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# Effective Asymmetric Synthesis of 1,2,9,9a-Tetrahydrocyclopropa[*c*]benzo[*e*]indol-4-one (CBI)

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A short, asymmetric synthesis of the 1,2,9,9a-tetrahydrocyclopropa[*c*]benzo[*e*]indol-4-one (CBI) analogue of the CC-1065 and duocarmycin alkylation subunits is detailed that employs an effective enzymatic desymmetrization reaction of prochiral diol **12** using a commercially available *Pseudomonas* sp. lipase. The optically active monoacetate (*S*)-**13** is furnished in exceptional conversions (88%) and optical purity (99% ee) and serves as an intermediate for the preparation of either enantiomer of CBI. Similarly, the *Pseudomonas* sp. lipase resolved the racemic intermediate **19**, affording advanced intermediates of CBI in good conversions and optical purity (99% ee), and provided an alternative approach to the preparation of optically active CBI derivatives.

CC-1065 (**1**)[1] and the duocarmycins (**2**−**3**)[2,3] represent the parent members of a class of potent antitumor antibiotics[4] that derive their biological properties through a sequence selective alkylation of duplex DNA (Figure 1).[5−10] In studies to define fundamental relationships between structure, chemical reactivity, and biological properties, the 1,2,9,9a-tetrahydrocyclopropa[*c*]benzo[*e*]-indol-4-one (CBI) analogue of the natural product alkylation subunits has been found to possess especially interesting properties. The natural enantiomers of the CBI analogues have been shown to be 4 times more stable, 4 times more potent, and synthetically more accessible than the corresponding compounds incorporating the natural CPI (7-methyl-1,2,8,8a-tetrahydrocyclopropa[*c*]pyrrolo[3,2-*e*]indol-4-one) alkylation subunit of CC-1065.[11−17] Additionally, they alkylate DNA with an unaltered sequence selectivity at an enhanced rate and with a greater efficiency than the corresponding CPI analogues. Although not quite as effective as duocarmycin SA (DSA) analogues, the ability to perform comprehensive structural and biological studies with CBI makes these analogues especially attractive.[18−23] These and several additional features including its enhanced inherent reaction regioselectivity (>20:1 vs 4−6:1 (**3**), 4:1 (**1**), 1.5:1 (**2**)) have made CBI the most widely examined alkylation subunit not only in our studies but in those of many others as well.[24−29]

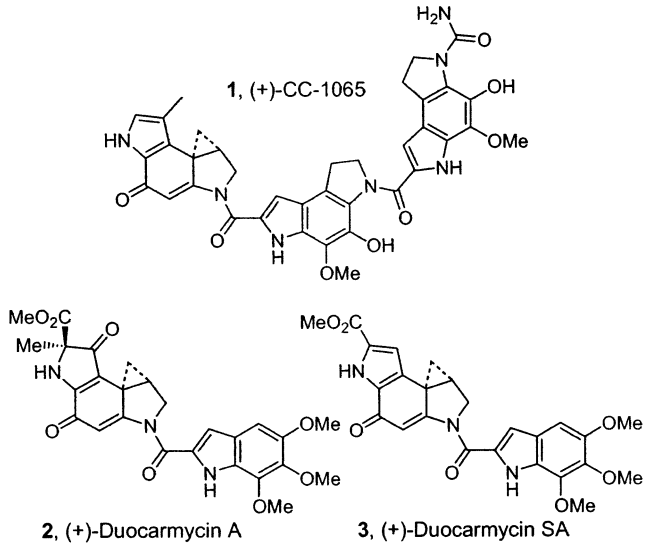


**FIGURE 1.** CC-1065 and the duocarmycins.

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Despite this interest, most studies detailing the preparation of optically active CBI derivatives have relied on an effective semipreparative Chiralcel OD chromatographic resolution[30] of a racemic precursor for access to the materials. Given the efficiency of the resolution ($\alpha$ = 1.30) and the material requirements for such potent agents (L1210 $IC_{50}$ = 5−50 pM), a semipreparative OD column that separates up to 100 mg per injection satisfies most laboratory needs. Although several approaches to the asymmetric synthesis of optically active precursors have been disclosed, none have supplanted this or related chromatographic resolutions.[11] In part, this may be attributed to the stringent optical purity (≥99−99.9% ee) required to distinguish the activity of an unnatural enantiomer from that of its contaminant natural enantiomer with many of the derivatives. The asymmetric approaches include our own introduction[31] of two complementary strategies that rely on an asymmetric hydroboration (80% ee)[32] or a Jacobsen epoxidation (92% ee),[33] a route based on a Sharpless AD reaction (30−60%, 70% ee),[16] Lown's lipase-catalyzed resolution of **4** (1st cycle 48%, 74% ee; 2nd cycle 78%, 96−99% ee),[34] and Mohamadi's asymmetric hydroboration (58%, 40% ee)[35] (Figure 2).

Over the course of many years, we have periodically examined an attractive approach that is based on the enzymatic desymmetrization of diol **12**. The lipases that were examined all provided low conversions or low ee's and typically required near stoichiometric, rather than catalytic, amounts of enzyme. In line with these findings, Lown reported a resolution of **4** (Figure 2, vs desymmetrization) that requires 3.1 g of enzyme/g of substrate and two reaction cycles to achieve satisfactory results (37%, 96−99% ee).[34] To date, the most successful implementation of such an approach was described by Chênevert with supported PPL (porcine pancreatic lipase) in an asymmetric synthesis of a precursor to the CI (1,2,7,7a-tetrahydrocyclopropa[*c*]indol-4-one) alkylation subunit (Scheme 1).[36] Still, modest conversions and nonoptimal ee's were observed especially for the approach leading to the natural enantiomer, and the analogous CBI precursors are not effective substrates for PPL.

Recently, Martin reported a total synthesis of FR900482, illustrating what may be the first example of a lipase capable of effectively acting on substrates resembling the size and structure of typical CBI precursors.[37] A diol substrate similar to the one we examined was enantioselectively acylated with a highly purified, commercially available *Pseudomonas* sp. lipase (Sigma), affording excellent yields and ee's (68%, >95% ee) even when used in a catalytic versus near stoichiometric quantity. In Martin's efforts, alternative and less effective lipases were examined with results analogous to our own observations. Herein, we report an effective asymmetric

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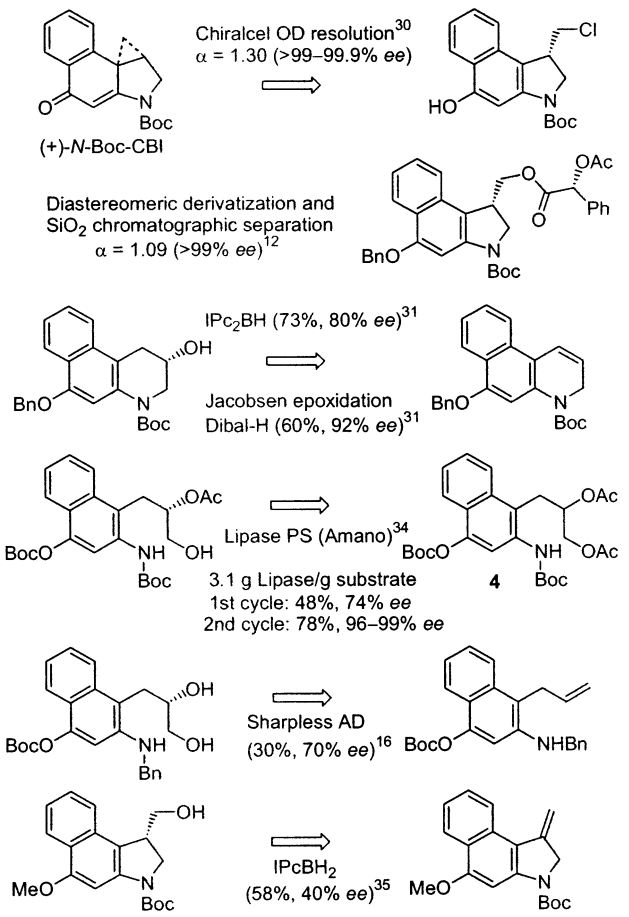
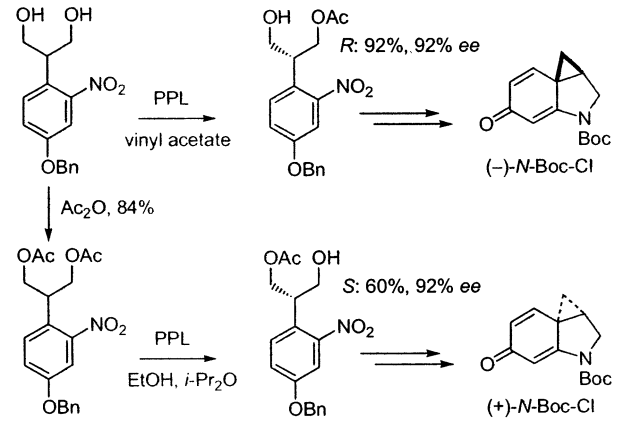



**FIGURE 2.** Approaches to the asymmetric synthesis of CBI.

**SCHEME 1**




synthesis of CBI, enlisting this commercially available *Pseudomonas* sp. lipase (Sigma) to desymmetrize prochiral diol **12**, providing (*S*)-**13** in exceptional conversions (88%) and optical purity (99% ee). In addition to the superb chemical yields and optical purities, this procedure employs catalytic quantities of the enzyme, requiring 40-fold less enzyme than the Chênevert PPL desymmetrization of a CI precursor[36] and 400-fold less enzyme than the Lown CBI resolution.[34]

**Asymmetric Synthesis by Desymmetrization of Prochiral Diol 12.** An effective six- to seven-step synthesis of prochiral diol **12** was developed starting with **5**,[38] in which the intermediates could be isolated by

**SCHEME 2**

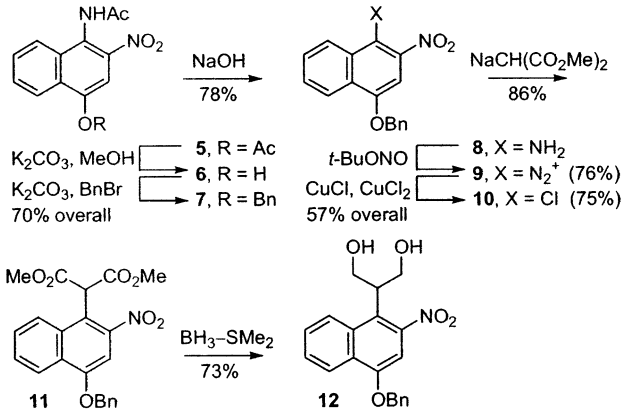



**TABLE 1. Desymmetrization of 12 at 35 °C**

| substrate (mg) | enzyme[a] (mg) | time (h) | diol **12** (%) | % monoacetate (*S*)-**13** (% ee) | diacetate (%) |
|---|---|---|---|---|---|
| 20 | 1 | 24 | – | 70 (96) | 10 |
| 100 | 1 | 48 | 35 | 47 (96) | 2 |
| 100 | 2 | 28 | 7 | 82 (97) | 4 |
| 100 | 4 | 20 | – | 88 (99) | 8 |
| 200 | 4 | 26 | 3 | 92 (96) | 5 |
| 50 | 3 | 16 | – | 77 (99) | 9 |
| 50 | 4 | 14 | 1 | 80 (98) | 7 |

[a] *Pseudomonas* sp. lipase (Sigma).

precipitations and purified by crystallization, avoiding chromatographic purifications (Scheme 2). This follows an approach that had been developed for CPI[39] and CI,[40] and its extension here for **12** proved straightforward. The exception to this generalization was the diester reduction of **11** to provide diol **12**. Initial methods examined including Dibal-H which has been reported in the CI synthesis provided modest yields of the diol (typically 33–42%) and many additional products. In contrast, the reduction of **11** with $BH_3$–$SMe_2$[41] proceeded exceptionally well, providing **12** cleanly in good conversions (73%).

Although not extensively optimized (Table 1), the desymmetrization of **12** was run in vinyl acetate, which serves as both solvent and acyl donor (35 °C, 20 h), with the *Pseudomonas* sp. lipase (PSL, 4 mg/100 mg of **12**), providing a single enantiomer of **13**[42] in 88% yield and 99% ee. The corresponding enzyme-catalyzed deacylation desymmetrization of the diacetate of **12** was not as successful. Thus, treatment of the diacetate with PSL (1 mg, 20 mg substrate) in either *i*-$Pr_2O$–EtOH[36] (35 °C, 5 days, 6% at <5% ee and 83% recovered diacetate) or 0.02 M pH 7 phosphate buffer (35 °C, 5 days, 39% at 79% ee and 52% recovered diacetate) provided (*R*)-**13** in much less satisfactory conversions. The stereochemistry of (*S*)-

(38) Compound **5** is available in two steps from commercially available 4-amino-1-naphthol hydrochloride: $Ac_2O$, $Et_3N$, $CH_2Cl_2$, 0 °C, 74–84%; 90% $HNO_3$, 18 °C, 69–78%. See: Kamel, M.; Nasr, H. I. *Kolor. Ert.* **1968**, *10*, 177. Jacobson, P. *Chem. Ber.* **1891**, *14*, 1794. Han, G.; Shin, K. J.; Kim, D. C.; Yoo, H. H.; Kim, D. J.; Park, S. W. *Heterocycles* **1996**, *43*, 2495.

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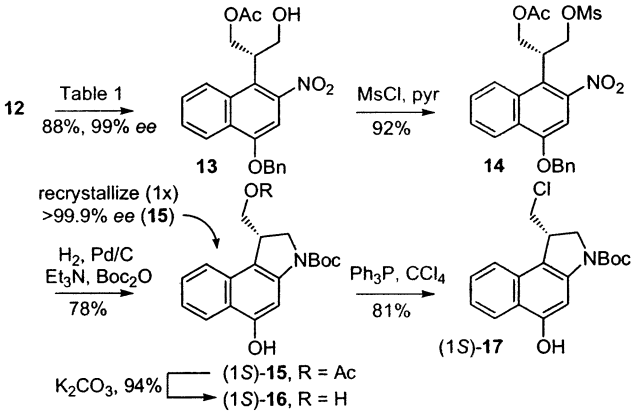
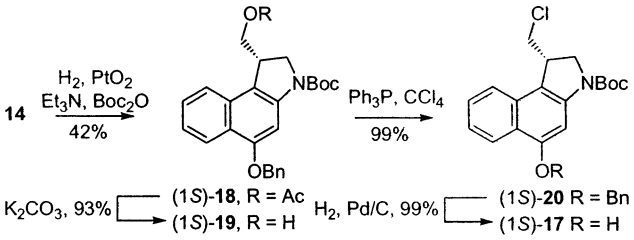
(42) A sample of racemic **13** was prepared by treatment of **12** with $Ac_2O$ (1 equiv, pyridine, 25 °C, 3 h, 41%).

**SCHEME 3**




**SCHEME 4**




**SCHEME 5**

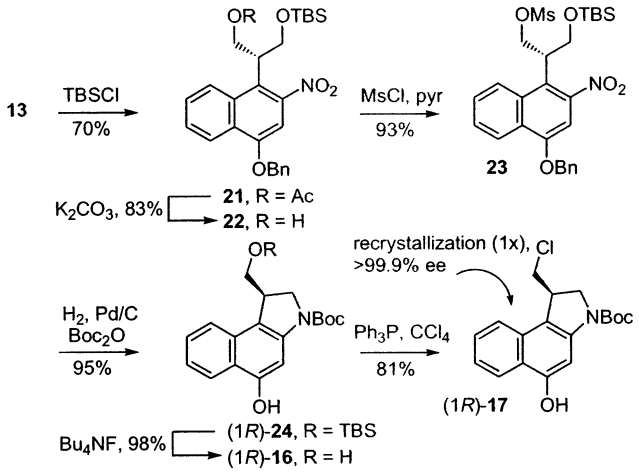



**TABLE 2. Desymmetrization of 25 at 35 °C**

| substrate (mg) | enzyme[a] (mg) | time (h) | diol **25** (%) | % monoacetate (*S*)-**26** (% ee) | diacetate (%) |
|---|---|---|---|---|---|
| 50 | 1 | 48 | 17 | 73 (91) | 9 |
| 50 | 2 | 48 | 24 | 66 (93) | 9 |
| 50 | 4 | 43 | – | 85 (93) | 12 |

[a] *Pseudomonas* sp. lipase (Sigma).

**13** was established upon conversion to optically active *N*-Boc-CBI precursors (**16**−**20**), which correlated with the natural 1*S* configuration of authentic materials (Scheme 3). Thus, activation of the primary alcohol of **13** by conversion to mesylate **14** using conditions which do not promote acetate migration and partial racemization (established by chiral HPLC), followed by nitro reduction and subsequent in situ cyclization and *N*-Boc protection, provides **15**. This intermediate, an oil in racemic form, solidified when enantiomerically enriched. Recrystallization afforded **15** in ≥99.9% ee and provides a convenient stage and procedure to further enrich and ensure the optical purity of subsequent intermediates. Acetate hydrolysis provided **16**, a key intermediate in the CBI synthesis, and its one-step conversion to chloride **17** provides the key *seco*-*N*-Boc-CBI derivative.[11]

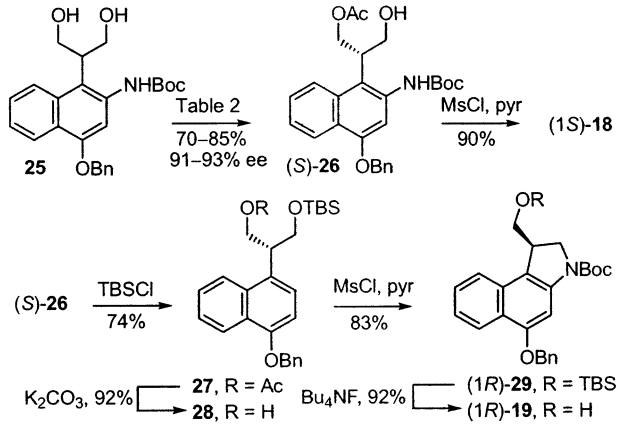
The reductive cyclization of **14** (and **23**) initially proved to be a problematic step. Using Adam's catalyst ($PtO_2$), $H_2$ (1 atm), $Et_3N$, and $Boc_2O$ in THF in one pot provided **18** in modest yields of 35−60% (Scheme 4). Other procedures including the use of Al(Hg) and Lindlar's catalyst did not proceed as well. Variations of the reaction sequence (hydrogenation, then filtration, and then addition of $Et_3N$ and $Boc_2O$ vs hydrogenation in the presence of $Et_3N$, then filtration, and then addition of $Boc_2O$) did not provide better conversions than the one-pot procedure. We consistently observed partial benzyl removal, incomplete Boc protection, and decomposition of the unstable secondary aniline formed. Nonetheless, under carefully controlled conditions, satisfactory amounts of **18** are produced and can be used to prepare precursors (i.e., **18**−**20**) that maintain the phenol benzyl ether protection. Circumventing these problems and further shortening the sequence, we found that the one-pot reaction sequence using 10% Pd/C as the hydrogenation catalyst cleanly provided both nitro reduction and benzyl ether hydrogenolysis to afford **15** in high yields (Scheme 3).

The intermediates required for preparation of the CBI unnatural enantiomer were generated by orthogonal protection of the free alcohol of **13**, acetate hydrolysis, mesylate formation, and subjection of **23** to the reductive cyclization conditions described above (Scheme 5). Notably, we also found that a single recrystallization of (*R*)-**17** (EtOAc−hexanes) serves to enrich its optical purity (≥99.9%), ensuring that analogues in the unnatural enantiomer series are free of contaminant natural enantiomer. Importantly, although not highlighted above, the recrystallization of (*S*)-**17** can also serve as an alternative, convenient stage at which to enrich and ensure the optical purity in the natural enantiomer series.

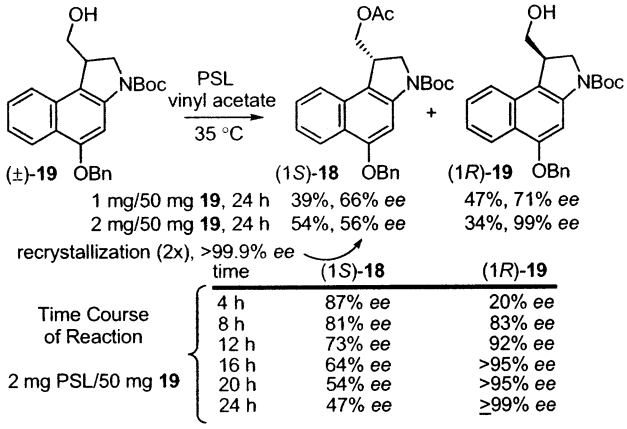
**Asymmetric Synthesis by Desymmetrization of Prochiral Diol 25.** In a similar study, the *Pseudomonas* sp. lipase was also found to be capable of asymmetric desymmetrization of diol **25**[43] (4−8 mg of PSL/100 mg of **25**, vinyl acetate solvent, 35 °C, 48 h), providing (*S*)-**26** in good chemical yields (70−85%) and excellent ee's (91−93%, Table 2 and Scheme 6). Although this was not investigated in the same detail as diol **12**, the conversions appeared to occur more slowly and the yields and ee's were slightly lower. Nonetheless, effective conversions were observed using comparable amounts of catalytic enzyme even with a substrate that now contains a large *N*-Boc protecting group proximal to the prochiral diol center. Interestingly, efforts to enrich the optical purity of (*S*)-**26** by recrystallization led to diminished ee's in the solvent examined (EtOAc−hexanes) resulting from pref-

(43) Prepared from **12** in four steps: $Me_2C(OMe)_2$, TsOH, DMF, 25 °C, 16 h, 62%; $H_2$, Lindlar's catalyst (5% Pd/$CaCO_3$), quinoline, 25 °C, 16 h, 68%; $(Boc)_2O$, THF, 70 °C, 24 h, 80%; TsOH, MeOH, 25 °C, 1 h, 88%.

**SCHEME 6**




**SCHEME 7**




erential crystallization of the racemate (with enhanced ee's of the recrystallization mother liquor). However, an interesting distinction with **26** [($\alpha = 1.7$) vs **13** ($\alpha = 1.38$)] was that a direct chiral phase HPLC separation (Chiralcel OD) of the enantiomers is very effective. This level of resolution ($\alpha = 1.7$) provides not only the opportunity to enhance the optical purity of **26** by a preparatively useful chromatography on a chiral phase but also the option of a direct and preparatively useful chromatographic resolution in itself. A single-step formation of the corresponding mesylate and subsequent in situ −NHBoc displacement with closure of the five-membered ring provided (*S*)-**18**, confirming the assigned stereochemistry and providing an alternative approach to the synthesis of natural enantiomer (*S*)-**17**. Notably, the optical purity of (*S*)-**17** could be enriched by recrystallization at this stage, as detailed beforehand.

Similarly, the unnatural enantiomer series was accessed by alcohol protection to provide **27** and acetate hydrolysis to provide alcohol **28**, followed by single-step mesylate formation and subsequent in situ −NHBoc displacement to provide (*R*)-**29** (Scheme 6). Silyl ether deprotection provided (*R*)-**19** and access to the unnatural enantiomer series.

**Asymmetric Synthesis with Resolution of 19.** There is precedence[34] with CPI for the asymmetric synthesis of an alkylation subunit by the enzymatic resolution of a racemic alcohol precursor. An alternative approach to the asymmetric synthesis of CBI that proceeds through racemic intermediate **19** was also explored with the purified *Pseudomonas* sp. lipase. Notably, the synthesis of (±)-**19** requires only seven steps from readily available 1,3-dihydroxynaphthalene and is straightforward to implement.[17] The resolution of alcohol **19** (Scheme 7) provided the acetylated natural enantiomer in 39−54% yield (56−68% ee) and the unreacted unnatural enantiomer in 34−47% yield and up to 99% ee. The enriched acetylated natural enantiomer can be obtained in optically pure form (≥99.9% ee) by successive recrystallizations (two times, EtOAc−hexanes).

## Conclusions

Effective asymmetric syntheses of key CBI precursors were developed that provide the optically active intermediates in good yields and sufficient optical purities (≥99−99.9% ee) to be useful in the preparation and evaluation of CC-1065 and duocarmycin analogues. The first entails the desymmetrization of **12** enlisting a highly purified *Pseudomonas* sp. lipase (PSL, Sigma) which provided (1*S*)-**13** in superb yield (88%) and excellent optical purity (99% ee). All material is converted to a single enantiomerically pure product, (1*S*)-**13**, from which either enantiomer of CBI may be accessed. An alternative and nearly as effective approach was developed that entailed the PSL desymmetrization of diol **25**, providing (*S*)-**26** in good chemical yield (70−85%) and satisfactory optical purity (91−93% ee). A second approach enlisted PSL for resolution of the racemic alcohol (±)-**19** and offers an attractive alternative late stage access to both enantiomers. Because the studies indicate that the PSL is substantially more effective on CBI-like precursors than any other enzyme previously disclosed, they also suggest that it may be applicable to all related alkylation subunit precursors (e.g., CPI, DSA, and CI).

## Experimental Section

**(*S*)-1-Acetoxy-2-(4-benzyloxy-2-nitronaphthalen-1-yl)-propan-3-ol ((*S*)-13).** A sample of **12** (100 mg, 0.283 mmol), 4 Å molecular sieves (100 mg), and *Pseudomonas* sp. lipase (4 mg, Sigma) were dissolved in vinyl acetate (1.5 mL, distilled from $CaCl_2$). The reaction was stirred at 35 °C for 20 h and filtered through a Celite plug. The Celite was washed with $CH_2Cl_2$, and the combined organic solutions were concentrated in vacuo. Flash chromatography ($SiO_2$, 33% EtOAc−hexanes) afforded monoacetate (*S*)-**13** (98.2 mg, 88%) and diacetate (9.3 mg, 8%). The sample of (*S*)-**13** was determined to be 99% ee by HPLC (Chiralcel AS column; 0.46 cm × 25 cm; 4:1 hexanes−*i*-PrOH; 1 mL/min; retention times, 21 min for (*S*)-**13** and 29 min for (*R*)-**13**).[42] For (*S*)-**13**: yellow oil; $[\alpha]_D^{23}$ −73 (*c* 1.0, $CHCl_3$); $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 8.46 (1H, d, $J = 9.2$ Hz), 8.14 (1H, br s), 7.68 (1H, br t), 7.63 (1H, t, $J = 7.5$ Hz), 7.52 (2H, d, $J = 7.0$ Hz), 7.46 (2H, t, $J = 7.0$ Hz), 7.43 (1H, t, $J = 7.0$ Hz), 7.06 (1H, s), 5.27 (2H, s), 4.86 (1H, br s), 4.55 (1H, dd, $J = 6.2, 4.8$ Hz), 4.28 (1H, br s), 4.18 (1H, br s), 3.86 (1H, br s), 2.03 (3H, s), 1.96 (1H, br s); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 171.3, 154.8, 150.6, 135.8, 132.0, 129.0 (2C), 128.75, 128.66, 127.81 (2C), 127.76, 127.6, 126.4, 123.7, 121.4, 99.9, 70.9, 65.2, 63.8, 44.0, 21.1; IR (film) $\nu_{max}$ 3395, 1734, 1593, 1527, 1237 cm$^{-1}$; MALDIFT-HRMS (DHB) *m*/*z* 418.1265 (M + Na$^+$, $C_{22}H_{21}NO_6$ requires 418.1261).

For the diacetate [2-(4-benzyloxy-2-nitronaphthalen-1-yl)-1,3-diacetoxypropane]: $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ 8.45 (1H, d, $J = 8.3$ Hz), 8.09 (1H, br s), 7.68 (1H, br s), 7.64 (1H, br s), 7.52 (2H, d, $J = 7.4$ Hz), 7.46 (2H, t, $J = 7.5$ Hz), 7.41 (1H, t, $J = 7.4$ Hz), 7.07 (1H, br s), 5.27 (2H, s), 4.85 (1H, br s), 4.64

(1H, br s), 4.55 (1H, d, $J$ = 6.1 Hz), 4.54 (1H, d, $J$ = 6.1 Hz), 3.99 (1H, br s), 2.02 (6H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 171.0 (2C), 155.0, 150.6, 135.8, 131.8, 129.0 (2C), 128.7, 127.8 (2C), 127.6, 126.2, 124.9, 123.9, 123.4, 120.4, 99.9, 71.0, 64.6 (2C), 40.3, 21.0 (2C); IR (film) $\nu_{max}$ 1738, 1532, 1231 cm$^{-1}$; MALDIFT-HRMS (DHB) $m/z$ 460.1377 (M + Na$^+$, $C_{24}H_{23}NO_7$ requires 460.1367).

**(*R*)-1-Acetoxy-2-(4-benzyloxy-2-nitronaphthalen-1-yl)-3-(methanesulfonyloxy)propane ((*R*)-14).** A solution of (*S*)-**13** (106 mg, 0.268 mmol) in pyridine (1.0 mL) cooled to 0 °C was treated dropwise with MsCl (41.0 $\mu$L, 0.536 mmol), and the mixture was stirred at 0 °C for 1 h and then at 25 °C for 1 h. Ice water (5 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 1 M aqueous HCl (3 × 5 mL), dried ($Na_2SO_4$), and concentrated in vacuo to provide (*R*)-**14** (116 mg, 92%) as a tan oil which was used in the next reaction without further purification: $[\alpha]_D^{23}$ −38 (*c* 1.2, $CHCl_3$); $^1$H NMR ($CDCl_3$, 500 MHz, 25 °C) $\delta$ 8.48 (1H, d, $J$ = 8.4 Hz), 8.40 and 8.02 (1H, two br s), 7.72 (1H, br s), 7.66 (1H, br s), 7.53 (2H, d, $J$ = 7.3 Hz), 7.46 (2H, t, $J$ = 7.0 Hz), 7.42 (1H, t, $J$ = 7.3 Hz), 7.12 (1H, br s), 5.27 (2H, s), 4.92 (2H, br s), 4.63 (2H, br s), 4.56 (1H, dd, $J$ = 5.7, 5.2 Hz), 2.94 (3H, s), 2.05 (3H, s); $^1$H NMR ($CDCl_3$, 500 MHz, 50 °C) $\delta$ 8.48 (1H, d, $J$ = 8.4 Hz), 8.17 (1H, br s), 7.73 (1H, t, $J$ = 7.0 Hz), 7.66 (1H, t, $J$ = 8.1 Hz), 7.53 (2H, d, $J$ = 7.0 Hz), 7.46 (2H, t, $J$ = 7.0 Hz), 7.42 (1H, t, $J$ = 7.3 Hz), 7.14 (1H, br s), 5.30 (2H, s), 4.88 (2H, br s), 4.69 (2H, br s), 4.56 (1H, dd, $J$ = 5.9, 5.5 Hz), 2.93 (3H, s), 2.04 (3H, s); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 170.9, 155.3, 150.7, 135.7, 131.7, 129.0 (2C), 128.7, 127.8 (2C), 127.6, 125.9, 124.7, 124.1, 123.5, 119.3, 100.0, 71.0, 69.1, 64.0, 40.6, 37.7, 21.0; IR (film) $\nu_{max}$ 1741, 1530, 1360, 1229 cm$^{-1}$; MALDIFT-HRMS (DHB) $m/z$ 496.1041 (M + Na$^+$, $C_{23}H_{23}NO_8S$ requires 496.1037).

**(*S*)-1-Acetoxymethyl-3-(*tert*-butyloxycarbonyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole ((*S*)-15).** A solution of (*R*)-**14** (213 mg, 0.450 mmol) in THF (8.0 mL) was treated with 10% Pd/C (15 mg), $Et_3N$ (120 mL, 0.900 mmol), and $Boc_2O$ (196 mg, 0.900 mmol), and the mixture was stirred at 25 °C for 8 h under 1 atm of $H_2$. The reaction mixture was filtered through Celite and concentrated in vacuo. Flash chromatography ($SiO_2$, 1−10% EtOAc−hexanes) provided (*S*)-**15** (122 mg, 76%; typically 71−78%) as a beige solid: mp 147−148 °C (white needles, EtOAc−hexanes); $[\alpha]_D^{23}$ −1 (*c* 1.0, $CHCl_3$); $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 8.17 (1H, d, $J$ = 7.0 Hz), 7.77 (1H, d, $J$ = 8.1 Hz), 7.75 (1H, br s), 7.51 (1H, t, $J$ = 8.0 Hz), 7.33 (1H, t, $J$ = 7.3 Hz), 4.57 (1H, d, $J$ = 8.4 Hz), 4.07 (2H, d, $J$ = 8.1 Hz), 3.95 (1H, m), 3.87 (1H, t, $J$ = 9.9 Hz), 2.11 (3H, s), 1.61 (9H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 171.5, 153.9, 153.2, 141.2, 130.9, 127.6, 123.5, 123.0, 122.7, 121.7, 114.0, 99.3, 81.7, 66.2, 52.9, 38.5, 28.7 (3C), 21.2; IR (film) $\nu_{max}$ 3381, 1698, 1390, 1144 cm$^{-1}$; MALDIFT-HRMS (DHB) $m/z$ 357.1574 (M$^+$, $C_{20}H_{23}NO_5$ requires 357.1574).

The recrystallization of (*S*)-**15** (EtOAc−hexanes) may be used to further enrich the optical purity of this and the following synthetic intermediates (Figure 3).

**(*S*)-3-(*tert*-Butyloxycarbonyl)-5-hydroxy-1-hydroxymethyl-1,2-dihydro-3*H*-benz[*e*]indole ((*S*)-16).** A solution of (*S*)-**15** (41.7 mg, 0.117 mmol) in MeOH (1.0 mL) at 25 °C was treated with $K_2CO_3$ (64.5 mg, 0.467 mmol) and stirred for 1 h. A solution of 1 M aqueous HCl was added to adjust the pH to 6, and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with aqueous saturated NaCl (5 mL), dried ($Na_2SO_4$), and concentrated in vacuo, providing (*S*)-**16** (35.0 mg, 94%; typically 84−94%) as a beige film which did not require further purification. The ee of (*S*)-**16** was determined by HPLC (Chiralcel AS column; 0.46 cm × 25 cm; 19:1 hexanes−*i*-PrOH; 1 mL/min; retention times, 27.4 min for (*R*)-**16** and 31.9 min for (*S*)-**16**) before recrystallization of (*S*)-**15** (96% ee) and after recrystallization of (*S*)-**15** (99.9% ee) (Figure 3). For (*S*)-**16**: $[\alpha]_D^{23}$ −1.4 (*c* 0.8, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.19 (1H, d, $J$ = 8.2 Hz), 7.77 (1H, br s), 7.65 (1H, d, $J$ = 8.2 Hz), 7.43 (1H, td, $J$ = 6.8, 1.1 Hz), 7.30 (1H, t, $J$ = 8.2 Hz), 4.20 (1H, d, $J$ = 11.2 Hz), 4.10 (1H, d, $J$ = 8.8 Hz), 3.93 (1H, dd, $J$ = 10.3, 3.2 Hz), 3.82 (1H, m), 3.75 (1H, t, $J$ = 7.3 Hz), 1.56 (s, 9H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 153.8, 153.2, 141.6, 130.9, 127.4, 123.7, 122.9, 122.5, 121.8, 114.3, 99.4, 81.5, 64.9, 52.7, 41.5, 28.7 (3C); IR (film) $\nu_{max}$ 3363, 2978, 1673, 1584, 1145 cm$^{-1}$; MALDIFT-HRMS (DHB) $m/z$ 315.1466 (M$^+$, $C_{18}H_{21}NO_4$ requires 315.1465).

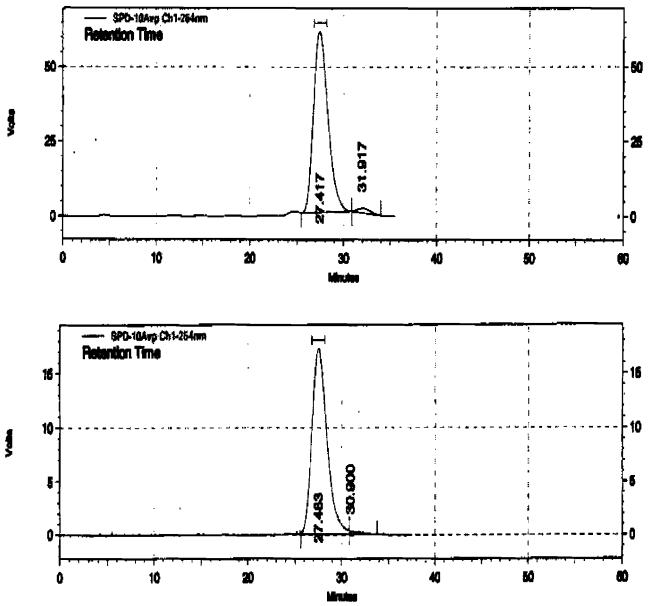



**FIGURE 3.** HPLC trace of (*S*)-**16** before (96% ee) and after recrystallization (≥99.9% ee) of (*S*)-**15** from EtOAc−hexanes (Chiralcel AS; 0.46 cm × 25 cm; 19:1 hexanes−*i*-PrOH; 1 mL/min; retention times, 27.4 min for (*S*)-**16** and 31.9 min for (*R*)-**16**).

**(*S*)-3-(*tert*-Butyloxycarbonyl)-1-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole ((*S*)-17).** A solution of (*S*)-**16** (89.8 mg, 0.285 mmol) in $CH_2Cl_2$ (2.0 mL) at 25 °C was treated with $Ph_3P$ (262 mg, 0.854 mmol) and $CCl_4$ (246 $\mu$L, 2.56 mmol) and stirred for 3 h. The reaction mixture was concentrated in vacuo. Flash chromatography ($SiO_2$, 10−20% EtOAc−hexanes) provided (*S*)-**17** (77.0 mg, 81%, typically 71−81%) as a white solid (mp 161 °C)[11] which was identical in all respects to authentic compound. Compound (*S*)-**17** exhibits a concentration dependent optical rotation: $[\alpha]_D^{23}$ −65 (*c* 1.0, $CH_2Cl_2$), −44 (*c* 0.31); lit. $[\alpha]_D^{23}$ −70 (*c* 1.04, $CH_2Cl_2$), −48 (*c* 0.30, $CH_2Cl_2$).

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**Supporting Information Available:** Experimental details and compound characterization for the preparation of **12**, **18**, and **19**, the conversion of (*S*)-**13** to (*R*)-**17** and of **12** to **25**, the desymmetrization of **25**, and the conversion of (*S*)-**26** to (*S*)-**18** or (*R*)-**19**, details of the resolution of (±)-**19**, and copies of the $^1$H NMR of all compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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