcohols. Thus we were unable to calculate any *E*-values.

Acetate, **4**, that is the product from the first lipase catalysed esterification, was then hydrolysed by treatment with sodium hydroxide in refluxing methanol (step d in Scheme 1).

Jones oxidation of each of the enantiomers of alcohol *c*,*t*-**3** gave the desired enantiomers of cryptone. Under the conditions used, the sulfide was presumably oxidised to a sulfoxide, which spontaneously underwent elimination to give α,β-unsaturated ketone **1** (step e in Scheme 1). As depicted in Scheme 1, racemic cryptone could also be recovered from the products *c*-**2**, *c*,*c*-**3** and *t*,*t*-**3** by Jones oxidation. In this case, however, elimination was not complete. According to Evarts et al.,[8] elimination of phenylsulfinic acid is facilitated by base in combination with a polar solvent. Thus, in order to obtain a reasonable yield of recycled cryptone, we had to use Et_3N in a solvent mixture of water and THF to achieve complete elimination of the sulfinate from the mixture after oxidation of *c*-**2,** *c*,*c*-**3** and *t*,*t*-**3**. It is unclear why the oxidative elimination of the sulfide moiety should be more difficult from *c*-**2** than from *t*-**2.**

Despite several efforts to improve the conditions for the GC-analysis (chiral column, β-dex120) of racemic cryptone **1** (prepared according to Queiroga et al.[11]), such analysis gave, at best, two overlapping peaks without base-line separation. Consequently, each of the enantiomerically enriched cryptone products gave rise to what appeared to be a single peak. Thus, we were unable to use GC to accurately determine the enantiomeric purity of the samples of (*S*)-(+)- or (*R*)-(−)-cryptone we had prepared. Although optical rotation is not a very reliable way to assess ee-values, we ultimately had to use this method. Thus, optical rotation measurements were conducted using ethanol as solvent. Although a higher rotation has been found for (−)-cryptone (Galloway et al.[21]), the correct rotation of pure (−)-**1** seems to have been reliably determined by Gillespie et al.[22] to be $[\alpha]_D^{20} = -91.7$ (*c* 2.2 EtOH). From the rotations we obtained the enantiomeric purity which was determined to be 76% ee and 98% ee for (*R*)-(−)-**1** and (*S*)-(+)-**1**, respectively.

3. Conclusion

We have shown that it is possible to separate the enantiomers of racemic cryptone in a five/six-step procedure. The procedure involves a lipase catalysed resolution of 4-isopropyl-3-thiophenylcyclohexan-1-ol formed from racemic cryptone. Enantiomerically enriched cryptone is easily obtained from the resolved alcohols by simple oxidation using Jones reagent.

4. Experimental

4.1. General

Except for the resolution reactions, all reactions carried out in dry solvents were performed under an argon atmosphere in dry glassware.

Flash column chromatography was performed on silica gel (Merck 60, 0.040–0.063 mm) using a gradient system of pentane and ether as eluent according to the following: Diethyl ether vol% in pentane: 0, 1.25, 2.5, 5, 10, 20, 40, 80 and 100 (the volume of each mixture was the same as the column void volume).

All chemicals and enzymes were used as received from suppliers unless otherwise stated. Dichloromethane and diisopropylether was dried over 4 Å molecular sieves prior to use.

CAL-B: (*Candida antarctica* lipase B) Novozym 435, Novonordisk Batch no LC2 00009;
PPL: (crude from porcine pancreas) Sigma, [9001-62-1], Lot 108H1379;
Lipase PS: (*Pseudomonas cepacia*) Amano PS, Amano Enzyme Inc.

Gas chromatography: Glass capillary columns, either a Varian 3400 (Column: EC-1, 30 m, 0.32 mm i.d., $d_f = 0.25$ μm, carrier gas N_2, 13 psi, air + N_2 243 mL/min, split 1:50, program: 50 °C, 3 min, 10 °C/min to 250 °C) or a Varian 3300 (Column: β-dex 120, 30 m, 0.25 mm i.d., $d_f = 0.25$ μm, carrier gas He, Air + He 292 mL/min, split 1:6, program 100 °C, 0 min, 0.5 °C/min to 180 °C).

NMR spectra were recorded on a Bruker Avance 500 (500 MHz ^{1}H, 125.7 MHz ^{13}C) using $CDCl_3$ as solvent and TMS as internal reference. Optical rotation was determined using a Perkin–Elmer model 341 with a 1 cm cell. Elemental analyses were performed by Mikrokemi AB (www.mikrokemi.se).

4.2. Response factors

Alcohol *c*,*t*-**3** (3.47 mg, $1.39 * 10^{-5}$ mol) and the corresponding acetate **4** (3.11 mg, $1.06 * 10^{-5}$ mol) were dissolved in diethyl ether. Three injections were performed on GC to determine the integrated areas. $Rf_{c,t\text{-}3}$ was set to 1 and a mean value of $Rf_{\text{acetate 4}}$ was determined to be 0.71 (mol/mol).

4.3. Experimental procedures

4.3.1. 4-Isopropyl-3-(phenylsulfanyl)cyclohexanone 2. Racemic cryptone (*rac*-**1**, 0.997 g 7.2 mmol) and thiophenol (0.74 mL, 7.2 mmol) were dissolved in dichloromethane (7 mL) in a 25 mL round-bottomed flask. After cooling to −15 °C in an ice/acetone bath, triethylamine (0.05 mL, 0.36 mmol) was added and the reaction mixture stirred at −15 °C. After 1 h, the temperature was −8 °C. Saturated $NaHCO_3$ (10 mL, aq) was added and the mixture stirred for 5 min and transferred to a separatory funnel. After the addition of aqueous NaOH (1 M, 10 mL) and diethyl ether (30 mL), the phases were shaken and separated, and the organic phase was washed with water (2 × 10 mL) followed by 10 mL brine. The combined water phases were extracted with Et_2O (10 mL). The combined organic phases were dried over Na_2SO_4 overnight. Filtration, concentration, purification by flash chromatography and recrystallization in pentane gave crystalline *t*-**2** (0.915 g, 51% yield). As the product tended to decompose to cryptone and thiophenol on silica gel, the time spent on the column was minimised. Racemic *t*-**2**: Anal. Calcd for $C_{15}H_{20}OS$: C, 72.53; H, 8.12. Found: C, 72.8; H, 8.3. mp 51–54 °C. ^{1}H NMR: δ 0.88 (3H, d, $J = 6.8$ Hz, CH_3), 1.04 (3H, d, $J = 6.9$ Hz, CH_3), 1.54 (1H, m), 1.66 (1H, m), 2.08 (1H, m), 2.25–2.33 (1H, dddd, $J = 1.1$, 5.7, 11.6, 16.2 Hz), 2.35–2.43 (2H, m), 2.43–2.51 (1H, m), 2.66 (1H, ddd, $J = 1.9$, 4.6, 14.8 Hz CH_{eq}H), 3.31 (1H, ddd, $J = 4.6$, ~9.5, ~9.5 Hz CH), 7.27–7.33 (3H, m, Ph), 7.42 (2H, m, Ph). ^{13}C NMR: δ 16.47 (CH_3), 21.21 (CH_3), 23.53 (CH_2), 27.71 (CH), 39.84 (CH_2), 45.44 (CH), 47.05 (CH_2), 49.02 (CH), 127.94 (CH), 129.09 (2C, CH), 132.89 (C), 133.82 (2C, CH), 209.45 (C=O). Cryptone and racemic *c*-**2** (in total 0.642 g) were also recovered. Further purification by flash chromatography provided pure *c*-**2**: ^{1}H NMR: δ 1.04 (3H, d, $J = 6.6$ Hz, CH_3), 1.13 (3H, d, $J = 6.5$ Hz, CH_3), 1.70–1.92 (2H, m), 2.17 (1H, m), 2.26–2.33 (2H, m), 2.47–2.58 (3H, m), 3.81 (1H, m), 7.25–7.32 (3H, m), 7.43 (2H, m). ^{13}C NMR: δ 20.82 (CH_3), 21.36 (CH_3), 26.19 (CH_2), 29.83 (CH), 40.76 (CH_2), 46.25 (CH_2), 47.37 (CH), 50.25 (CH), 127.67 (CH), 129.14 (2C, CH), 133.36 (C), 133.70 (2C, CH), 209.21 (C=O).

4.3.2. 4-Isopropyl-3-(phenylsulfanyl)cyclohexanol *c*,*t*-3. To a methanol solution (10 mL) of $NaBH_4$ (0.152 g, 4.0 mmol) and $CeCl_3 \cdot 7H_2O$ (1.40 g 3.8 mmol) was added *t*-**2** (0.915 g, 3.7 mmol). After stirring for 1 h, hydrochloric acid (~1 mL, 0.1 M, aq) was added to quench the reaction. After mixing with brine (20 mL) and diethyl ether (20 mL), the phases were separated and the water phase extracted with Et_2O (2 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography to give colourless crystalline solid *c*,*t*-**3** (0.611 g, 66%, >95% by GC). Anal. Calcd for $C_{15}H_{22}OS$: C, 71.95; H, 8.86. Found: C, 71.9; H, 9.0. Mp 88–91 °C. ^{1}H NMR: δ 0.80 (3H, d, $J = 6.8$ CH_3), 0.96 (3H, d, $J = 7.0$ CH_3), 1.03–1.30 (3H, m), 1.39 (1H, ddd (app q), $J \approx 11.2$, 12, 12), 1.45 (1H, s, O*H*), 1.78 (1H, m), 2.0 (1H, m), 2.28 (1H, m), 2.52 (1H, m), 2.88 (1H, ddd, $J = 3.7$, 11.5, 11.5 Hz, C*H*SPh), 3.5 (1H, m, C*H*OH) 7.25–7.32 (3H, m), 7.42 (2H, m). ^{13}C NMR: δ 15.23 (CH_3), 21.36 (CH_3), 22.22 (CH_2), 27.20 (CH), 34.89 (CH_2), 43.60 (CH_2), 46.25 (CH), 48.35 (CH), 70.19 (CH), 127.34 (CH), 128.86 (2C, CH), 133.82 (2C, CH), 134.03 (C).

4.3.3. (1*R*,3*R*,4*S*)-4-Isopropyl-3-(phenylsulfanyl)cyclohexyl acetate 4. Vinyl acetate (0.370 mL, 4 mmol) was added to a solution of *c*,*t*-**3** (0.206 g, 0.8 mmol) in diisopropylether (10 mL) in a 16 mL vial. The reaction

was started by addition of CAL-B (9.7 mg) and stirred by putting the vial on a roller board. The conversion was followed by GC analysis of samples withdrawn every hour. Response factors (see 4.2) had to be used in order to estimate the conversion of *c*,*t*-**3** to **4**. After 2 h (~40% conversion), the lipase was removed by filtration through a glass filter funnel. The filtrate was concentrated and purified by flash chromatography to give ester **4** as a colourless oil (83 mg, 34.5%, 99.6% pure by GC). $[\alpha]_D^{20} = -29.7$ (*c* 2.19, EtOH). ^{1}H NMR: δ 0.79 (3H, d, $J = 6.9$ Hz, CH_3), 0.95 (3H, d, $J = 7.0$ Hz, CH_3), 1.1–1.3 (3H, m), 1.49 (1H, (app q) ddd $J \approx 11.9$, 11.9, 11.9), 1.79 (1H, m), 2.0 (4H, m), 2.28 (1H, m), 2.54 (1H, m), 2.93 (1H, (app dt) ddd, $J = 3.8$, ~11.7, ~11.8), 4.6 (1H, m), 7.27 (3H, m), 7.41 (2H, m). ^{13}C NMR: δ 15.12 (CH_3), 21.30 (CH_3), 21.31 (CH_3), 22.12 (CH_2), 27.18 (CH), 31.21 (CH_2), 39.81 (CH_2), 46.23 (CH), 48.05 (CH), 72.01 (CH), 127.29 (CH), 128.89 (2C, CH), 133.16 (2C, CH), 133.96 (C), 170.38 (C=O). The residual alcohol substrate (+)-*c*,*t*-**3** from the resolution above (113 mg), was subjected to a second resolution step, see below.

4.3.4. (1*R*,3*R*,4*S*)-4-Isopropyl-3-(phenylsulfanyl)cyclohexanol (−)-*c*,*t*-3. Acetate **4** (~83 mg) was refluxed for 1 h in methanol (5 mL) containing aqueous NaOH (1 M, 1 mL). After mixing with water (10 mL) and Et_2O (10 mL), the phases were separated. The organic phase was then washed with brine (10 mL). The combined aqueous phase was extracted with Et_2O (5 mL). The combined organic phase was dried over Na_2SO_4. Filtration and concentration gave colourless crystals of (−)-*c*,*t*-**3** (58 mg, 82%, 99.4% (pure by GC), $[\alpha]_D^{20} = -118$ (*c* 1.94, EtOH), mp 103.3–104.2 °C)

4.3.5. (1*S*,3*S*,4*R*)-4-Isopropyl-3-(phenylsulfanyl)cyclohexanol (+)-*c*,*t*-3. The residual alcohol substrate (+)-*c*,*t*-**3** from the resolution above (113 mg), 87.9% (pure by GC), $[\alpha]_D^{20} = +56.0$ (*c* 2.11, EtOH), was subjected to a second resolution step with CAL-B and vinyl acetate in an effort to improve both the enantiomeric and chemical purity. After 25% conversion (7 h) no further reaction took place and the acetate was removed by flash chromatography to furnish crystalline (+)-*c*,*t*-**3**, 63 mg, 56%, 92.7% (pure by GC), $[\alpha]_D^{20} = +104$ (*c* 1.95 g/100 mL, EtOH), mp 91–93 °C.

4.3.6. Formation of cryptone 1 from *c*,*t*-3 general procedure. Jones reagent [267 g CrO_3 dissolved in a mixture of concd. H_2SO_4 (230 mL) and H_2O (400 mL), diluted to 1 L with water] was added dropwise to a solution of *c*,*t*-**3** (47 mg, 0.19 mmol) in acetone (5 mL). After the addition of 15 drops, the solution remained orange and the reaction mixture was stirred for 10 min. Methanol (0.5 mL) was added to quench the residual Jones reagent. The mixture was diluted with water (10 mL) and Et_2O (20 mL). The water phase was then extracted with Et_2O (2 × 5 mL). The combined organic phases were washed with saturated Na_2CO_3 (5 mL) and brine (5 mL) and dried over Na_2SO_4. Filtration followed by concentration of the filtrate and flash chromatography provided cryptone **1** (22.4 mg, 86%). Using the same procedure (−)-*c*,*t*-**3** was converted to (+)-cryptone [(+)-(*R*)-**1**]. $[\alpha]_D^{20} = +89.9$ (*c* 2.27, EtOH). Similarly (+)-*c*,*t*-**3** was converted to (−)-cryptone [(−)-(*S*)-**1**]. $[\alpha]_D^{20} = -69.7$ (*c* 1.85, EtOH) {lit.[22]: $[\alpha]_D^{20} = -91.7$ (*c* 2.2, EtOH)}. The spectroscopic data were identical to that previously published.

4.3.7. Recycling of cryptone from *rac*-1 from *c*-2, *c*,*c*- and *t*,*t*-3. Using Jones reagent as described under 4.3.6, mixtures of *c*-**2**, *c*,*c*-**3** and *t*,*t*-**3** were oxidised. However in this case, cryptone **1** did not form spontaneously. Therefore, the reaction product was dissolved in THF (100 mL) and water (40 mL) and triethylamine (1 mL) was added. The mixture was left stirring overnight. Et_2O (50 mL) was added and the phases separated. The water phase was extracted with Et_2O (30 mL). The combined organic phase was washed with brine (20 mL) and dried over $MgSO_4$, filtered and concentrated to furnish racemic cryptone *rac*-**1**.

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