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Enantiocontrolled Synthesis of a Tetracyclic Aminal Corresponding to the Core Subunit of Diazonamide A

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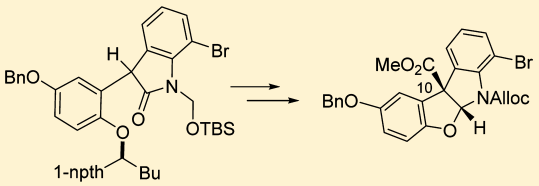
Supporting Information

ABSTRACT: A chiral benzylic ether serves as an auxiliary for oxindole carboxylation (dr 5.2:1.0) that sets C_{10} configuration in a potential diazonamide precursor. The chiral substituent allows diastereomer separation and departs during a subsequent acid-catalyzed ring closure to form a tetracyclic aminal. With suitable N-protection, crystallization affords the aminal with 98−99% ee.



INTRODUCTION

The unusual structure of diazonamide A (**1a**)[1] and its interesting biological effects have stimulated extensive synthetic studies.[2] In most cases, the synthetic approaches have relied on a "left to right" strategy where the peptidic macrocycle is formed prior to the indolyl bisoxazole macrocycle. This has resulted in substantial opportunities to modify and simplify the latter subunit as part of the quest for improved activity.[2d,3] An early effort in our group opted to follow the alternative "right to left" strategy where the peptidic macrocycle might be closed last.[4] In principle, this approach allows late-stage modification of the peptidic ring and may enable preparation of unnatural analogues corresponding to generalized structures **1b** in addition to the natural structure **1a**. With these goals in mind, we initiated a study that was intended to probe the assembly of the indolyl bisoxazole macrocycle via a ketone **2** using relatively conventional methods for cyclization and biaryl coupling (Scheme 1). However, we restricted the choice of alternative routes to ensure that the delicate aminal subunit would be present in the correct oxidation state from an early stage as a way to streamline the eventual investigation of peptidic ring modifications.

Our approach succeeded in preparing *rac*-**2** by a simple base-induced "aza-Dieckmann" cyclization from *rac*-**3** in moderate (29%) yield at partial conversion, but challenges were encountered at several stages. Thus, the unprotected aminal nitrogen in *rac*-**3** was necessary for an acceptable rate of Stille coupling from **4** and *rac*-**5**. However, the NH aminal proved sensitive to fragmentation to form indolic side products, one of which (**6**) was isolated from attempted Pd-catalyzed Stille coupling experiments. This problem could be controlled by using the isolable organopalladium intermediate **4** for coupling with *rac*-**5** to increase the rate of coupling versus fragmentation. Of course, that means using a stoichiometric palladium reagent, but a larger concern was the need for a 1.8-fold excess of *rac*-**5** to obtain a respectable yield of coupled material (54%). That limitation argues against a similar Stille coupling strategy using analogous nonracemic halides because the latter would presumably be even more valuable than the achiral **4**. Furthermore, the route required to prepare *rac*-**5** from a N-protected bromoisatin via *rac*-**7** required approximately 12 steps, including five to attach, remove, and reattach protecting groups. Efforts were therefore initiated to develop a shorter intermolecular Suzuki coupling strategy using a halide similar to **7**, as described in the accompanying paper by Suna et al.[5] Meanwhile, there has been continued interest in the biological activity of diazonamide.[3] Accordingly, our laboratory has been involved in developing an enantiocontrolled synthesis of a tetracyclic aminal halide that is suitable for the Suzuki coupling. Those efforts are described in the current article.

RESULTS AND DISCUSSION

The enantiocontrolled approach described below was designed to parallel our prior synthesis of the racemic aminal halide where the quaternary C_{10} carbon of *rac*-**8** had been generated by a simple carboxylation of a protected oxindole enolate using the Mander reagent. Although one could easily imagine using a chiral Mander reagent R*O_2CCN to prepare nonracemic material,[6] we opted against that approach because it raises unknowns in the macrocyclization step unless the chiral alkoxide R*O is swapped for MeO at some intermediate stage. Given the sensitivity of the aminal carboxylates to fragmentation, as already mentioned in connection with **6**, we considered ways to exploit a chiral auxiliary that is preactivated to depart after it has served its purpose. Several options were considered and tested[6c] before it was realized that our original route provides a built-in opportunity for departure of a chiral auxiliary because of the nature of the aminal-forming step. The aminal *rac*-**7** had been prepared from *rac*-**8** in several steps via cyclization of a presumed cationic intermediate **9a**. Since this process involves heterolysis of the benzylic C−O bond, a chiral benzyl group, as in **9b**, is all that is necessary to meet the requirement for auxiliary departure. The remaining issue is to find an auxiliary that gives useful diastereoselectivity in the Mander carboxylation step and that also facilitates diastereomer

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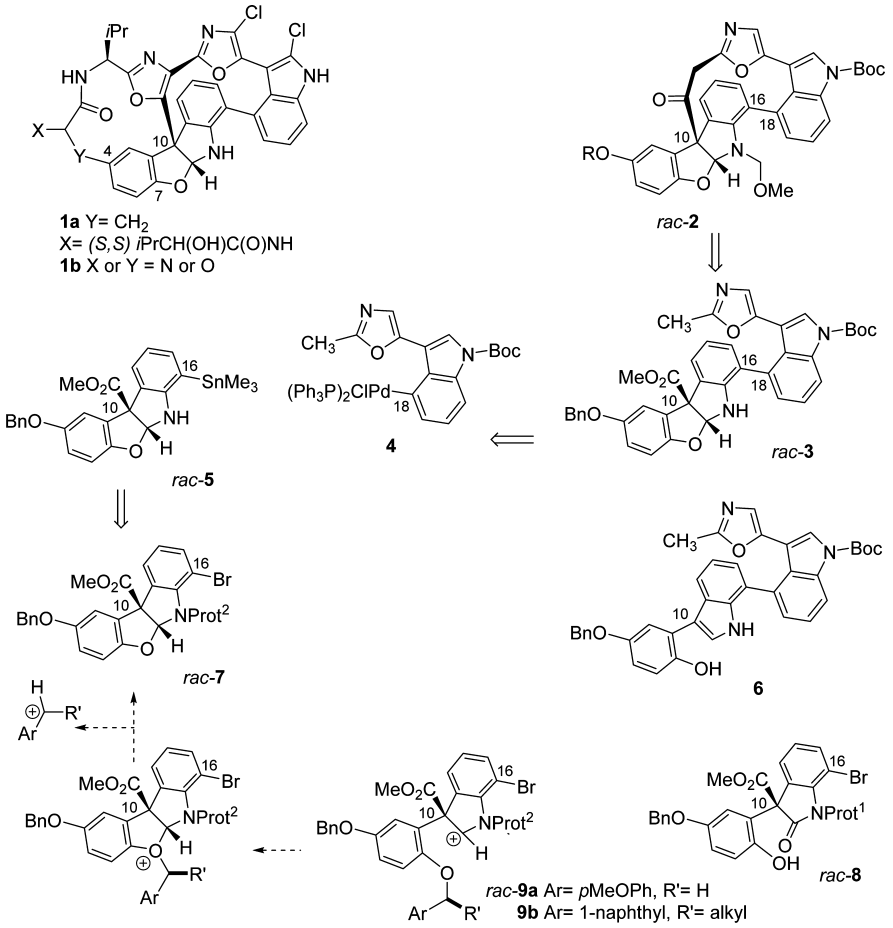
Scheme 1. Access to Aminal Precursors of Macrocyclic Ketone 2



separation if necessary to achieve an acceptable diastereomeric ratio as required for eventual enantiomeric purity.

After a preliminary screening of several chiral naphthyl ethers, a suitable auxiliary was identified and could be prepared from the naphthyl-substituted alcohol **10** (Scheme 2). Preparation of (*R*)-**10** used the precedented[7] enantioselective reduction of 1-naphthylpentan-1-one with (+)-DIP-chloride and provided the alcohol with 95% ee or better, depending on the purity of commercial reagent. The experimental conditions advised for DIP-Cl reductions[8] were instrumental for the processing of multigram quantities of ketone (typically, 12 g scale, 84% yield). The configuration of alcohol (*R*)-**10** was assigned according to the usual model[8] and was also supported by comparing the sense of optical rotation of (*R*)-**10** with material prepared using a different method.[9] Similarly, (*S*)-**10** was obtained using (−)-DIP-chloride, and both enantiomers (*R*)-**10** or (*S*)-**10** were then reacted with 4-benzyloxy-2-bromophenol[10] under Mitsunobu conditions (Bu_3P and diisopropyl azodicarboxylate, DIAD). As illustrated in Scheme 2, this gave (*S*)-**11** with excellent S_N2 stereospecificity (inversion at carbon) from chiral alcohol (*R*)-**10**, and a similar sequence was used to prepare the enantiomeric (*R*)-**11** from (*S*)-**10**. Reliable conditions for Mitsunobu coupling required the use of excess phenol (2.2 equiv) and gave high yields (84%), while efficient temperature control promoted excellent stereospecificity, resulting in **11** with 95% ee or better.

Eventually, it was shown that (*S*)-**11** has the desired directing effect to guide the intended C_{10} Mander carboxylation from the correct face. However, this was not known initially, and many experiments were conducted in the "incorrect" enantiomeric series. The configurations will be revisited at the aminal stage, and some data for the *ent* series are mentioned in the Experimental Section, but the subsequent synthetic steps will be illustrated using the "correct" series until the last stage.

With ample supplies of (*S*)-**11** available, lithium−halogen exchange was performed using *n*-butyllithium at −95 °C. Despite the low temperature and the usual precautions, significant (ca. 10−20%) protonolysis could not be prevented over the sequence involving addition to the bromoisatin **12**,[4] but formation of the desired alcohol intermediate **13** could be confirmed by quenching with thionyl chloride to give the relatively stable and easily isolated chloride **14**. Adaptation of the $SOCl_2$ methodology to multigram scale required careful temperature control because the exotherm is capable of increasing temperature by 20 °C or more. It was found that $SOCl_2$ was well behaved below −40 °C, and starting from **11** (4.6 g scale), a synthetically useful and reproducible yield of chloride **14** could be obtained (53% overall from **11**, diastereomer mixture). However, alcohol **13** was difficult to purify due to minor impurities that coelute with the desired product, and crude **13** was usually taken directly on to chloride **14**.

Similar issues were encountered in the next stage, where stepwise conversion of **14** to the parent lactam **15** had been planned. This could be done using Zn/HOAc, and **15** could be isolated and characterized. However, the easily enolized lactam proved to be somewhat sensitive to air oxidation, and it was best to use the crude **15** in the crucial next step (Mander

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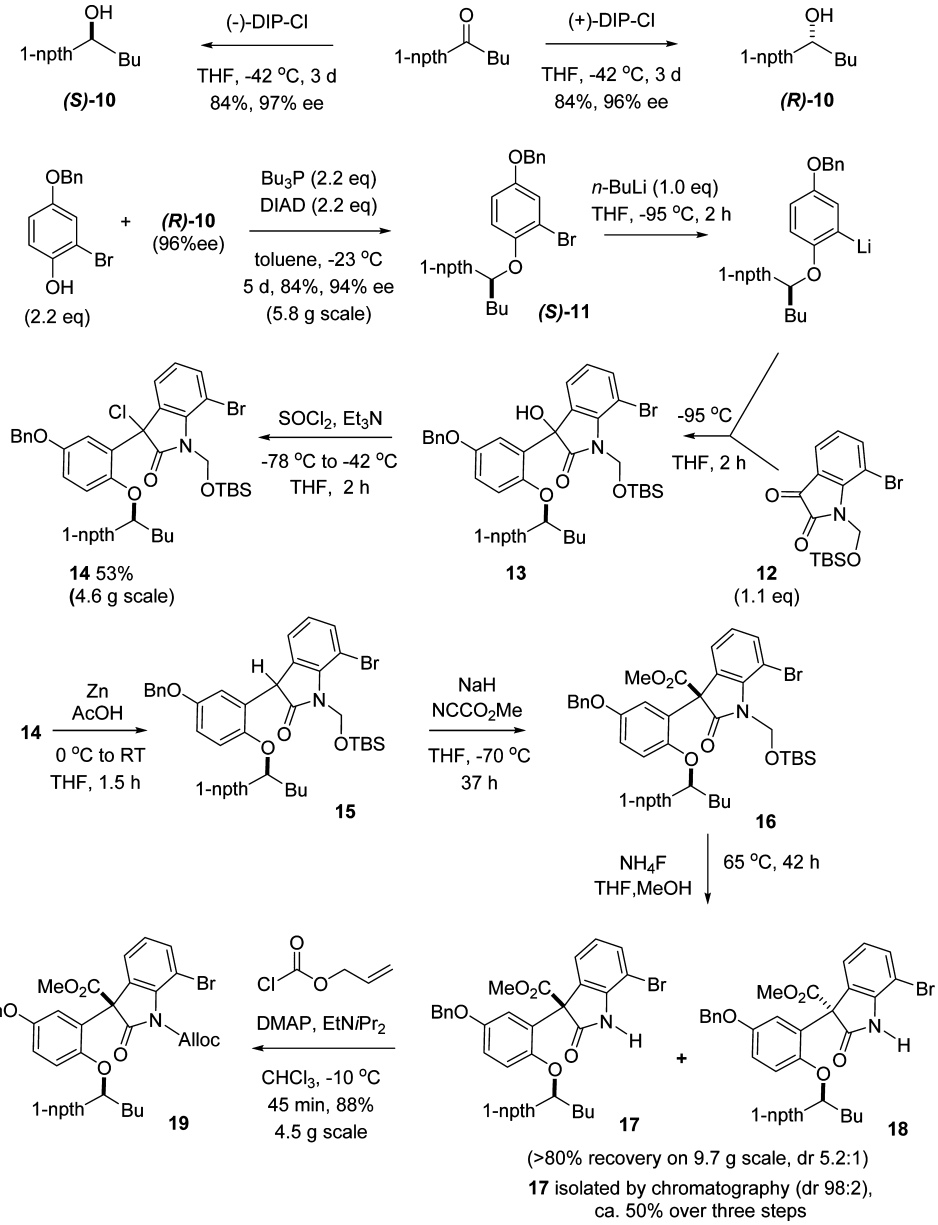
Scheme 2. Quaternary Carbon Formation by Enolate Carboxylation



carboxylation). Furthermore, it was difficult to assay the initially formed N-CH_2OTBS lactam **16**. For that reason, the desired C_{10} carboxylation was followed by deprotection of crude **16** using NH_4F, and the resulting N−H lactam **17** was purified. This amounts to a three-step sequence from **14** before purification at the stage of **17**.

In the event, this strategy presented a practical solution to problems of stability as well as product assay. Deprotonation with NaH was conducted at −70 °C in THF, and treatment with $NCCO_2Me$ was allowed to proceed slowly (37 h) at the same low temperature to maximize diastereoselection. The resulting product mixture was then deprotected with NH_4F at 65 °C in THF/MeOH to give a diastereomer mixture of oxindoles **17** and **18** (5.2:1 **17**/**18**) isolated in >80% yield over the three steps (Scheme 3). The mixture was separated by careful column chromatography, so that about 50% of the major diastereomer **17** was routinely isolated in the first elution (dr = 98:2 **17**/**18**) with a further 5−10% of **17** recovered by recycling mixed fractions. Finally, **17** was converted into the *N*-alloc (*N*-allyloxycarbonyl) derivative **19** (88%) using allyl chloroformate in the presence of DMAP/$EtNiPr_2$. Initially, alloc protection was intended to intercept the known tetracyclic aminal in the racemic series,[4] but the nonracemic *N*-alloc aminal proved especially advantageous because its excellent crystallinity could be exploited for upgrading enantiomeric purity.

The *N*-alloc lactam *ent*-**19** was then taken on to the tetracyclic aminal via reduction to the hemiaminal *ent*-**20a**, followed by acid-catalyzed cyclization (Scheme 3). In one of the first test experiments, imide *ent*-**19** was reduced with $NaBH_4$, and the resulting hemiaminal *ent*-**20** was cyclized to aminal *ent*-**22** upon brief exposure to cold methanesulfonic acid in low yield (28%). Although the product compared well with *rac*-**22** according to the usual NMR characteristics,[4] we were dismayed to find that *ent*-**22** had been formed with 67% ee even though the starting lactam *ent*-**19** has 96% ee based on the enantiomeric purity of the precursor **11**. A similar experiment from *ent*-**20** using trifluoroacetic acid (TFA) as catalyst in

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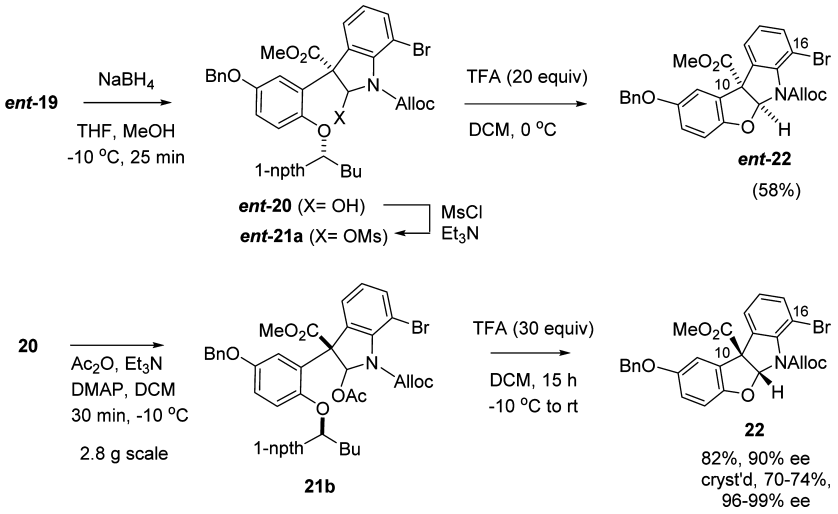
Scheme 3. Aminal Formation



$CDCl_3$ at room temperature gave improved stereospecificity (79% ee) but a slower reaction. Preliminary control experiments indicated that *ent*-**22** is not racemized by TFA, but other attempts to probe the origin of partially racemic aminal were not definitive.

The above observations prompted a re-evaluation of the aminal-forming step and raised suspicions that some form of acid-catalyzed retro-aldol cleavage by *ent*-**20** may be responsible for partial loss of C_{10} stereochemistry. In an attempt to induce aminal formation without exposing *ent*-**20** to acid, a sample of carefully purified *ent*-**19** was reduced on small (27 mg) scale with $NaBH_4$ and the resulting *ent*-**20** was treated with MsCl/Et_3N at 0 °C. The mesylate *ent*-**21a** apparently was formed in situ as a nonpolar intermediate according to TLC assay, but it did not cyclize appreciably within 15 min at 0 °C, and the reaction proceeded only slowly at room temperature. On the other hand, the presumed *ent*-**21a** did cyclize within 30 min upon addition of excess TFA at 0 °C to give the aminal *ent*-**22** in modest (50−58%) yield but with 97% ee. This encouraging experiment confirmed that TFA does not racemize the product aminal and also that borohydride reduction takes place without racemization. These findings implicate the hemiaminal *ent*-**20** as the intermediate that is at risk for epimerization at C_{10}, resulting in formation of partially racemic **22**.

A major benefit of the exploratory experiments was the realization that the highly crystalline *ent*-**22** can be upgraded by simple recrystallization to give material having 97% ee or better (HPLC assay). Although this procedure was not quantified in the *ent* series, it afforded high-quality crystals suitable for X-ray crystallography. The resulting crystal structure (see Supporting Information) established that intermediates derived from (*R*)-**11** are converted into the unnatural C_{10} configuration during the Mander carboxylation. Accordingly, further optimization studies were performed using substrates having the correct absolute stereochemistry, shown for simplicity in most intermediates that appear in Schemes 1 and 2.

The above experiments stimulated a cyclization attempt using the conveniently generated acetate **21b** (correct C_{10} series). Thus, treatment of hemiaminal **20** with Ac_2O/DMAP formed **21b** in situ and addition of excess TFA gave the desired aminal **22** (Scheme 3). This procedure was then adapted for preparative scale experiments and proved straightforward in a multigram protocol. Only two variables were ultimately readjusted: (1) the $NaBH_4$ reduction was performed at −10 °C and (2) the in situ mesylation step was replaced by in situ acetylation of **20** with Ac_2O/DMAP to generate **21b**. These adjustments improved the yield of the three-step sequence to 82% starting from imide **19** (2.8 g batch) and had no effect on the stereochemical outcome of the cyclization compared to small scale (90% ee or better in chromatographically purified fractions of aminal **22**). The starting imide **19** was processed as a 98:2 mixture of C_{10} diastereomers according to HPLC assay, and each diastereomer would have consisted of the same 97.5:2.5 ratio of enantiomers as in the starting chiral ether (*S*)-**11**. Therefore, an empirical value of 90% ee would mean <3% racemization, given the limits of assay uncertainty. On a preparative scale, tetracycle (−)-**22** was easily upgraded to 97−99% ee by simple crystallization. Typically, this gave **22** in 70−74% yield, although one experiment gave 99% ee material in 79% yield, apparently due to a more successful chromatographic purification of the starting **19**. The reason for convenient crystallizations, in general, became clear when the enantiopure crystals of **22** (mp 129−131 °C) were found to melt at a higher temperature than the racemate (mp 108 °C),[11] but the quality of the immediate synthetic precursors was also a factor.

While the mechanistic details of racemization from **20** to **22** as well as for the TFA-induced cyclization via **21b** remain unclear, the procedure shown in Scheme 3 has proven to be a reliable source of highly enriched aminal **22**. Overall, seven workup stages and five purifications are required from the chiral alcohol **10** to aminal **22**, and the overall yield is 13% or better, depending on the effort made to recycle mixed fractions from chromatography and crystallization.

■ CONCLUSIONS

A number of total syntheses or formal syntheses of diazonamide have been reported.[2] In most cases, the priorities dictated by complex multistep synthesis have resulted in the installation of the aminal subunit near the end of the sequence, usually after separating partially enriched C_{10} diastereomer mixtures. Total control over C_{10} stereochemistry was reported in a formal total synthesis by taking advantage of intramolecular C_{10}−C_{30} bond formation governed by conformational preferences along a peptidic tether,[2f] and a similar principle was used earlier by Harran et al. in their remarkably short total

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synthesis.[2b] Also remarkable is the recent MacMillan synthesis where the C_{10} quaternary carbon (4.2:1 dr) was set by intermolecular reaction of a chiral propynal iminium species with a C_{10}–Ar indole (diazonamide numbering; Ar has OH at C_7 and a peptide side chain at C_4).[2g] After spontaneous aminal formation, degradation of the newly formed (C_{10})–CH=CHCHO to (C_{10})–CHO, and exchange of aminal N-protecting groups without ring opening,[12] the synthesis was completed with the correct aminal in place. So far, this appears to be the most direct approach to nonracemic, tetracyclic aminals analogous to **22**. In principle, the MacMillan approach does not rely on internal directing groups, although diastereomer separation was used to obtain enriched material.

Many model studies have been reported describing promising approaches to the C_{10} quaternary carbon.[2,13] Among these efforts, Moody's approach is noteworthy because it has also reached the tetracyclic aminal stage using an oxidative carboxyl migration to introduce a C_{10} ester group.[13a] The latter study did not attempt to control diastereoselection, but 11:1 dr at the relevant oxindole C_{10} was achieved in a second study using a simplified substrate and a chiral carboxamide as the migrating group.[13b]

The sequence reported in Schemes 2 and 3 has proven useful for the preparation of multigram quantities of **22** with the correct C_{10} configuration (>98% ee) and has enabled the investigation of an intermolecular C_{16}–C_{18} Suzuki coupling approach to the nonracemic macrocyclic ketone **2**.[5] We note that one of the steps in the MacMillan synthesis employs an intramolecular version of Suzuki coupling and also assembles the macrocyclic ring by bond formation at C_{16}–C_{18} with the aminal already present. Our approach requires diastereomer separation to solve the C_{10} problem, as do all of the total syntheses reported to date. There are inherent advantages in separating C_{10} diastereomers **17** and **18** at a relatively simple and early stage, but evaluation must await the demonstration of an efficient version of the "right to left" strategy in a fully elaborated target structure.

EXPERIMENTAL SECTION

General. High-resolution mass spectra were obtained using a magnetic sector analyzer with an electron impact ionization source.

(1*R*)-1-Naphthalen-1-yl-pentan-1-ol ((*R*)-10). 1-Naphthalen-1-yl-pentan-1-one[7] (12.60 g, 59.35 mmol, 1.0 equiv) was placed in an oven-dried flask and dissolved in dry THF (60 mL, 1.0 M). The resulting colorless solution was cooled to −42 °C. (+)-DIP-Cl[8] (19.99 g, 62.32 mmol, 1.05 equiv) was placed in an oven-dried flask in the glovebox. The flask was then removed from the glovebox and cooled to −42 °C. The ketone solution was then cannulated dropwise into the solid (+)-DIP-Cl while stirring the solid. The flask containing the ketone was rinsed with 4.0 mL of THF, and the rinses were cannulated into the reaction flask, as well. The resulting yellow solution was stirred at −42 °C for 3 days. At this point, THF was removed under a N_2 stream. The resulting thick yellow oil was dissolved in dry Et_2O (200 mL), and diethanolamine (12.7 mL, 125 mmol, 2.2 equiv) was added by syringe in one portion. The resulting cloudy white suspension was stirred at room temperature for 2 h. The precipitate was filtered and washed with 700 mL of hexanes, and the filtrate was collected and concentrated under reduced pressure. The resulting clear, colorless oil was purified by flash column chromatography (9 cm × 18 cm; 50 mL fractions; eluting with 1.5 L hexanes, 1 L 9:1 hexanes/Et_2O, 1 L 8:2 hexanes/Et_2O, and 2 L 7:3 hexanes/Et_2O) to yield 10.8 g (84%) of (*R*)-**10** as a clear oil that solidified upon standing: TLC, 8:2 hexanes/Et_2O, R_f = 0.44; mp = 50–51 °C. The NMR spectra are consistent with published spectra for the known substance,[9] but ^{1}H data are included below because our analysis of splittings is more detailed: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.12 (1H, d, J = 8.3 Hz), 7.88 (1H, d, J = 9.3 Hz), 7.78 (1H, d, J = 8.3 Hz), 7.65 (1H, d, J = 6.8 Hz), 7.53–7.47 (3H, m), 5.48 (1H, ddd, J = 7.3, 3.9, 3.4 Hz), 2.01–1.88 (2H, m), 1.90 (1H, d, J = 3.4 Hz), 1.58–1.33 (4H, m), 0.91 (3H, t, J = 7.3 Hz); HPLC (Chiralcel OD, 1 mL/min, 95:5 hexanes/isopropyl alcohol) 10.62 min (1.98% area), 19.30 min (98.2% area), 96% ee. The same procedure was used to prepare (*S*)-**10** using (−)-DIP-Cl:[8] HPLC (Chiralcel OD, 1 mL/min, 95:5 hexanes/isopropyl alcohol) 11.01 min (99.5% area), 21.98 (0.5% area), 99% ee; $[\alpha]_D^{25}$ = −75 (*c* 1.300, $CHCl_3$); previous literature,[9] $[\alpha]_D^{25}$ = −72 (*c* 1.0, $CHCl_3$) for (*S*)-**10** having 91% ee.

1-[(1*S*)-1-(4-Benzyloxy-2-bromophenoxy)pentyl]-naphthalene ((*S*)-11). 4-Benzyloxy-2-bromophenol[10] (16.44 g, 59.4 mmol, 2.2 equiv) and (*R*)-(**10**) (96% ee) (5.78 g, 27.0 mmol, 1.0 equiv) were dissolved in 45 mL of freshly distilled toluene (0.6 M) and cooled to −42 °C. Tributylphosphine (15.5 mL, 62.1 mmol, 2.3 equiv) was syringed into the reaction in one portion. Then, a room temperature solution of DIAD (12.0 mL, 62.1 mmol, 2.3 equiv) in 9.0 mL of toluene was cannulated dropwise. The resulting red solution was stirred at −42 °C for 5 days. This was poured into 200 mL of saturated NH_4Cl(aq) and extracted with Et_2O. Organics were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting orange oil (53.4 g) was purified by flash column chromatography (gradient of 8:2 hexanes/toluene (2 L), then 6:4 hexanes/toluene (1 L), then 1:1 hexanes/toluene (2 L) to yield 10.82 g (84% yield) of (*S*)-**11** as a clear, colorless oil: TLC, 6:4 hexanes/toluene, R_f = 0.54; ESI-MS calcd for $C_{28}H_{27}BrO_2Na^+$ m/z 499.1072; found 499.1096, error = 5 ppm; IR (neat, cm^{-1}) 2952, 1486, 1202; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.16 (1H, d, J = 8.8 Hz), 7.89 (1H, d, J = 7.8 Hz), 7.78 (1H, d, J = 7.8 Hz), 7.61–7.54 (2H, m), 7.51 (1H, dd, J = 7.3, 6.8 Hz), 7.42 (1H, dd, J = 8.3, 7.2 Hz), 7.37–7.26 (5H, m), 7.19 (1H, d, J = 2.9 Hz), 6.54 (1H, dd, J = 9.3, 2.9 Hz), 6.43 (1H, d, J = 8.9 Hz), 5.77 (1H, dd, J = 8.1, 3.9 Hz), 4.88 (2H, s), 2.24–2.01 (2H, m), 1.75–1.47 (2H, m), 1.41–1.36 (2H, m), 0.91 (3H, t, J = 7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ 152.8, 149.1, 137.1, 136.7, 133.9, 130.1, 129.1, 128.5, 128.0, 127.4, 126.2, 125.6, 125.5, 123.8, 122.8, 120.0, 120.0, 115.0, 114.3, 112.6, 79.0, 70.6, 37.5, 28.3, 22.5, 14.0; HPLC (OD Chiralcel, 1 mL/min, 95:5 hexanes/isopropyl alcohol) 6.28 min (97.22%), 15.87 min (2.78%). The same procedure was used to prepare (*R*)-**11** from (*S*)-**10** (97% ee): HPLC (OD Chiralcel, 1 mL/min, 95:5 hexanes/isopropyl alcohol) 6.32 min (2.0% area), 13.75 min (98.0% area); 96% ee, $[\alpha]_D^{25}$ = −114 (*c* 1.035, $CHCl_3$).

3-[5-Benzyloxy-2-((1*S*)1-naphthalen-1-ylpentyloxy)phenyl]-7-bromo-1-(*tert*-butyldimethylsilanyloxymethyl)-3-chloro-1,3-dihydroindol-2-one (14). A solution of BuLi (5.90 mL of a 1.53 M solution in hexanes; 9.12 mmol, 1.0 equiv) in 40 mL of dry THF (0.08 M is targeted final concentration) was cooled to −95 °C in an oven-dried three-neck round-bottom flask equipped with a thermometer adapter and two oven-dried jacketed addition funnels. Aryl bromide **11** (4.56 g, 9.60 mmol, 1.0 equiv) was placed in an oven-dried round-bottom flask as a solution in Et_2O; the volatiles were removed under reduced pressure, and the resulting colorless oil was exposed to high vacuum for 1 h. Then, aryl bromide **11** was dissolved in 30 mL of dry THF, syringed into a jacketed addition funnel, and cooled to −78 °C. Isatin **12** (3.91 g, 10.6 mmol, 1.1 equiv)[4] was placed in an oven-dried round-bottom flask and exposed to high vacuum for 1 h. Next, isatin **12** was dissolved in 30 mL of dry THF and syringed to a jacketed addition funnel and cooled to −78 °C. The aryl bromide solution was added to the BuLi solution over a period of 18 min, maintaining the internal temperature of the reaction solution below −90 °C. After a minute pause, the isatin solution was added into the reaction solution over 10 min, maintaining the internal temperature below −90 °C. The resulting dark purple solution was stirred at −95 °C for 2 h 45 min. At this point, the reaction mixture was quenched cold with a solution of AcOH (1.0 mL) in 5 mL of Et_2O; the resulting orange solution was warmed to room temperature, neutralized with saturated aqueous $NaHCO_3$ solution, and poured into a separatory funnel, where it was extracted with Et_2O. The organic extracts were combined, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to yield the

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crude alcohol **13** (1:1 mixture of diastereomers, R_f = 0.08, 0.13, 9:1 hexanes/Et_2O) as a thick orange-red oil. This material was exposed to high vacuum for 30 min before dissolving it in 41 mL of dry THF. To this solution was added Et_3N (5.1 mL, 36.5 mmol, 4.0 equiv) with syringe. A solution of $SOCl_2$ (distilled over CaH_2, 1.30 mL, 18.2 mmol, 2.0 equiv) in 50 mL of THF (0.1 M is the targeted final concentration) was cooled to −78 °C in an oven-dried three-neck round-bottom flask equipped with a thermometer adapter and an oven-dried jacketed addition funnel. The solution of crude alcohol/Et_3N was added by syringe into the addition funnel, cooled to −78 °C, and added to the $SOCl_2$ solution over 12 min, maintaining the internal temperature below −70 °C. The resulting brown solution was stirred at −78 °C for 15 min and then warmed to −42 °C for 45 min. At this point, it was cautiously poured into 250 mL of saturated aqueous $NaHCO_3$ and stirred for 10 min. The biphasic mixture was transferred to an addition funnel and extracted with Et_2O. The organic extracts were combined and washed sequentially with 250 mL of a 0.1 M HCl aqueous solution and 250 mL of a saturated aqueous $NaHCO_3$ solution. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield a red oil. This was purified by flash column chromatography (95:5 hexanes/Et_2O) to yield 3.42 g (53% for the two steps, contaminated with ca. 2% impurities) of a 1:1 mixture of chloride **14** diastereomers as a fine off-white powder: TLC, 7:3 hexanes/Et_2O, R_{f1} = 0.33, R_{f2} = 0.41; ESI-MS calcd for $C_{43}H_{47}BrClNO_4SiNa^+$ m/z 806.2044; found 806.2043, error = 0.1 ppm; IR (neat, cm^{-1}) 2955, 2929, 1746, 1488, 1218; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 7.88 (0.5H, d, J = 7.3 Hz), 7.82−7.78 (2H, m), 7.71 (0.5H, d, J = 7.8 Hz), 7.62 (0.5H, d, J = 8.3 Hz), 7.56 (0.5H, d, J = 7.8 Hz), 7.53−7.29 (9H, m), 7.04−6.99 (2H, m), 6.91 (0.5H, t, J = 7.8 Hz), 6.59−6.54 (1H, m), 6.23 (0.5H, d, J = 9.3 Hz), 6.15 (0.5H, d, J = 8.8 Hz), 5.94 (0.5H, br s), 5.82−5.74 (2 overlapping ABq, 2H, m), 5.68 (0.5H, br s), 5.51 (0.5H, br d, J = 7.3 Hz), 4.98 (1H, s), 4.96 (1H, s), 1.75−1.58 (2H, m), 1.44−1.12 (4H, m), 0.93 (4.5H, s), 0.88 (4.5H, s), 0.75 (3H, t, J = 7.3 Hz), 0.23 (1.5H, s), 0.15 (3H, s), 0.09 (1.5H, s); ^{13}C NMR (126 MHz, $CDCl_3$, ppm) 174.2, 173.9, 152.2, 152.2, 147.8, 139.9, 139.6, 137.0, 137.0, 136.5, 136.2, 135.6, 135.4, 134.4, 134.33, 133.7, 133.6, 130.0, 129.6, 129.3, 129.2, 128.5, 127.9, 127.8, 127.6, 127.6, 127.5, 126.4, 126.1, 125.5, 125.5, 125.3, 124.4, 124.3, 124.2, 123.9, 123.6, 123.4, 123.2, 121.8, 117.9, 117.5, 115.4, 115.3, 112.7, 112.5, 103.3, 103.2, 77.5 (benzylic OCH_2, partly obscured by solvent signals), 70.8, 70.7, 66.4, 66.2, 65.1, 64.8, 37.5, 28.8, 28.3, 26.0, 25.8, 25.7, 22.8, 22.6, 18.3, 18.0, 14.0, 14.0, −4.7, −4.9, −5.2, −5.3. In addition, small signals at 31.6, 22.6, and 14.1 ppm were present that could not be attributed to the structure and are presumed to be due to unknown impurities. For the diastereomer mixture, as many as 54 sp^2 carbon signals (27 pairs) are possible, but several pairs of aromatic signals were not resolved. The expected pair of methylene signals ArOCH(Npth)CH_2 at 37.5 ppm was also not resolved.

3-[5-Benzyloxy-2-(1-naphthalen-1-ylpentyloxy)phenyl]-7-bromo-1-(*tert*-butyldimethylsilanyloxymethyl)-3-hydroxy-1,3-dihydroindol-2-one (13). For characterization purposes, the following procedure for isolation of alcohol **13** was used, but it was normally used as the crude material (see above procedure for **14**). The adduct derived from lithium−halogen exchange starting from **11** (369 mg, 0.775 mmol) and addition to isatin **12** (660 mg, 1.782 mmol, 2.3 equiv) was worked up as described above to give 901 mg of crude orange oil. The crude was purified by flash column chromatography (8:2 DCM/hexanes) to yield 309 mg in the best fractions (52%) of **13** as a clear, colorless foam, isolated as a 1:1 mixture of diastereomers: TLC, 8:2 hexanes/Et_2O, R_f = 0.25; ESI-MS calcd for $C_{43}H_{48}BrNO_5SiNa^+$ m/z 790.2362; found 790.2334, error = 4 ppm; IR (neat, cm^{-1}) 3373, 1720, 1220; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 7.90−7.79 (2H, m), 7.72 (0.5H, dd, J = 6.8, 1.9 Hz), 7.64−7.26 (10.5H, m), 7.11−6.97 (2H, m), 6.91 (0.5H, t, J = 7.8 Hz), 6.54 (0.5H, dd, J = 8.8, 2.9 Hz), 6.50 (0.5H, dd, J = 8.8, 2.9 Hz), 6.23 (0.5H, d, J = 8.8 Hz), 6.18 (0.5H, d, J = 9.3 Hz), 6.05 (0.5H, br s), 5.81−5.67 (2.5H, m), 5.55 (0.5H, br d, J = 6.3 Hz), 4.94 (2H, ABq, J = 11.7 Hz, $\Delta\nu$ = 11.1 Hz), 3.18 (0.5H, br s), 3.02 (0.5H, br s), 1.84−1.63 (2H, m), 1.50−1.09 (4H, m), 0.91 (4.5H, s), 0.88 (4.5H, s), 0.76 (3H, t, J = 7.3 Hz), 0.20 (1.5H, s), 0.12 (1.5H, s), 0.11 (1.5H, s), 0.10 (1.5H, s); ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ 177.7, 177.6, 152.4, 152.3, 147.9, 141.0, 140.9, 137.2, 137.1, 136.7, 136.7, 135.4, 135.3, 133.8, 133.7, 133.7, 133.6, 130.0, 129.8, 129.3, 129.1, 128.5, 128.4, 128.4, 128.0, 127.8, 127.8, 127.7, 127.6, 127.4, 127.4, 126.2, 126.1, 125.6, 125.4, 125.3, 124.3, 123.9, 123.6, 123.3, 121.9, 121.8, 115.0, 114.7, 114.2, 114.0, 112.5, 112.4, 103.5, 103.2, 75.5, 75.3, 70.4, 64.7, 64.5, 37.8, 37.5, 28.8, 28.5, 25.8, 25.7, 22.8, 22.6, 18.3, 18.0, 14.0, −4.8, −4.9, −5.2, −5.3. For the diastereomer mixture, as many as 54 sp^2 carbon signals (27 pairs) are possible, but several pairs of aromatic signals were not resolved. The expected pair of methylene signals at 70.4 ppm and the methyl signals at 14.0 ppm were also not resolved.

(3*R*)-3-[(1*S*)-5-Benzyloxy-2-(1-naphthalen-1-ylpentyloxy)-phenyl]-7-bromo-2-oxo-2,3-dihydro-1*H*-indole-3-carboxylic Acid Methyl Ester (17) and the Minor Diastereomer (18). Chloride **14** (9.74 g, 12.39 mmol, 1.0 equiv) was placed in an oven-dried round-bottom flask and flushed with N_2 for 10 min before dissolving it in THF (124 mL)/AcOH (12 mL) and cooling the resulting light yellow solution to 0 °C. Zn dust (<10 μm, 16.21 g, 247.9 mmol, 20.00 equiv) was added in one portion, and the resulting gray suspension was warmed to room temperature and vigorously stirred for 1.5 h. Then, the AcOH was cautiously quenched with saturated aqueous $NaHCO_3$; the ensuing biphasic mixture was transferred to a separatory funnel, where it was extracted with Et_2O. The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield the intermediate oxindole **15** as a colorless foam (R_f = 0.45, 8:2 hexanes/Et_2O). The purity of the crude oxindole was sufficient for the carboxylation reaction, which was initiated by exposing the oxindole to high vacuum for 30 min before dissolving it in anhydrous THF (124 mL, 0.1 M) and cooling the resulting colorless solution to 0 °C. NaH (2.48 g of a 60% dispersion in mineral oil, 62 mmol, 5.0 equiv) was charged in one portion, and the resulting suspension was warmed to room temperature. The reaction slowly acquired a yellow color which, after 30 min, had changed to green. At this point, the reaction mixture was cooled to −78 °C; methyl cyanoformate (9.8 mL, 123.9 mmol, 10 equiv) was syringed in dropwise, and the reaction flask was placed in a cryocool equilibrated to −70 °C. After 37 h, the reaction mixture was quenched cold with 4 mL of AcOH and was warmed to room temperature. The excess acetic acid and methyl cyanoformate were decomposed by stirring the quenched reaction mixture with saturated aqueous $NaHCO_3$ for 45 min. The resulting biphasic mixture was extracted with Et_2O, and the organic extracts were combined, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting orange oil was subjected to flash column chromatography (6.5 cm wide, 15 cm long; 1.5 L 9:1 hexanes/Et_2O, 1 L 8:2 hexanes/Et_2O; 50 mL fractions; desired material elutes in fractions 24 to 49) to yield 9.621 g of the intermediate *N*-TBOM carboxylated oxindole **16** (R_f = 0.36, 8:2 hexanes/Et_2O) contaminated with minor impurities as an off-white foam. This crude mixture was dissolved in THF/MeOH (100 mL, 148 mL, 0.05 M) in a round-bottom flask equipped with a condenser. To the resulting solution was added NH_4F (9.18 g, 247.9 mmol, 20 equiv) in one portion, and the light yellow suspension was heated to 70 °C for 42 h. At this point, the reaction mixture was cooled to room temperature, diluted with 1.2 L of Et_2O, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to yield 10.38 g of a yellow-orange thick oil. The crude dr was 5.2:1.0 by NMR assay; the dr was measured by the relative integration values for a doublet centered at 6.70 ppm (d, J = 2.9 Hz, major diastereomer) and a doublet centered at 6.83 ppm (d, J = 2.9 Hz, *minor* diastereomer). This was purified by flash column chromatography (6.5 cm × 18.0 cm; 1.5 L 6:2:1 hexanes/DCM/Et_2O, 1.7 L 4:2:1 hexanes/CH_2Cl_2/Et_2O; 50 mL fractions) to yield 7.20 g of **17** + **18** as a white foam with a diastereomeric ratio of 5.2:1 (87% yield).

Diastereomer separation: On 100−200 mg scale, the two diastereomers are easily separated by preparatory TLC (1:1 hexanes/Et_2O). With larger amounts of material (>200 mg), the following procedure was implemented. To a solution of **17** + **18** from above (7.20 g) in DCM (~50 mL) was added 72 mL of silica gel. The resulting slurry was slowly evaporated under reduced pressure, and it was loaded on top of a silica gel column (9 cm × 20 cm). The silica

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plug was then sequentially eluted with 8 L (8:2 hexanes/Et_2O), 6 L (7:3 hexanes/Et_2O), and 3 L (65:35 hexanes/Et_2O); at this point, the major diastereomer (**17**, 4.14 g) was collected over the next 3.5 L of eluate (65:35 hexanes/Et_2O) and mixed fractions of both diastereomers (2.88 g, 1:1 dr by NMR) over the following 3 L of eluate. Major diastereomer **17**: TLC, 1:1 hexanes/Et_2O, R_f = 0.45. ESI-MS calcd for $C_{38}H_{34}BrNO_5Na^+$ m/z 686.1518; found 686.1519, error = 0.1 ppm; IR (neat, cm^{-1}) 3169, 2952, 1726, 1493, 1224; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 7.96 (1H, d, J = 8.3 Hz), 7.94 (1H, d, J = 7.8 Hz), 7.74−7.73 (2H, m), 7.59−7.41 (5H, m), 7.33−7.26 (6H, m), 6.97 (1H, t, J = 8.0 Hz), 6.70 (1H, d, J = 2.9 Hz), 6.52 (1H, dd, J = 2.9, 9.3 Hz), 6.26 (1H, d, J = 9.3 Hz), 5.71 (1H, dd, J = 7.3, 3.4 Hz), 4.82 (2H, s), 3.85 (3H, s), 1.86−1.78 (2H, m), 1.27−1.21 (2H, m), 1.09 (2H, m), 0.81 (3H, t, J = 7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$, ppm) 172.7, 168.3, 152.1, 149.9, 140.6, 136.9, 136.8, 133.8, 131.7, 130.0, 129.8, 129.24, 128.5, 127.9, 127.7, 127.4, 126.2, 125.4, 125.1, 124.7, 124.0, 123.4, 122.1, 117.1, 114.5, 113.8, 102.6, 77.8, 70.6, 64.3, 53.5, 37.6, 28.1, 22.6, 14.0. One of the sp^2 carbon signals was not resolved (28 expected): HPLC (Chiralcel OD, 1 mL/min, 85:15 hexanes/isopropyl alcohol) 7.90 min (major diastereomer, 98.5%); 18.43 min (minor diastereomer, 1.5%). A similar procedure was used starting from aryl ether (*R*)-**11** (96% ee) via *ent*-**14** to prepare *ent*-**17**: $[\alpha]_D^{25}$ = −103 (*c* 2.09, $CHCl_3$). Minor diastereomer **18**: TLC, 1:1 hexanes/Et_2O, R_f = 0.37; ESI-MS calcd for $C_{38}H_{34}BrNO_5Na^+$ m/z 686.1518; found 686.1533, error = 2 ppm; IR (neat, cm^{-1}) 3169, 1729, 1493, 1225; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 7.93 (1H, d, J = 8.3 Hz), 7.86 (1H, d, J = 7.8 Hz), 7.67 (1H, d, J = 7.8 Hz), 7.54−7.45 (4H, m), 7.34−7.28 (6H, m), 7.19 (1H, t, J = 7.8 Hz), 7.04 (1H, t, J = 7.8 Hz), 6.83 (1H, d, J = 2.9 Hz), 6.71 (1H, br s), 6.52 (1H, dd, J = 2.9, 8.8 Hz), 6.28 (1H, br d, J = 8.8 Hz), 5.80 (1H, br s), 4.85 (2H, s), 3.85 (3H, s), 1.90−1.82 (2H, br), 1.52−1.50 (1H, br), 1.40−1.35 (3H, br), 0.90 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 172.9, 168.1, 152.0, 149.4, 140.8, 137.0, 136.5, 133.7, 131.6, 130.5, 130.0, 129.2, 128.5, 127.9, 127.7, 127.4, 126.3, 125.7, 125.4, 125.1, 124.8, 123.8, 123.2, 121.9, 117.3, 114.5, 113.3, 102.5, 70.6, 64.4, 53.5, 37.5, 28.0, 22.8, 14.0. In addition, a minor unassignable signal was observed at 29.6 ppm and is presumed to be an impurity. The methane carbon signal for the chiral auxiliary benzylic carbon (typically 77−78 ppm) was not detected and is presumed to be obscured by solvent $CDCl_3$ signals.

3-[5-Benzyloxy-2-((1*R*)-1-naphthalen-1-ylpentyloxy)phenyl]-7-bromo-1-(*tert*-butyldimethylsilanyloxymethyl)-1,3-dihydroindol-2-one (*ent*-15). For purposes of characterization at the intermediate stage, a sample of *ent*-**15** was prepared by repeating the borohydride reduction from *ent*-**14** to the hemiacetal following the above procedure on a smaller scale (corresponding to the first stages of the procedure leading to **17** from chloride **14** via **13**). The resulting intermediate hemiacetal *ent*-**13** (215 mg, 0.281 mmol, 1.0 equiv) was placed in an oven-dried flask and dissolved in dry DCM (5.6 mL), and the colorless solution was cooled to 0 °C. Diisopropylethylamine (0.15 mL, 0.843 mmol, 3.0 equiv) was syringed into the reaction followed by the dropwise addition of $SOCl_2$ (distilled over CaH_2, 22 μL, 0.309 mmol, 1.1 equiv). The resulting brown solution of *ent*-**14** was stirred at 0 °C for 5 min and was then poured into 50 mL of saturated $NaHCO_3$(aq) and extracted with Et_2O. Organics were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting orange oil was dissolved in THF (5.6 mL) and AcOH (0.6 mL) and cooled to 0 °C. Next, Zn dust (<10 μm, 276 mg, 4.22 mmol, 15 equiv) was added in one portion, and the resulting gray suspension was slowly warmed to room temperature for 18 h. At this point, the suspension was cautiously poured into saturated $NaHCO_3$ (100 mL) and extracted with Et_2O. Organics were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by flash column chromatography (2.5 cm wide by 15 cm tall; 10 mL fractions, 200 mL 14:1 hexanes/Et_2O, 200 mL 9:1 hexanes/Et_2O) to yield 159 mg (75%) of *ent*-**15** as a clear, colorless oil (1:2 mixture of isomers): TLC, 8:2 hexanes/Et_2O, R_f = 0.46; ESI-MS calcd for $C_{43}H_{48}BrNO_4SiNa^+$ m/z 772.2434; found 772.24.08, error = 3 ppm; IR (neat, cm^{-1}) 2954, 2928, 1728, 1497; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 7.90−7.83 (2H, m), 7.73−7.66 (1H, m), 7.53−7.28 (10H, m), 7.03−6.86 (3H, m), 6.54−6.49 (1H, m), 6.30−6.23 (1H, m), 5.84−5.72 (2.3H, m), 5.54 (0.7H, br s), 4.91 (2H, two overlapping br s), 4.62 (1H, very br s), 1.88−1.58 (2H, m), 1.43−1.18 (4H, m), 0.93, 0.89 (9H, two singlets in a 1:2 ratio), 0.76 (3H, t, J = 7.0 Hz), 0.21 (1H, s), 0.14−0.12 (5H, m); ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ 176.6, 152.3, 140.7, 140.4, 137.1, 137.0, 136.8, 133.7, 133.7, 133.6, 132.4, 130.0, 129.8, 129.2, 129.1, 128.5, 127.8, 127.5, 127.4, 127.4, 126.2, 126.0, 125.4, 125.3, 123.6, 123.4, 122.9, 122.1, 114.3, 114.2, 102.6, 70.6, 70.5, 64.4, 64.3, 37.7, 28.5, 28.3, 25.8, 25.8, 22.7, 22.6, 18.3, 18.2, 14.0, 14.0, −4.9, −5.0, −5.1, −5.2. In addition, a minor signal at 25.7 ppm could not be attributed to a specific structure (tautomer, diastereomer, or unknown impurity). For the isomer mixture, a large number of sp^2 carbon signals is possible, depending on the ratio of diastereomers and tautomers. The title compound **15** shows the typical line broadening of oxindoles, especially for the C_3−H signal (4.62 ppm), the methine in the chiral auxiliary (5.54 ppm), and for all of the butyl protons (1.88−1.18 ppm), except for the terminal methyl signal (0.76 ppm), suggesting a role for the enolized oxindole in the complex spectra.

(3*R*)-3-[(1*S*)-5-Benzyloxy-2-(1-naphthalen-1-ylpentyloxy)-phenyl]-7-bromo-2-oxo-2,3-dihydroindole-1,3-dicarboxylic Acid 1-Allyl Ester 3-Methyl Ester (19). Oxindole **17** (4.56 g, 6.86 mmol, 1.0 equiv) was placed in an oven-dried round-bottom flask along with DMAP (8.38 g, 68.6 mmol, 10 equiv) and exposed to high vacuum for 2 h before dissolving the solids in 85.7 mL of $CHCl_3$ (0.08 M). The colorless solution was cannulated to a flame-dried three-neck round-bottom flask equipped with a thermometer adapter. Dry diisopropylethylamine (11.9 mL, 68.6 mmol, 10 equiv) was syringed into the reaction, and the reaction flask was cooled to −15 °C. At this point, allyl chloroformate (distilled at atmospheric pressure, 7.3 mL, 68.6 mmol, 10 equiv) was syringed slowly so that the internal temperature of the solution was kept below −10 °C. The resulting orange solution was warmed to room temperature and stirred for 30 min, at which point the reaction flask was cooled to 0 °C, and the reaction was quenched with 50 mL of saturated aqueous $NaHCO_3$. The biphasic mixture was warmed to room temperature and stirred for 30 min to ensure complete destruction of the unreacted chloroformate. This was then diluted with 150 mL of water and extracted with Et_2O. The organic extracts were sequentially washed with 200 mL of a 0.1 M HCl solution and 200 mL of saturated aqueous $NaHCO_3$. After combining the organic extracts, these were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 9.0 g of a yellow oil. This was purified by flash column chromatography (4.0 cm × 16.0 cm; 2.5 L 75:25 hexanes/Et_2O; 25 mL fractions) to yield 4.510 g of **19** (88% yield) as a white foam: TLC, 1:1 hexanes/Et_2O, R_f = 0.53; ESI-MS calcd for $C_{42}H_{38}BrNO_7Na^+$ m/z 770.1729; found 770.1733, error = 0.5 ppm; IR (neat, cm^{-1}) 2953, 1782, 1742, 1493, 1223; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 7.95 (1H, d, J = 8.3 Hz), 7.88 (1H, d, J = 8.3 Hz), 7.73 (1H, d, J = 7.8 Hz), 7.56−7.53 (3H, m), 7.50 (1H, t, J = 7.3 Hz), 7.43 (1H, t, J = 7.8 Hz), 7.56−7.27 (6H, m), 7.07 (1H, t, J = 7.8 Hz), 6.77 (1H, d, J = 1.9 Hz), 6.53 (1H, dd, J = 9.3, 2.9 Hz), 6.28 (1H, d, J = 9.3 Hz), 6.04−5.97 (1H, m), 5.66 (1H, dd, J = 7.8, 3.9 Hz), 5.47 (1H, dd, J = 17.1, 1.5 Hz), 5.28 (1H, dd, J = 10.3, 1.0 Hz), 4.92 (2H, dd, J = 5.4, 1.0 Hz), 4.84 (2H, s), 3.83 (3H, s), 1.88−1.81 (2H, m), 1.25−1.20 (2H, m), 0.98 (2H, br s), 0.78 (3H, t, J = 7.3, 1.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.3, 167.6, 152.1, 149.9, 149.5, 138.8, 137.0, 134.2, 133.8, 131.0, 130.7, 130.0, 129.2, 128.5, 127.9, 127.7, 127.4, 126.2, 126.2, 125.7, 125.4, 124.9, 124.4, 123.6, 122.1, 119.8, 117.5, 115.0, 113.8, 106.3, 78.1, 70.7, 69.0, 63.7, 53.6, 37.3, 28.1, 22.5, 13.9. The same sequence was repeated from *ent*-**17** obtained from chiral aryl ether **11** (96% ee) to give *ent*-**19**: $[\alpha]_D^{25}$ = −104 (*c* 2.80, $CHCl_3$).

6-Benzyloxy-1-bromo-9-oxa-10-azaindeno[1,2-*a*]indene-4b,10-dicarboxylic Acid 10-Allyl Ester 4b-Methyl Ester (22). Imide **19** (2.848 g, 3.80 mmol, 1.0 equiv) was placed in a flame-dried round-bottom flask and flushed with N_2 for 10 min. The solid was dissolved in THF/MeOH (51 mL/25 mL, 0.05 M) and cooled to −10 °C. $NaBH_4$ (432 mg, 11.41 mmol, 3.0 molar equiv) was charged in one portion. The resulting solution was stirred at −10 °C for 25 min, after which no starting material remained. The reaction was diluted

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with 50 mL of Et_2O and quenched by the cautious addition of ice chips and 200 mL of a 0.2 M HCl(aq) solution. This was stirred for 10 min at room temperature. The resulting biphasic mixture was extracted with Et_2O. The organic extracts were combined and washed with 200 mL of saturated $NaHCO_3$(aq), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield crude hemiaminal **20** (R_f = 0.36, 9:1 toluene/Et_2O) as a colorless oil. This material was exposed to high vacuum for 30 min, before dissolving it in 60 mL of dry DCM and cannulating the solution into a three-neck round-bottom flask equipped with a thermometer adapter and a jacketed addition funnel. DMAP (93 mg, 0.761 mmol, 0.2 equiv) was placed in the reaction vessel, and Et_3N (1.6 mL, 11.8 mmol, 3.1 equiv) was syringed in. The solution was then cooled to −10 °C, and Ac_2O (distilled over K_2CO_3, 1.1 mL, 11.4 mmol, 3.0 equiv) was syringed in dropwise. After 30 min, only acetate **21** (R_f = 0.56, 9:1 toluene/Et_2O) was detected by TLC. At this time, a solution of TFA (distilled over P_2O_5, 9.1 mL, 118 mmol, 30 equiv) in 15 mL of dry DCM was syringed into the jacketed addition funnel and cooled to −10 °C. This solution was added slowly into acetate **21** so that the internal reaction temperature did not rise above −5 °C. The resulting light yellow solution was allowed to warm to room temperature and was stirred for 15 h. At this point, the reaction was cooled to −10 °C, and the TFA was carefully quenched with 16 mL of dry Et_3N. The resulting solution was diluted with 200 mL of EtOAc and washed with 250 mL of a 0.5 M HCl(aq) solution. The aqueous phase was extracted with EtOAc, and the organic extracts were combined and sequentially washed with saturated $NaHCO_3$(aq), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture contained aminal (−)-**22** and nonpolar byproducts derived from the chiral auxiliary according to NMR assay and was obtained as a yellow oil (5.68 g). Purification by flash column chromatography (96:4 toluene/Et_2O) produced 1.67 g (82%) of aminal (−)-**22**: HPLC (Chiralcel OD, 1 mL/min, 9:1 hexanes/*i*-PrOH) 12.60 min (4.8% area), 19.72 min (95.2% area); 90% ee. The enantiopurity of the tetracycle could be upgraded from 90 to 99% ee by crystallization from hexanes/EtOAc (74% yield of crystals): mp (99% ee, hexanes/EtOAc) = 129−131 °C. *ent*-**22** was obtained by executing a similar experimental sequence described for (-)-**22** but on a smaller scale via *ent*-**21a**, starting from the enantiomeric aryl bromide (*R*)-**11** (96% ee). In this case, crystallization for hexanes/DCM gave *ent*-**22**: HPLC (Chiralcel OD, 1 mL/min, 9:1 hexanes/*i*-PrOH) 13.46 min (98.6% area), 23.55 min (1.4%); optical rotation, 97% ee, $[\alpha]_D^{25}$ = +188 (*c* 1.71, $CHCl_3$). The NMR spectra of enantiomers **22** and *ent*-**22** were consistent with the data published for *rac*-**22**.[4]

■ ASSOCIATED CONTENT

Supporting Information

X-ray data for *ent*-**22** and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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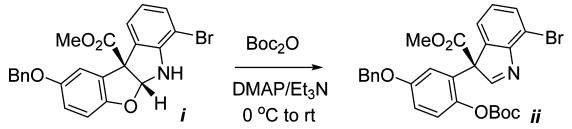
(12) N-Protection is nontrivial in the aminal environment. Structure **22** can be deprotected (see ref 5), but reprotecting the N−H aminal *i* is challenging. Thus, treatment of *i* with Boc_2O in the presence of DMAP/Et_3N affords *ii* and not the desired tetracyclic *N*-Boc aminal according to NMR evidence recorded by Suna et al. However, MacMillan et al. (ref 2g) were able to successfully *N*-trifluoroacetylate their N−H aminal intermediate under similar conditions, apparently due to the greater electrophilicity of the trifluoroacetyl reagent.



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