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Utilization of whole cell mediated deracemization in a chemoenzymatic synthesis of enantiomerically enriched polycyclic chromeno[4,3-*b*] pyrrolidines†

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Various aryl and alkyl substituted optically pure propargyl alcohols were obtained with excellent ee (up to >99%) and isolated yields (up to 87%) by deracemization using whole cells of *Candida parapsilosis* ATCC 7330. The whole cells show substrate specificity towards alkyl substituted propargyl alcohols and a switch in the enantioselectivity has been observed from '*R*' to '*S*' upon increasing the chain length. For the first time, enantiopure (*R*)-4-(3-hydroxybut-1-ynyl)benzonitrile, (*R*)-4-(biphenyl-4-yl)but-3-yn-2-ol, (*S*)-ethyl 3-hydroxy-5-phenylpent-4-ynoate and (*S*)-4-phenylbut-3-yne-1,2-diol were obtained using this strategy. Optically pure propargyl alcohol thus obtained was used as a chiral starting material in the synthesis of enantiomerically enriched poly-substituted pyrrolidines and a pyrrole derivative successfully demonstrating a chemoenzymatic route.

Introduction

Pyrrolidines and their structural analogues have a significant role in heterocyclic and natural product chemistry due to their wide range of biological activities.[1] Compounds containing the hexahydrochromeno[4,3-*b*] pyrrolidine skeleton (Fig. 1, **I**) are reported as acetylcholinesterase inhibitors[2] where they exhibit non-competitive antagonism on the muscular nicotinic receptor and structurally resemble rivastigmine analogues.[3] It is interesting to know that natural compounds such as the sceletium alkaloid A-4 and martinelline (Fig. 1, **II** & **III**) contain a similar five membered heterocyclic ring system[4] and they were the first naturally occurring non-peptide bradykinin B1 and B2 receptor antagonists.[5] Given the importance of such molecules, synthesis of these diversely substituted pyrrole/pyrrolidine derivatives is an important research area in synthetic and medicinal chemistry.

[3 + 2] Dipolar cycloaddition is a powerful tool for the synthesis of pyrrolidine derivatives.[6,7] Furthermore, enantiopure pyrrolidine synthesis is well established[8] and includes asymmetric 1,3-dipolar cycloaddition with chiral Lewis acids, metallo- and organocatalysts.[9,10] This study presents a chemoenzymatic synthesis of enantiomerically enriched pyrrolidines and a pyrrole *via* a chiral intermediate, *i.e.* enantiopure propargyl alcohol obtained through whole cell mediated deracemization followed by [3 + 2] dipolar cycloaddition of *O*-propargylic salicylaldehyde with *N*-methyl amino esters (Scheme 1).

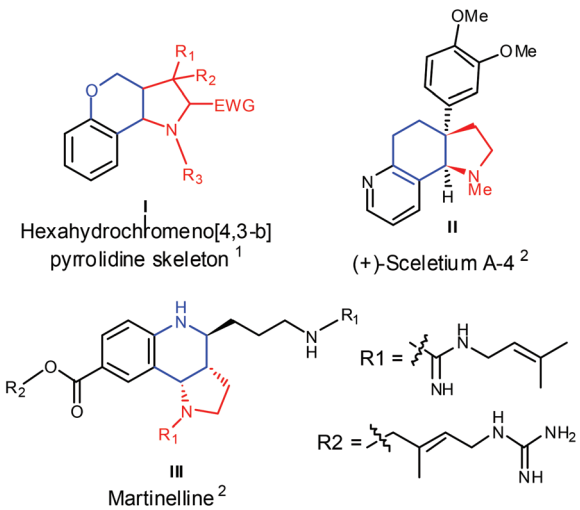

Fig. 1 Biologically important pyrrolidine derivatives.

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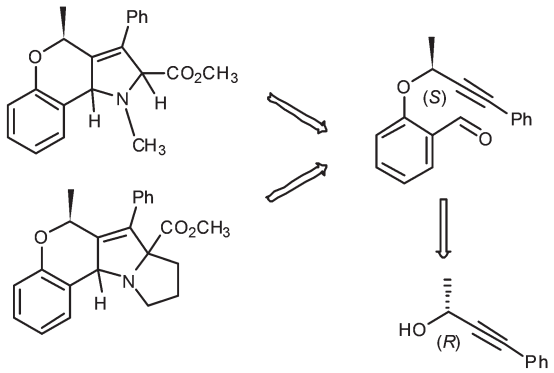
†Electronic supplementary information (ESI) available: General experimental procedure, spectral data, copies of ^{1}H NMR and ^{13}C NMR spectra, HPLC chromatograms and XRD data. CCDC 982489 and 982490. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob00615a



Scheme 1 Synthetic route to synthesize pyrrolidine derivatives.

acetylenic ketones[14–16] and enantioselective alkyne additions to both aliphatic and aromatic aldehydes[17–21] are the available chemical methods. Biocatalytic preparation of enantiopure propargyl alcohols mainly involves kinetic resolution,[22–24] asymmetric reduction[25] and deracemization.[26–28] Among the available strategies deracemization of racemates is an efficient methodology to produce a single enantiomer in 100% theoretical yield unlike resolution. In particular whole cell mediated deracemization has the advantage of eliminating the addition of cofactors especially when stereoinversion of one enantiomer to the other involves oxidation followed by reduction. Reports on biocatalytic deracemization of propargyl alcohol *via* stereoinversion are scarce in the literature. Ogawa *et al.* reported the stereoinversion of *rac*-3-pentyn-2-ol to produce both (*R*) and (*S*)-3-pentyn-2-ol using wet cells of *Nocardia fusca* and *Nocardia pseudosporangifera* in 24 h and 72 h respectively[29] and the cofactor NADPH and glucose dehydrogenase were added externally to the reaction medium.

As we have reported earlier, *Candida parapsilosis* ATCC 7330 is a versatile biocatalyst for deracemization[30] and oxidative kinetic resolution[31] of secondary alcohols, asymmetric reduction of prochiral ketones and imines,[32] resolution of *N*-acyl amino esters and acylation of anilines.[33] Recently we also reported the biocatalytic deracemization of *sec*-propargyl hydroxy esters using the whole cells of *C. parapsilosis* ATCC 7330 with excellent ee (up to >99%) and isolated yields (up to 81%).[34] Biocatalytic deracemization was shown by us to follow a stereoinversion mechanism in which the biocatalyst is not only enantioselective (*i.e.* preferring one enantiomer over the other), but also stereoselective (*i.e.* inverting one enantiomer, while the other remains intact).[34,35] In the present study, whole cells of *C. parapsilosis* ATCC 7330 were used for deracemization of various *rac*-aryl and alkyl substituted *sec*-propargyl alcohols and the corresponding enantiopure propargyl alcohols were obtained as the product thus increasing the substrate repertoire of this whole cell system. An enantiopure propargyl alcohol thus obtained was further derivatized into polycyclic pyrolidines and a pyrrole derivative (Scheme 1).

Results & discussion

A variety of propargyl alcohols were synthesized and incubated with *C. parapsilosis* ATCC 7330. The product was monitored for deracemization. Preliminary studies which were carried out with the model substrate *rac*-4-phenyl-3-butyne-2-ol **1a** showed low enantioselectivity (6% ee) under the previously optimized conditions[34] (6 mM of substrate in 50 mL water, 3 h, 25 °C). Hence the reaction conditions (time & substrate concentration) were re-optimized to obtain maximum ee and yield. Enantioselectivity improved to 89% by increasing the reaction time from 3 h to 12 h. Furthermore the substrate concentration was optimized in the range of 1 mM to 8 mM and reducing the substrate loading (from 6 mM to 5 mM) led to a significant increase in enantioselectivity giving up to >99%. To study the generality of the biocatalytic deracemization with respect to electronic effects and size of the substrate molecules, various aryl and alkyl substituted propargyl alcohols were used under the newly optimized reaction conditions.

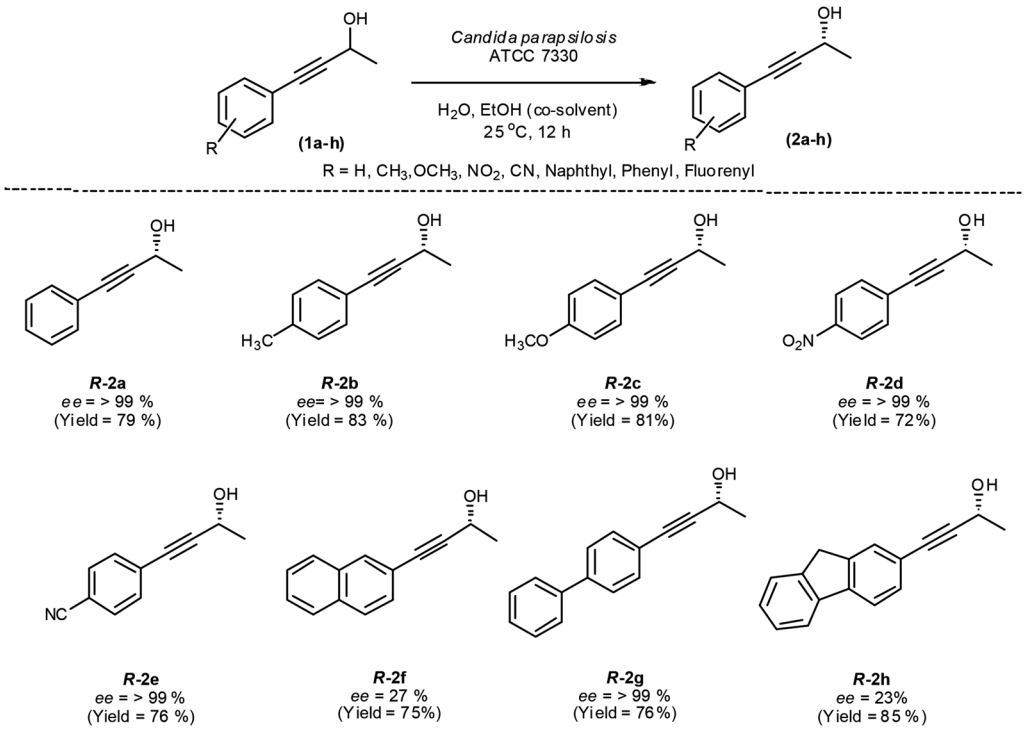
Biocatalytic deracemization of aryl substituted propargyl alcohols

Both electron releasing *p*-CH_3 and *p*-OCH_3 substituted aryl propargyl alcohols gave the corresponding *R*-alcohols with excellent ee (>99%) and yields (83 and 81% respectively) (Scheme 2, **2b** & **2c**). Electron withdrawing *p*-NO_2 and *p*-CN substituted aryl propargyl alcohols on deracemisation showed excellent ee (>99%) and a slight decrease in yields (72 and 76%) compared to the model substrate (Scheme 2, **2d** & **2e**).

Deracemization of *rac*-4-(naphthalen-2-yl)but-3-yn-2-ol showed low ee (27%) possibly due to steric reasons and the bulky nature of the molecule (Scheme 2, **2f**). This was also seen in the case of the deracemization of (*E*)-methyl 2-hydroxy-4-(naphthalen-1-yl)but-3-enoate using the whole cells of *C. parapsilosis* ATCC 7330.[35] However, the substrate 4-(biphenyl-4-yl)but-3-yn-2-ol when subjected to deracemization gave the *R*-enantiomer with excellent ee (>99%) and isolated yield (76%) (Scheme 2, **2g**). The possible reason could be that free rotation is possible between the two phenyl rings unlike the fused naphthyl ring. Another substrate 4-(9*H*-fluoren-2-yl)but-3-yn-2-ol was designed where the free rotation of phenyl rings was blocked by a $-CH_2$ group. As anticipated the whole cells gave low ee (23%) upon deracemization (Scheme 2, **2h**). Notably, the synthesis of enantiomerically pure (*R*)-4-(3-hydroxybut-1-ynyl)benzonitrile **2e** and (*R*)-4-(biphenyl-4-yl)but-3-yn-2-ol **2g** by biocatalytic deracemization is reported here for the first time.

Biocatalytic deracemization of alkyl substituted propargyl alcohols

Various alkyl substituted propargyl alcohols (Scheme 3) were designed to study the effect of chain length towards *C. parapsilosis* ATCC 7330 mediated deracemization. As discussed earlier the model substrate 4-phenyl-3-butyne-2-ol gave *R*-alcohol **2a** (>99% ee) in which the alkyl group is methyl. When methyl was replaced by an ethyl group, *i.e.* 1-phenylpent-1-yn-3-ol, the



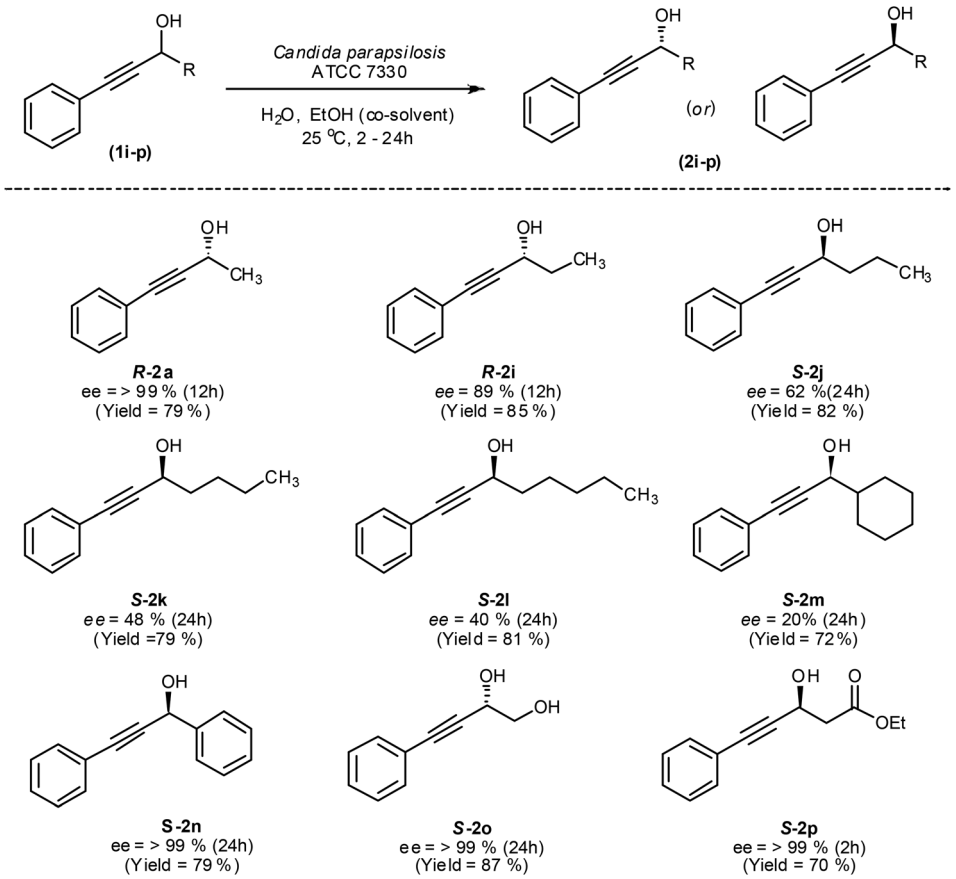
Scheme 2 Deracemization of aryl substituted propargyl alcohols. Enantiomeric excess was determined by HPLC using chiral columns & isolated yield is given in parentheses. Absolute configuration was determined by comparison of specific rotation and HPLC elution profile with the literature.

corresponding *R*-alcohol **2i** was obtained with a slight decrease in ee (89% ee and 85% yield).

On increasing the chain length from propyl to pentyl, the corresponding *S*-alcohols **2j–2l** were obtained with <10% ee for all substrates in 12 h and ee for these substrates were further increased (62%, 48% & 40% ee respectively) by prolonging the reaction time to 24 h. The alkyl chain length induced reversal of stereoselectivity from *R* to *S*. When the alkyl groups are small (methyl and ethyl) *R*-alcohols were obtained with moderate to good ee, whereas a larger alkyl group (more hydrophobic) takes a longer reaction time and gives *S*-alcohols with low ee. Keinan *et al.*[36] and Zhou *et al.*[37] have reported similar inversions of stereoselectivity with respect to chain length within structurally related substrates. A substrate with a cyclohexyl group, *i.e. rac*-1-cyclohexyl-3-phenylprop-2-yn-1-ol, gave the corresponding *S*-alcohol **2m** in 24 h with poor ee (20%), which could be attributed to steric factors. When the cyclohexyl group was replaced by a phenyl group, the *S*-alcohol **2n** was obtained with excellent ee (>99%) and yield (79%) in 24 h. Biocatalytic deracemization was carried out for *rac*-4-phenylbut-3-yne-1,2-diol using whole cells of *C. parapsilosis* ATCC 7330. Asymmetric synthesis to obtain enantiopure 4-phenylbut-3-yne-1,2-diol is rarely reported in the literature using both chemo- and biocatalytic methods. Jeong *et al.* reported osmium catalyzed asymmetric dihydroxylation of enynes using multiple cinchona alkaloid derivatized chiral ligands to obtain (*R*)-4-phenylbut-3-yne-1,2-diol with 73% ee and 91% yield.[38] Microbial hydrolysis of acetylene epoxide using *Aspergillus niger* to obtain the (*R*)-4-phenylbut-3-yne-1,2-diol (40% yield, ee not mentioned) has been reported by Veliyev *et al.*[39] Herein we report for the first time, synthesis of enantiopure (*S*)-4-phenylbut-3-yne-1,2-diol (Scheme 3, **2o**) with excellent ee (>99%) and isolated yield (87%) *via* deracemization using whole cells of *C. parapsilosis* ATCC 7330. For this substrate the stereorecognition (*i.e.* hydride transfer) is similar to the model substrate but absolute configuration is altered as per the CIP rules. Thus the hydride from the cofactor is transferred to the '*Re*' face of carbonyl carbon resulting in the formation of *S*-enantiomer.[30] *rac*-Ethyl 3-hydroxy-5-phenylpent-4-ynoate (with ester functionality) was subjected to biocatalytic deracemization to obtain the optically pure *S*-alcohol **2p**. To the best of our knowledge, synthesis of (*R*)-ethyl 3-hydroxy-5-phenylpent-4-ynoate (92% ee & 95% yield, 48 h) by asymmetric hydrogenations using tethered Ru(II)/TsDPEN-derived catalyst is the only example mentioned in the literature so far.[40] We report here for the first time, synthesis of optically pure (*S*)-ethyl 3-hydroxy-5-phenylpent-4-ynoate **2p** *via* biocatalytic deracemization with excellent ee (>99%) and isolated yield (70%) in much lesser time (2 h) compared to the reported chemical method (48 h).

Chemoenzymatic synthesis of enantiomerically enriched polycyclic pyrrolidine and pyrrole derivatives

Asymmetric synthesis of pyrrolidines by chemical methods using chiral reagents, metallo- and organo catalysts has been well documented.[8] Chemoenzymatic synthesis is an important method to synthesize enantiomerically enriched pyrrolidines, which employs an enzymatic reaction as well as derivatization using chemical reagents.[41–43] For example, Felluga *et al.* syn-



Scheme 3 Deracemization of alkyl substituted propargyl alcohols. Enantiomeric excess was determined by HPLC using chiral columns. Isolated yield is given in parentheses. Absolute configuration was determined by comparison of specific rotation and HPLC elution profile with the literature.

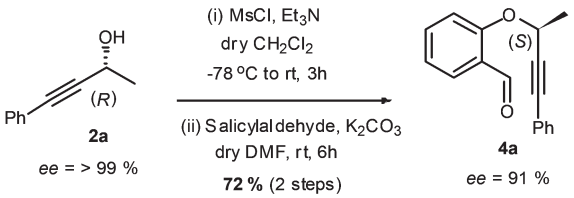
thesized both the enantiomers of the heterocyclic GABA analogue 3-pyrrolidineacetic acid by a chemoenzymatic method using two enantiocomplementary lipases (PLE & PPL) in the desymmetric hydrolysis of 3-nitromethylglutaric acid diethyl ester.[44] Diversity oriented chemoenzymatic synthesis of functionalized pyrrolidines has been reported by Cerulli *et al.* through enzymatic monoacetylation using Amano *PS* lipase followed by a diastereoselective multicomponent reaction.[45] Asymmetric total synthesis of (−)-rosmarinecine was achieved by Nemoto *et al. via* lipase-catalyzed (immobilized CAL-B) domino reactions followed by the intramolecular [3 + 2] dipolar cycloaddition reaction.[46,47] Most of these chemoenzymatic methods to prepare pyrrolidines involve lipase mediated resolution with limitations of producing the desired enantiomer in a maximum theoretical yield of 50% and they require long reaction times.

Herein we describe a chemoenzymatic synthesis of enantiomerically enriched polycyclic pyrrolidines *via* whole cell mediated deracemization of propargyl alcohol (>99% ee, 79% yield) followed by intramolecular [3 + 2] cycloaddition of *O*-propargylic salicylaldehyde. This whole cell mediated deracemization method has the advantages of producing a single enantiomer in maximum theoretical yield of 100% and does not require the external addition of expensive co-factors.

Various achiral versions of intramolecular [3 + 2] cycloaddition of *O*-propargylic salicylaldehyde with amino acid derivatives have been reported using chemical methods.[4,48–50] Bashiardes *et al.* synthesized plurisubstituted pyrroles, pyrrolizines and indolizines using intramolecular [3 + 2] cycloaddition reactions wherein the azomethine ylides were generated in the presence of the achiral/racemic *O*-substituted propargylic moiety.[51,52] In the present study, we report for the first time, the intramolecular cycloaddition reaction of enantiomerically enriched chiral intermediate (*S*-*O*-propargylic salicylaldehyde) to achieve the optically enriched pyrrolidines and a pyrrole derivative *via* a convenient chemoenzymatic approach.

Initially (*R*)-4-phenyl-3-butyne-2-ol **2a** was converted into the corresponding mesylate (**3a**) which undergoes S_N2 substitution with salicylaldehyde in DMF using potassium carbonate as a base to obtain (*S*)-*O*-propargylic salicylaldehyde **4a** in good yield (72%) and ee (91%) (Scheme 4).

Intramolecular cycloaddition of (*S*)-*O*-propargylic salicylaldehyde **4a** carried out by *in situ* generation of azomethine ylides from methyl sarcosinate **5a** gave a mixture of tricyclic pyrrolidines **6a** & **6b** in 70% yield with 1 : 0.8 dr (Scheme 5). Both diastereomers were isolated by column chromatography and fully characterized. The enantiopurity of both the isomers



Scheme 4 Synthesis of (*S*)-*O*-propargylic salicylaldehyde.

was analysed by HPLC using a chiral stationary phase and showed that the enantiopurity (ee 91%) was retained after cyclization (Scheme 5).

When NMR was recorded in deuterated solvents ($CDCl_3$ & CD_3OD), a trace amount of pyrrole derivative, **7a** (10%) was observed due to the aromatization. Bashiardes *et al.* reported a similar type of intermediate formation in the synthesis of tricyclic pyrroles *via* azomethine ylide based cycloaddition reaction.[51]

After complete characterization, both the diastereomers **6a** & **6b** were converted into the pyrrole derivative **7a** using Pd/C in ethyl acetate under reflux conditions in 87% yield and 91% ee. Initially, the feasibility of the reaction was examined using *rac*-4-phenyl-3-butyne-2-ol and the reaction proceeded smoothly to afford the corresponding cyclized products, *rac*-**6a** & **6b** and aromatized pyrrole *rac*-**7a**. The compounds *rac*-**6b** & **7a** were crystallized and subjected for single crystal X-ray crystallographic analysis (Fig. 2 and 3). The relative stereochemistry of **6b** was assigned from these crystal data (Fig. 2) in which the methine protons (H_7 & H_9; H_9 & H_{12}) are *anti* to each other. Likewise, NOE analysis was carried out to assign

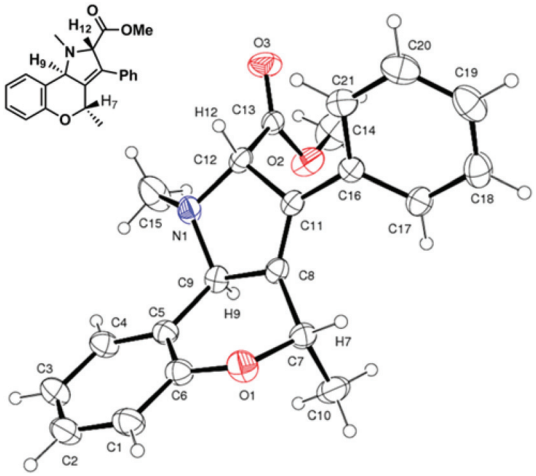
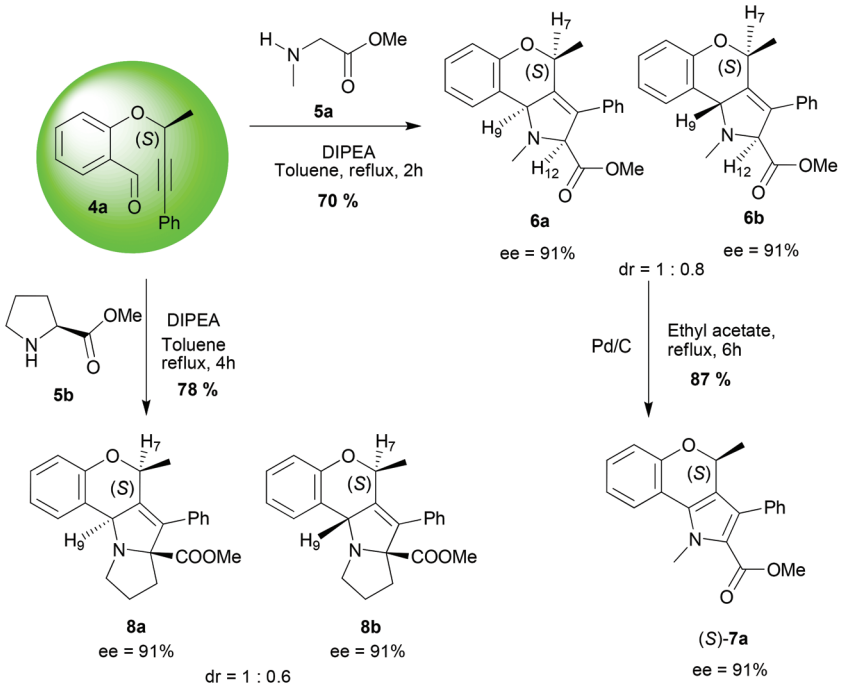


Fig. 2 X-ray crystallographic ORTEP diagram of **6b**.

the relative stereochemistry of **6a** which showed that the methine protons (H_7, H_9 & H_{12}) are *syn* to one another.

In order to obtain a tetracyclic pyrrolidine with a quaternary chiral center, intramolecular cycloaddition of azomethine ylides generated from aldehyde **4a** and methyl prolinate **5b** (Scheme 5) afforded the cycloadducts **8a** & **8b** (inseparable) with good yield (78%) in 1 : 0.6 dr and the enantiomeric excess was found to be 91% for each. The relative stereochemistry of the diastereomers **8a** & **8b** was assigned by NOE experiments. In major diastereomer **8a**, the methine protons H_7 & H_9 are *syn* to each other, whereas in minor diastereomers **8b** the methine protons H_7 & H_9 are *anti* to each other (Scheme 5). Notably, the intramolecular cycloaddition of (*S*)-*O*-propargylic



Scheme 5 Chemoenzymatic synthesis of enantiomerically enriched pyrrolidines and a pyrrole derivative.

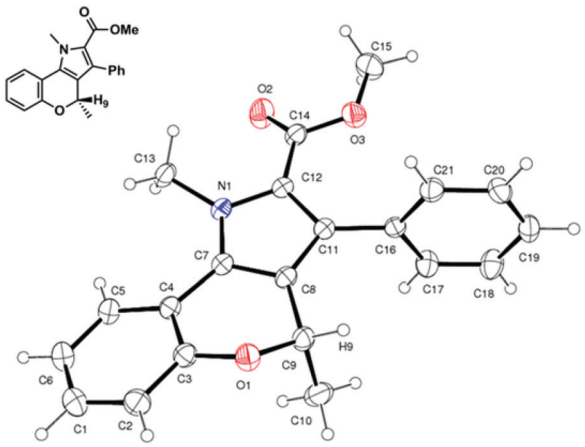


Fig. 3 X-ray crystallographic ORTEP diagram of **7a**.

salicylaldehyde **4a** with both amino esters (**5a** & **5b**) resulted in the formation of the *syn* adduct as a major product.

Conclusions

A broad variety of aryl and alkyl substituted propargyl alcohols were deracemized to the corresponding optically pure alcohols with excellent ee (up to >99%) and isolated yield (up to 87%) using whole cells of *Candida parapsilosis* ATCC 7330. Enantiopure (*R*)-4-(3-hydroxybut-1-ynyl)benzonitrile, (*R*)-4-(biphenyl-4-yl)but-3-yn-2-ol, (*S*)-ethyl 3-hydroxy-5-phenylpent-4-ynoate and (*S*)-4-phenylbut-3-yne-1,2-diol were obtained with excellent enantioselectivity *via* biocatalytic deracemization and are reported here for the first time. The whole cells showed substrate specificity towards alkyl substituted propargyl alcohols, notably the extended alkyl chain length induced reversal of stereoselectivity from '*R*' to '*S*'. Deracemized optically pure (*R*)-4-phenyl-3-butyne-2-ol was used as a chiral starting material for the first time to prepare enantiomerically enriched pyrrolidines and a pyrrole derivative with good ee (91%) *via* a chemoenzymatic approach.

Experimental section

General methods

C. parapsilosis ATCC 7330 was purchased from ATCC Manassas, VA 201018, USA and maintained at 4 °C in yeast malt agar medium that contained 5 g L^{-1} peptic digest of animal tissue, 3 g L^{-1} malt extract, 3 g L^{-1} yeast extract, 10 g L^{-1} dextrose and 20 g L^{-1} agar. The entire chemicals for media preparation were purchased locally. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-400 and Bruker AVANCE III 500 MHz spectrometers. Chemical shifts are expressed in ppm values using TMS as an internal standard. Infrared spectra were recorded on a Shimadzu IR 470 instrument. Mass spectra were recorded on a Q TOF micro mass spectrometer. TLC was carried out on Kieselger 60 F254 aluminium sheets (Merck1.05554). All chemicals used were of analytical grade and distilled prior to use. HPLC analysis was carried out on a Jasco PU-1580 liquid chromatograph with a PDA detector using Chiralcel OJ-H, OD-H, AD-H, OB-H (Daicel, 4.6 × 250 mm) and Lux 5u Amylose-2 (Phenomenex, 4.6 × 250 mm) chiral columns. Hexane–2-propanol was used as the mobile phase. Optical rotations were determined on an AutopalR digital polarimeter. X-ray crystallographic analysis was performed with a Bruker AXS Kappa APEX II single crystal CCD Diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) at room temperature.

Growth conditions for *C. parapsilosis* ATCC 7330[53]

C. parapsilosis ATCC 7330 was grown in yeast malt broth medium (50 mL) in 250 mL Erlenmeyer flasks incubated at 25 °C, 200 rpm. The cells were harvested by centrifuging the 14 h culture broth at 10 000 rpm for 10 min at 4 °C and subsequent washing with distilled water. The process was repeated twice and the wet cells were used for biotransformation.

Typical procedure for deracemization of *rac*-propargyl alcohols using the whole cells of *C. parapsilosis* ATCC 7330[34,54]

The substrate *rac*-4-phenyl-3-butyne-2-ol (5 mM) dissolved in ethanol (1 mL) was added into a Erlenmeyer flask containing the harvested *C. parapsilosis* ATCC 7330 cells (12 g) in water (50 mL). The reaction was carried out in an orbital shaker at 200 rpm and 25 °C for 12 h. After incubation, the product formed was isolated using ethyl acetate and the organic layer was dried over anhydrous sodium sulphate. The solvent was removed by evaporation and the optically pure (*R*)-4-phenyl-3-butyne-2-ol **2a** was obtained as a yellow liquid after purification by silica gel column chromatography using hexane–ethyl acetate (90 : 10) as a mobile phase eluent (79% yield). The ee was found to be >99%, as determined by HPLC using the chiral OJ-H column. The yield of the isolated product was 79%. The rest of the propargyl alcohols were used as substrates for deracemization under the same reaction conditions (Scheme 1 and 2). Under identical conditions control experiments were done in parallel without the whole cells.

Synthesis of (*R*)-4-phenylbut-3-yn-2-yl methanesulfonate 3a.[22] (*R*)-4-Phenyl-3-butyne-2-ol **2a** (1 mmol) and triethylamine (2 mmol) were dissolved in dichloromethane (5 mL) at −78 °C. Mesylchloride (2 mmol) was added slowly. The reaction mixture was stirred at −78 °C for 1 h and then warmed to room temperature slowly. The mixture was quenched with saturated aqueous sodium bicarbonate solution (5 mL). The organic phase was separated and the aqueous layer was extracted with methylene chloride (10 mL × 3). The combined organic phases were washed with water and dried over sodium sulfate. The solids were filtered off, and the solvent was removed under reduced pressure to give (*R*)-4-phenylbut-3-yn-2-yl methanesulfonate **3a** as a light brown liquid which was used for the next step without purification.

Synthesis of (*S*)-2-(4-phenylbut-3-yn-2-yloxy)benzaldehyde 4a.[48] To a solution of K_2CO_3 (1.5 mmol) and salicylaldehyde (0.5 mmol) in 3 mL of dry DMF, (*R*)-4-phenylbut-3-yn-2-yl

methanesulfonate **3a** in DMF (2 mL) was added dropwise. The reaction mixture was stirred at room temperature for 6 h and subsequently cooled to 0 °C. Then the reaction was quenched by addition of 10 mL of a sat. NH_4Cl solution. This solution was exacted with diethyl ether (10 mL × 3). The combined organic phases were washed with water (2 × 20 mL) and dried over Na_2SO_4. After the removal of the solvent under reduced pressure, the crude mixture was purified by column chromatography using hexane–ethyl acetate (97 : 03) as a mobile phase eluent to afford (*S*)-2-(4-phenylbut-3-yn-2-yloxy)benzaldehyde **4a** as a slightly yellow oil.

Typical experimental procedure for the cycloaddition of (*S*)-2-(4-phenylbut-3-yn-2-yloxy)benzaldehyde 4a[51,52]

To a solution of *O*-propargylic salicylaldehyde **4a** (0.5 mmol) in dry toluene were added hydrochloride of amino ester **5a** (0.75 mmol) and diisopropyl ethyl amine (0.75 mmol). The resulting solution was heated to reflux and the progress of the reaction was monitored by TLC. After completion, the excess solvent was removed under reduced pressure and the crude mixture was purified by silica gel column chromatography using hexane–ethyl acetate (95 : 05) as a mobile phase eluent to provide pyrrole **6a** and **6b**. The cyclo adducts **8a** and **8b** were also obtained under the identical reaction conditions.

Synthesis of (*S*)-methyl 1,4-dimethyl-3-phenyl-1,4-dihydrochromeno[4,3-*b*]pyrrole-2-carboxylate 7a.[55] To a solution of **6a** and **6b** (0.3 mmol) in ethyl acetate 10% Pd/C was added and refluxed for 6 h. Then the mixture was filtered to remove the Pd/C and the resulting solution was evaporated under reduced pressure. The crude mixture was then purified by column chromatography on silica gel to give pyrrole (*S*)-**7a**.

Spectral data

(*R*)-4-(Naphthalen-2-yl)but-3-yn-2-ol (2f). Yield 75%; 27% ee; colourless solid; Mp 98–99 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 1.60 (3H, d, J = 6.4 Hz), 2.02 (1H, s), 4.81 (1H, q, J = 6.5 Hz), 7.46–7.50 (3H, m), 7.76–7.82 (3H, m), 7.96 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$): 24.4, 59.0, 84.4, 91.3, 119.9, 126.5, 126.7, 127.7, 128.0, 128.4, 131.6, 132.8, 132.9; IR (ν, cm^{-1}): 3443, 3060, 2973, 2878, 2226, 1265, 1103, 801, 764, 712; HRMS: *m*/*z*, calcd mass: 219.0780 [(M + Na)$^+$], found: 219.0781 [(M + Na)$^+$]. The compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL OJ-H column [hexanes–2-propanol = 90 : 10, 1.0 mL min^{-1}; retention times 25.1 min (major) and 29.2 min (minor)]; $[\alpha]_D^{25}$ = +2.2 (*c* 1, $CHCl_3$).

(*R*)-4-(9*H*-Fluoren-2-yl)but-3-yn-2-ol (2h). Yield 85%; 23% ee; pale yellow solid; Mp 139–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 1.58 (3H, d, J = 6.4 Hz), 3.87 (2H, s), 4.79 (1H, d, J = 6.4 Hz), 7.31 (1H, td, J = 7.2 Hz & 1.2 Hz), 7.36–7.38 (1H, m), 7.45 (1H, dt, J = 8 Hz & 0.8 Hz), 7.58–7. 60 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 24.7, 36.9, 59.2, 84.9, 91.1, 119.9, 120.4, 120.8, 125.3, 127.1, 127.4, 128.5, 130.7, 141.1, 142.2, 143.3, 143.7; IR (ν, cm^{-1}): 3476, 2985, 2257, 1407, 829, 769, 733; HRMS: *m*/*z*, calcd mass: 235.1117 [(M + H)$^+$], found: 235.1113 [(M + H)$^+$]; the compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL OJ-H column [hexanes–2-propanol = 90 : 10, 1.0 mL min^{-1}; retention times 25.8 min (major) and 34.2 min (minor)]; $[\alpha]_D^{25}$ = +5.4 (*c* 1, $CHCl_3$).

(*S*)-2-(4-Phenylbut-3-yn-2-yloxy)benzaldehyde (4a). Yield 72%; 91% ee; pale yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): 2.12 (3H, d, J = 6.4 Hz), 5.49 (1H, q, J = 6.4 Hz), 6.60 (1H, dd, J = 8 & 1.2 Hz), 7.35–7.39 (1H, m), 7.56–7.62 (4H, m), 7.66–7.69 (2H, m), 7.84–7.89 (1H, m), 8.16 (1H, dd, J = 7.6 & 1.6 Hz), 10.84 (1H, d, J = 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 22.2, 65.6, 86.7, 87.2, 114.9, 121.5, 122.0, 125.8, 128.2, 128.3, 128.7, 131.7, 135.6, 160.0, 189.9; IR (ν, cm^{-1}): 3076, 2990, 1686, 1479, 1452, 1287, 1233, 757, 691; HRMS: *m*/*z*, calcd mass: 273.0886 [(M + Na)$^+$], found: 273.0894 [(M + Na)$^+$]. The compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL OD-H column [hexanes–2-propanol = 98 : 02, 1.0 mL min^{-1}, retention times 6.7 min (major) and 7.9 min (minor)]; $[\alpha]_D^{25}$ = +14.8 (*c* 1, $CHCl_3$).

(4*S*)-Methyl 1,4-dimethyl-3-phenyl-1,2,4,9b-tetrahydrochromeno[4,3-*b*]pyrrole-2-carboxylate (6a). Yield 39%; 91% ee; pale yellow liquid; ^{1}H NMR (400 MHz, CD_3OD): 0.98 (3H, d, J = 6.4 Hz), 2.79 (3H, s), 3.61 (3H, s), 4.96 (1H, dd, J = 5.2 & 1.2 Hz), 4.97 (1H, d, J = 5.2 Hz), 5.44 (1H, qt, J = 6.4 & 1.2 Hz), 6.60 (1H, dd, J = 8 & 1.2 Hz), 7.06–7.08 (1H, m), 7.16–7.17 (1H, m), 7.18–7.19 (1H, m), 7.28–7.38 (4H, m), 7.41–7.43 (1H, m); ^{13}C NMR (100 MHz, CD_3OD): 19.7, 38.2, 52.2, 70.3, 74.1, 79.7, 119.9, 123.8, 125.7, 129.0, 129.4, 129.5, 129.8, 130.9, 132.4, 134.8, 143.0, 154.2, 173.0; IR (ν, cm^{-1}): 3061, 2978, 1735, 1482, 1452, 1387, 1286, 757, 700; HRMS: *m*/*z*, calcd mass: 336.1594 [(M + H)$^+$], found: 336.1601 [(M + H)$^+$]. The compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL AD-H column [hexanes–2-propanol = 95 : 05, 1.0 mL min^{-1}, retention times 9.3 min (major) and 11.6 min (minor)]; $[\alpha]_D^{25}$ = +70.0 (*c* 1, CH_3OH).

(4*S*)-Methyl 1,4-dimethyl-3-phenyl-1,2,4,9b-tetrahydrochromeno[4,3-*b*]pyrrole-2-carboxylate (6b). Yield 31%; 91% ee; viscous liquid; ^{1}H NMR (400 MHz, CD_3OD): 1.52 (3H, d, J = 6.8 Hz), 2.78 (3H, s), 3.64 (3H, s), 4.93 (1H, d, J = 4 Hz), 5.11 (1H, qd, J = 6.8 & 1 Hz), 5.13 (1H, d, J = 4 Hz), 6.81 (1H, dd, J = 8.4 & 1.2 Hz), 6.98 (1H, td, J = 7.2 & 0.8 Hz), 7.17–7.18 (1H, m), 7.27–7.29 (2H, m), 7.35–7.37 (1H, m), 7.40–7.42 (2H, m); 7.43–7.45 (1H, m); ^{13}C NMR (100 MHz, CD_3OD): 19.2, 38.3, 52.4, 66.2, 71.4, 78.5, 119.1, 122.4, 126.6, 128.6, 129.4, 129.8, 130.0, 130.9, 133.7, 134.8, 140.0, 153.8, 172.7; IR (ν, cm^{-1}): 2961, 2352, 1727, 1485, 1452, 1387, 1217, 762, 700; HRMS: *m*/*z*, calcd mass: 336.1594 [(M + H)$^+$], found: 336.1598 [(M + H)$^+$]. The compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL AD-H column [hexanes–2-propanol = 95 : 05, 1.0 mL min^{-1}, retention times 12.4 min (minor) and 18.0 min (major)]; $[\alpha]_D^{25}$ = −36.8 (*c* 0.5, CH_3OH).

(*S*)-Methyl 1,4-dimethyl-3-phenyl-1,4-dihydrochromeno[4,3-*b*]pyrrole-2-carboxylate (7a). Yield 87%; 91% ee; colorless solid; Mp 128–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 1.21 (3H, d, J = 6.4 Hz), 3.54 (3H, s), 4.19 (3H, s), 5.29 (1H, q, J = 6.4 Hz), 7.00–7.01 (2H, m), 7.17–7.22 (1H, m), 7.24–7.27 (2H, m), 7.29–7.34 (1H, m), 7.35–7.39 (2H, m); 7.63 (1H, dd, J = 7.6 & 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 21.4, 35.5, 50.8, 71.2, 117.7, 118.6, 121.1, 121.4, 121.8, 122.5, 126.8, 127.7, 128.4,

128.7, 129.0, 129.6, 135.1, 153.1, 162.2; IR (ν, cm^{-1}): 3061, 2974, 1697, 1454, 1435, 752; HRMS: *m*/*z*, calcd mass: 334.1438 [$(M + H)^+$], found: 334.1428 [$(M + H)^+$]. The compound was resolved by HPLC analysis at 25 °C, using a CHIRALCEL AD-H column [hexanes–2-propanol = 98 : 02, 1.0 mL min^{-1}, retention times 5.4 min (major) and 6.2 min (minor)]; $[\alpha]_D^{25}$ = −32.4 (*c* 0.5, CH_3OH).

(6*S*)-Methyl 6-methyl-7-phenyl-6,7a,8,9,10,11a-hexahydrochromeno[3,4-*b*]pyrrolizine-7a-carboxylate (8) (inseparable diastereomers, 1.0 : 0.6 ratio). Yield 78%; 91% ee; pale yellow liquid; ^1H NMR (400 MHz, CD_3OD): 1.03 (3H, d, *J* = 6.4 Hz, major), 1.32 (2H, d, *J* = 6.4 Hz, minor), 1.73–1.80 (3.22H, m, major & minor), 1.85–1.92 (0.62H, m, minor), 2.01–2.07 (1H, m, major), 2.19–2.30 (2.63H, m, major & minor), 2.42–4.48 (0.6H), 2.83–2.91 (1.6H, m, major & minor), 3.78 (3H, s, major), 3.80 (1.5H, s, minor), 4.72 (1H, qd, *J* = 6.4 & 0.8 Hz, major), 5.01 (0.5H, qd, *J* = 6.4 & 0.8 Hz, minor), 5.50 (0.53H, s, minor), 5.53 (1H, s, major), 6.79–6.84 (1.5H, m, major & minor), 6.95–7.00 (1.5H, m, major & minor), 7.13–7.20 (4.6H, m, major & minor), 7.36–7.42 (6.3H, m, major & minor); ^{13}C NMR (100 MHz, CD_3OD): 19.0, 19.2, 25.7, 26.1, 32.9, 33.3, 52.3, 52.6, 53.0, 53.2, 63.5, 67.5, 71.6, 73.1, 87.4, 88.5, 118.3, 119.2, 122.0, 122.2, 122.4, 123.3, 129.2, 129.3, 129.8, 129.9, 130.0, 130.2, 130.7, 130.8, 131.1, 134.8, 135.8, 137.2, 137.7, 138.1, 138.3, 154.7, 157.5, 174.3, 174.8; IR (ν, cm^{-1}): 3055, 2986, 2928, 2306, 1734, 896, 754, 735, 725, 707; HRMS: *m*/*z*, calcd mass: 362.1751 [$(M + H)^+$], found: 362.1734 [$(M + H)^+$]. The compound was resolved by HPLC analysis at 25 °C, using a phenomenex Lux 5u Amylose 2 column [hexanes–2-propanol = 95 : 05, 1.0 mL min^{-1}, retention times: **8a** major isomer 14.7 min (minor) and 17.7 min (major); **8b** minor isomer 11.8 min (major) and 13.7 min (major)]; $[\alpha]_D^{25}$ = −26.3 (*c* 2, CH_3OH).

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