JOC The Journal of Organic Chemistry

pubs.acs.org/joc Note

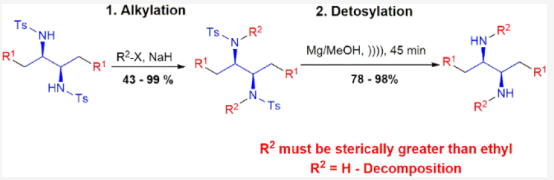
The Detosylation of Chiral 1,2-Bis(tosylamides)

Jayden J. Gaston, Andrew J. Tague, Jamie E. Smyth, Nicholas M. Butler, Anthony C. Willis, Nico van Eikema Hommes, Haibo Yu, Timothy Clark, and Paul A. Keller*

Cite This: J. Org. Chem. 2021, 86, 9163−9180 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The deprotection of chiral 1,2-bis(tosylamides) to their corresponding 1,2-diamines is mostly unsuccessful under standard conditions. In a new methodology, the use of Mg/MeOH with sufficient steric additions allows the facile synthesis of 1,2-diamines in 78−98% yields. These results are rationalized using density functional theory and the examination of inner and outer-sphere reduction mechanisms.



The *p*-toluenesulfonyl (tosyl) group is a versatile and robust protection for amines[1] with a trivial addition, involving the reaction of the amine with *p*-toluenesulfonyl chloride and a base.[1] The corresponding deprotection of the tosyl group is split into the following two mechanistic types: electron reductions (single-electron transfer (SET)[2−6] and two-electron transfers[7]) and nucleophilic displacement,[8] with SET reducing agents being the standard. There are many general procedures that have published for a range of monotosylamide deprotections;[2−6] however, procedures for the deprotection of 1,2-bis(tosylamide) substrates are limited (Figure 1, **A**−**C**).[9,10]

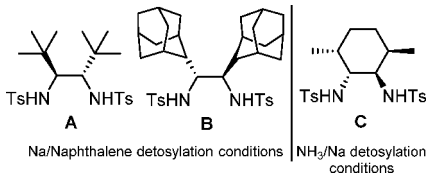
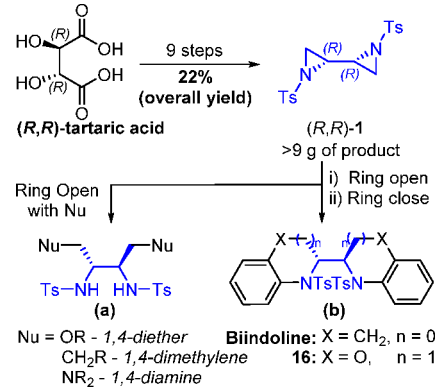


Figure 1. Compounds **A**, **B**,[9] and **C**[10] are published 1,2-bis(tosylamides) that were deprotected to the corresponding 1,2-diamines by the SET methods shown.

In a strategy designed to easily generate libraries of chiral 1,2-diamines from a late-stage chiral intermediate, a recent report detailed the facile synthesis of a small library of tosyl-protected chiral 1,2-bis(tosylamides) starting from (*R*,*R*)-biaziridine (*R*,*R*)-**1** (Scheme 1).[11] The next step to demonstrate the wide-ranging applicability of this strategy was the optimization of the tosyl deprotection as applied specifically to 1,2-bis(tosylamide) substrates, which is the subject of this report.

The biaziridine (*R*,*R*)-**1**, which was synthesized from (*R*,*R*)-tartaric acid,[11] was ring-opened with phenol, benzylmagnesium chloride, aniline, piperidine, and hexanol nucleophiles under newly optimized conditions, generating a small library of chiral acyclic scaffolds **2**−**6** (Scheme 2) of the type a (Scheme 1). Initial attempts at deprotection started with 1,2-bis-

Scheme 1. The Synthesis of Tosyl-Protected (*R*,*R*)-1 from (*R*,*R*)-Tartaric Acid with (a) Ring Opening to Produce an Acyclic 1,2-Bis(tosylamide) Scaffold and (b) Ring Closing to Produce a Cyclic 1,2-Bis(tosylamide)[a]



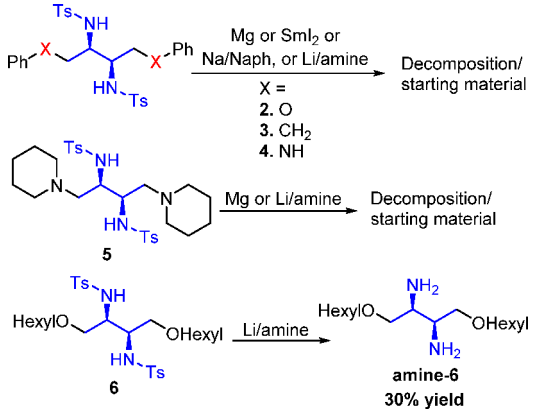
[a]See ref 11.

(tosylamide) **2** using the standard SET reductant Mg/MeOH, which resulted in complete decomposition upon sonication (45 min). Further attempts at 1,2-(bistosylamide) deprotection using a variety of conditions commonly employed for monotosylamides,[2,4,12−17] (SmI_2,[2,12−14] Na/naphthalene,[15] Mg/MeOH,[4,16] and Li/amine;[17] see Table S1 in the Supporting Information for data) also resulted in decomposition or the return of the starting material and did not allow for the deprotection of the tosyl moiety regardless of the substrate scaffold (Scheme 2, X = O, N, CH_2). Only 1,2-

Received: February 12, 2021
Published: June 21, 2021

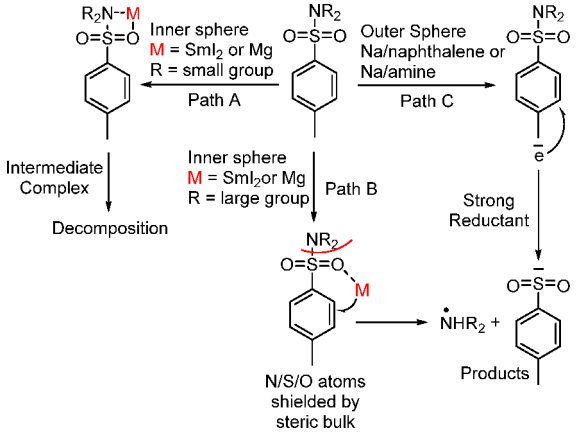
https://doi.org/10.1021/acs.joc.1c00359
J. Org. Chem. 2021, 86, 9163−9180

Scheme 2. Attempted *N*-Tosyl Deprotection of 1,2-Bis(tosylamides) 2−5 Resulted in Either the Starting Material or Decomposition[a]



[a]Only (1,2-bistosylamide) **6** underwent reduction to the product **amine-6** in the strong Li/amine Benkenser reducing conditions without the presence of reducible aromatic moieties. See Table S1 in the Supporting Information for data.

Scheme 3. There Are Two Potential Inner-Sphere SET Pathways (A and B) Depending on the Amount of Steric Hindrance at the 1,2-Bis(tosylamide) *N*-Atoms[a]



[a]Only one potential pathway for an outer-sphere SET pathway (C) can occur, which requires a high reduction potential for the SET reductant due to less interaction between the reductant and the substrate.

bis(tosylamide) **6** was capable of deprotection (Scheme 2), with the corresponding diamine isolated in a modest yield (30%). This example contained no functional groups (e.g., aromatic groups) that could undergo reduction in the presence of the strong Benkenser reducing conditions that utilize Li/propylamine/ethylenediamine.[17]

These results indicated that detosylation using SmI_2 and Na/naphthalene as SET reductants did not reduce the tosyl functionality (Scheme 2) and that decomposition occurs with Mg/MeOH and Li/propylamine/ethylenediamine, indicating that secondary reductions lead to the decomposition of the starting materials or products (Scheme 2). This result has not generally been observed with functionally similar monotosylamides.[2,3] An examination of previous mechanistic insights for the detosylation of monotosylamides indicates that SET cleavage results in a radical amine intermediate that leads to the formation of the protonated product.[2] Consequently, the stabilization of the intermediate radical N atom in 1,2-bis(tosylamides) **2−6** with the correct *N*-functionalities (e.g., benzyl groups) may prevent competing decomposition pathways and promote tosyl deprotection (Scheme 3). Therefore, the tertiary 1,2-bis(tosylamides) **7−15** (Table 1) were synthesized by the addition of the alkyl halide electrophile to the 1,2-bis(tosylamides) **2−5**, followed by NaH. The heterocycle **16** was synthesized by the cyclization of an *o*-halogenated derivative of **2** (1,2-bis(tosylamide) **17**) with CuI.

The tosyl deprotections of the 1,4-diether scaffold **8−13** and **16** under Mg/MeOH conditions proceeded in excellent yields, producing the corresponding 1,2-diamines in 78−98% yields (Table 1), and only small amounts of decomposition were observed. Under the same reaction conditions, the tertiary 1,4-dimethylene **14** gave a crude yield of 81% despite decomposition during deprotection, indicating that the absence of a heteroatom in the molecule backbone likely leads to secondary reductions and therefore invokes decomposition. The tertiary 1,4-diamine scaffold **15** also underwent complete decomposition, indicating it was unable to be accessed.

To ensure that the reaction success was not the result of functionalities that were not electron-withdrawing or capable of radical stabilization (e.g., Boc or benzyl), 1,2-bis(tosylamide) **7**, which contains bis(*N*-methyl) substitutions, was subjected to Mg/MeOH deprotection. This reaction gave decomposition under the deprotection conditions, while the Mg/MeOH deprotection using bis(*N*-ethyl) **8** gave the deprotected 1,2-diamine in an 80% yield (Table 1). The presence of *N*-ethyl or *N*-methyl substituents is expected to provide similar degrees of radical stabilization. Therefore, the variation in outcomes is likely a result of steric differences between the two groups. This indicates that the presence of an N−H (**2−6**) or *N*-methyl (**7**) is not sufficiently sterically demanding enough to allow deprotection (Tables 1 and Scheme 2), leading to decomposition. Substrates that contain substituents larger than *N*-methyl (e.g., **8−14** and **16**) at the 1,2-bis(tosylamide) core are required in order to undergo facile deprotection, e.g. 1,2-bis(tosylamides) **8−13** and **16** (Table 1).

An analysis of the results in Table 1 and Scheme 2 suggests that Mg/MeOH deprotection is likely to operate through an inner-sphere reduction mechanism (Scheme 3, path A or B). This mechanism requires the substrate and reductant to either form a bond or have a direct orbital interaction to allow the electron transfer to occur,[14,18] which could either occur with a free Mg^0 atom in solution or at the surface of the Mg^0 powder. A closely bound Mg−1,2-bis(tosylamide) intermediate could potentially cause decomposition via unwanted secondary reductions (Scheme 3, path A).

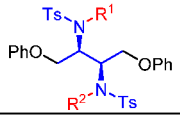
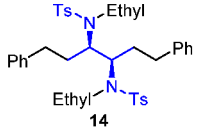
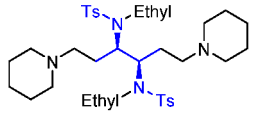
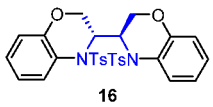
Steric hindrance at the 1,2-bis(tosylamide) core decreases the interaction between the Mg atom and the 1,2-bis(tosylamide) core, promoting deprotection by forcing the Mg atom away from the 1,2-bis(tosylamide) and facilitating single-electron transfer (SET) to the sulfonamide aromatic ring (Scheme 3, path B);[2] thus, this leads to successful tosyl deprotection. This hypothesis explains the observed differences between the *N*-methyl **7** and *N*-ethyl **8** deprotections, with the presence of steric interactions allowing electron transfer to the sulfonamide moiety of the 1,2-bis(tosylamide) and thereby hindering SET elsewhere.

To confirm this hypothesis, the LUMO and spin density plots of compounds **2−4**, **6**, **8**, and **16** and selected published

https://doi.org/10.1021/acs.joc.1c00359
J. Org. Chem. 2021, 86, 9163−9180

Table 1. Deprotection of *N*-Substituted Chiral 1,2-Bis(tosylamides)

1,2-bis(tosylamides) 7 to 16 — 1,2-diamines amine-7 to amine-16

Structure	Reagent[a]	Result[b]
		
7: $R^1 = R^2$ = Me	Mg	Decomp
	Na/Naph	Decomp
	SmI_2	S.M.
8: $R^1 = R^2$ = ethyl	Mg	**80%**
9: $R^1 = R^2$ = benzyl	Mg	**90%**
10: $R^1 = R^2$ = MeO-benzyl	Mg	**94%**
11: $R^1 = R^2$ = F-benzyl	Mg	**76%**
12: R^1 = benzyl; R^2 = fluorobenzyl	Mg	**98%**
13: $R^1 = R^2$ = Boc	Mg	**90%**
 **14**	Mg	**81%** (crude)
 **15**	Mg	Decomp
 **16**	Mg	**78%**
	Na/Naph (0 °C)	S.M.
	Na/Naph (30 °C)	S.M.
	SmI_2	S.M. + Decomp

[a]Procedures are reported in the Experimental Section. Napth, nathalene; Mg, magnesium in methanol with ultrasonication as described in general procedure 1; Na/Naphthalene, a sodium naphthalenide solution as described in general procedure 3; SmI_2 was prepared as a solution in THF, and the reaction performed with H_2O and pyrrolidine as described in general procedure 4; Li/amine, a modified Benkenser reduction using Na metal, propylamine, and ethylenediamine to give a Birch-type reduction as described in general procedure 5. [b]Values refer to the percent yield isolated. Decomp, decomposition with no product isolated after purification; S.M., starting material isolated after purification.

monotosylamides were calculated using DFT (B3PW91-D3(BJ)/6-311+G(d,p)//B3PW91-D3(BJ)/6-31G(d)).[19] These results indicated that in all cases the LUMO (neutral compound) and spin density (radical anion) were centered on the sulfonamide aromatic ring after a visual inspection of the data (Figure S79 and ESI). SET should therefore occur at the sulfonamide aromatic ring where the electron should enter the LUMO. This correlates with a published experimental report that established the necessity of an aromatic sulfonamide in SET tosyl deprotection with SmI_2 whereby electron transfer was suspected to occur at the sulfonamide aromatic ring.[2] However, the DFT analysis only indicates that reduction should occur at the tosylamide and does not explain where or when a secondary SET could occur during detosylation to lead to decomposition.

Vertical electron affinities (VEAs) for the synthesized 1,2-bis(tosylamides) were also calculated in MeOH (Table S3). No observable correlations were visible since all substrates had similar affinities for electrons, indicating that their relative ease to reduce is not a factor in the success of the reduction. Even the fully deprotected primary amine of **2** (**amine-2**) had too little of an affinity for electrons to allow any further reduction after the tosyl deprotection. This was expected since the further exposure of **amine-2** or **amine-16** to Mg/MeOH reduction conditions had no effect, and only the starting material was isolated. A 1,2-bis(tosylamide)−Mg chelate is then responsible for allowing the secondary reductions to occur, which is a species that was not analyzed under the DFT model and the only other species likely to exist in solution during deprotection. Preventing this unknown chelate is therefore important for successful tosyl deprotection to occur.

An examination of the VEAs for published monotosyl amides *N*-Boc-*N*-phenyltosylamide and 2-pyridylphenylsulfonamide (Figure S78 and Table S3) showed they undergo facile deprotection in Mg/MeOH, while phenyltosylamide does not react at all.[3,4] Similar to the 1,2-bis(tosylamides) **2**−**4**, **6**, **8**, and **16**, DFT calculations indicated only small differences in the VEAs for monotosylamides, indicating that it is not a factor that affects reduction. The only difference between the substrates appears to be their relative ability to chelate to the Mg atom. This should occur using the Boc or pyridyl moiety, where the heteroatoms in the *N*-substituent would chelate to the Mg atom and increase the likelihood of a SET transfer occurring (Figure S3). Chelation also appears to be important for the successful tosyl deprotection of monotosylamides and 1,2-bistosylamides when employing Mg/MeOH.

Chelation during reductive SmI_2 tosyl deprotections is likely an important factor as they also operate through inner-sphere electron transfer.[12] In this case, weak chelation may lead to a smaller effective reduction potential for SmI_2 compared to that of Mg/MeOH (Table S4), resulting in the observed starting material with no tosyl deprotection (Table 1 and Scheme 2). The small degree of decomposition during the attempted deprotection of **16** using SmI_2 does indicate that a reduction takes place, although not to the desired 1,2-diamine product. If a substrate undergoes deprotection with SmI_2, path A will likely need to be prevented using steric hindrance to stop the competing decomposition from Sm−1,2-bis(tosylamide) chelates similar to Me/MeOH reaction conditions since their SET reduction mechanisms are similar (Scheme 3).

The Na/naphthalene conditions also proved to be troublesome for the deprotection of **16** despite the use of elevated temperatures (30 °C). This is a confusing result as compounds **A** and **B** (Figure 1) have been reported to undergo facile reduction using Na/naphthalene.[9] However, considering the outer-sphere reduction mechanism,[20] it is likely that an outer-sphere reductant needs to be strong to account for the low likelihood of electron transfer without the ability to chelate to the substrate (Scheme 2, path C). The reaction conditions using Li/propylamine/ethylenediamine also face this issue as it

https://doi.org/10.1021/acs.joc.1c00359
J. Org. Chem. 2021, 86, 9163−9180

is an outer-sphere reductant;[17,21] however, the higher reduction potential ensures that any substrate interactions result in a fast electron transfer, leading to reduction and therefore successful tosyl deprotection (i.e., compound **6**, Scheme 2).

CONCLUSION

The developed strategy allows the general synthesis of 1,2-diamines from 1,2-bis(tosylamides) using Mg/MeOH deprotection conditions by sterically tuning the *N*-substituent in the substrate. It is now possible to employ 1,2-bis(tosylamides) in the routine synthesis of 1,2-diamines with the general deprotection protocol presented here. The mechanism of these deprotections was examined using standard SET reductants, which demonstrated that inner-sphere reductants required a degree of chelation to function. While too much chelation leads to a decomposition pathway, this can be tuned with steric hindrance from the *N*-substituent. Outer-sphere reductants required higher reduction potentials to facilitate the reduction of the tosylamide functionality due to their lack of chelation resulting in only a small possibility of reduction, that is, they have a low effective reduction potential without chelation despite their high reduction potential (Table S4).

EXPERIMENTAL SECTION

General Information. Compounds with known characterization data have characterization data and assignments listed in the Supporting Information. Unless stated otherwise, all reactions were stirred with a magnetic stirring bar under an atmosphere of N_2. Nitrogen gas was dried by passing it through a column of silica gel beads and then a column of dry $CaCl_2$, which was replaced every three months. Reaction vessels were fitted with a rubber septum, and sensitive reagents were introduced through the septa with a syringe under N_2. The vacuum pump used in all reactions placed the apparatus at a pressure of <0.01 mbar. "In vacuo" refers to the evaporation of the solvent by rotary evaporation at 40−45 °C (except for diethyl ether at 30 °C), followed by high vacuum (>0.1 mbar) for 4−6 h unless otherwise stated. Residues that required evaporation on high vacuum for longer than 6 h are stated in the method. Reactions that required heating used a paraffin oil bath unless otherwise stated. ^{1}H and ^{13}C NMR spectra in $CDCl_3$ were referenced to TMS (δ = 0), while ^{1}H NMR (δ = 2.05) and ^{13}C NMR (δ = 29.92) spectra in acetone-d_6 were referenced to the residual solvent. All NMR experiments were performed on Bruker Ascend 400 MHz NMR spectrometer or a Bruker Avance Neo 500 MHz NMR spectrometer, 1D NOE experiments were performed on a Bruker Avance Neo 500 MHz NMR spectrometer, and ^{19}F NMR experiments were ^{1}H coupled. The resolution of the spectra (MHz) is indicated in the individual characterization data along with the peaks and their assignments. For rotameric compounds that have multiple resonances for an atom, the resonances that were identified to the assigned H or C atom are indicated with a '/' between the resonances (e.g., 1.42/1.43 (s, 3H, H1) for proton H1 with two resonances due to rotamers). Low-resolution mass spectrometry was performed on a Shimadzu LCMS-2020 (ESI MS) or Shimadzu QP-5050 spectrometer in the EI mode (EI MS). Where no low-resolution mass spectrum was reported, no diagnostic ion was observed. High-resolution mass spectrometry (HRMS) was performed on a XEVO QToF instrument with LeuEnk as internal standard. FT-IR analysis was performed on a Bruker Vertex FT-IR spectrometer in the ATR mode. All compounds loaded neat, or a small amount of THF or diethyl ether was used.

General Methods for Purification. Flash column chromatography was performed with compressed air using the following internal diameter depending on the amount of silica or alumina used: < 10 (0.9 cm), 10−20 (1.1 cm), 21−40 (1.7 cm), and >41 g (3.5 cm). Either silica gel 60 (230−400 mesh, 40−63 μm) or neutral aluminum oxide 60 (70−230 mesh, 63−200 μm) was used for chromatography where indicated. When the compound was wet loaded, only the minimum amount of the indicated solvent was used. When the compound was dry loaded, the indicated solvent was used to dissolve the compound, dry silica was added, the mixture evaporated using rotary evaporation to a slurry, and the silica was further dried under high vacuum to a free-flowing powder. A syringe filter (nylon 0.45 μm) was attached to the vacuum line to prevent the bumping of the silica. TLC (thin-layer chromatography) was performed on aluminum backed plates (silica gel 60 or neutral aluminum oxide 60, F_{254} indicater, 5.0 cm length and 0.20 mm thickness). A stain was used for visualization as indicated. Only reactions monitored or purified by silica gel chromatography have the TLC R_f reported. Where the R_f is not reported, the reaction was monitored by NMR after workup. PLC (preparative-layer chromatography, silica gel 60, F_{254}, 20 × 20 cm wide, 0.5 mm thick) plates were purchased from Merck and prepared by drawing a line 2 cm above the bottom of the plate and then gently adding the dissolved sample using a pipet to ensure a thin even band of sample was added. Care was also taken to ensure that all loaded samples were 2 cm away from the edge of the PLC plate. The PLC plate was then dried with compressed N_2 and eluted in a glass chamber containing 100 mL of the eluent. After being removed, the plate was dried with compressed N_2 and then placed back into the chamber if the plate required further elution. Fractions were selected based upon color (where indicated) or by visualization under UV light. Fractions were then cut or scraped off carefully using a steel knife and a spatula, followed by sonication in the stated eluent and then vacuum filtration through a pad of Celite 545. It is indicated in the experimental data after the solvent system for cases where TLC and PLC plates were eluted multiple times under the same solvent system. Solvent system mixtures for separation are written with the polar solvent first then the nonpolar solvent, with the percentage in brackets, e.g., EtOAc/hexanes (20%).

Materials. $CaCl_2$ hydrate was dried in a furnace (300 °C) for 24 h, cooled in an oven (100 °C), then cooled in a desiccator (rt) before being ground to a powder and packed into a loose column. Molecular sieves were dried in a furnace (300 °C), cooled in an oven (100 °C), and allowed to cool to rt in a conical flask stoppered with a septum before use. THF was dried over 3 Å molecular sieves for 3 d in a stoppered conical flask,[22] except for Grignard reactions that required the distillation of THF from Na/benzophenone (purple indicator). Phenol was dried by the azeotropic removal of water with benzene and purified by the fractional distillation of the residual benzene and then pure phenol.[23] Hexanol was purchased from Sigma, dried over K_2CO_3, fractionally distilled, and stored over 3 Å molecular sieves.[23] Aniline was dried over KOH (24 h), decanted, fractionally distilled under vacuum, and stored in the dark.[23] Propylamine and ethylenediamine were purchased from Sigma, dried over 3 Å molecular sieves, and stored in a desiccator at either −20 °C or rt. NaH was purchased from Sigma and stored in a desiccator in the steel container it was received in; for reaction consistency, it required a replacement after 1.5 years. Magnesium powder was purchased from Sigma-Aldrich and stored in a vacuum sealed desiccator between use; it was replaced after ∼8 months. All bulk solvents were purchased from ChemSupply except for EtOAc, which was purchased from ThermoFisher. All solvents were HPLC grade except for benzene, THF, diethyl ether (BHT stabilized), $CHCl_3$ (ethanol stabilized), petroleum spirits (pet. spirit), and cyclohexane. Anhydrous DMF, DMSO, DME, benzene, and methanol were purchased from Sigma under a SureSeal and used as received. L-(+)-Tartaric acid, citric acid, pyridine, triethylamine (NEt_3), and Na metal were purchased from ThermoFisher. SmI_2 was purchased from Strem Chemicals. DMAP and CsOAc were purchased from AKScientific. $NaSO_4$, $MgSO_4$, and NH_4Cl were purchased from ChemSupply. All other reagents were purchased from Sigma. 4-Methoxybenzyl chloride was prepared by known procedures.[54,55]

Crystallographic Data. All crystallographic data can be accessed free of charge from the Cambridge Crystallography Data Centre (CCDC) database via www.ccdc.ac.uk/structures (CCDC 1998667−1998668).[24] Where a crystal structure was obtained by X-ray

https://doi.org/10.1021/acs.joc.1c00359
J. Org. Chem. 2021, 86, 9163−9180

diffraction, the relevant crystallization procedure can be found below the spectral data of the compound.

X-ray diffraction images for compound **2** were collected on an Agilent Xcalibur diffractometer (Mo Kα radiation, graphite monochromator, λ = 0.71073 Å), and images for compound **21** were collected on an Agilent SuperNova diffractometer (Cu Kα radiation, mirror monochromator, λ= 1.54184 Å). Data for each structure were extracted using the CrysAlis Pro package.[25] Structures were solved by direct methods (SIR92).[26] The structures were refined using the CRYSTALS program package.[27] Note that the numbering used in the X-ray ORTEP diagrams is different from the IUPAC systematic numbering of the structures.

Confirmation of Enantio- And Diastereo-Purity of All Synthesized Compounds. As addressed in our initial publications on the ring opening of biaziridine with nucleophiles,[11,28,29] all compounds synthesized by this methodology are enantiomerically and diastereomerically pure (ee > 99%), having been synthesized from the pure L-(+)-tartaric acid. No racemization during alkylation or tosyl deprotection was observed by ^{1}H and ^{13}C NMR analysis of the reaction mixtures, with the primary evidence being the lack of *meso*-diastereoisomers. Compound **9** was analyzed by chiral HPLC after the base-catalyzed *N*-alkylation using a Chiracel OD-H column eluted with *i*Pr−OH/hexanes (conditions previously used for enantiomeric separation of these products)[11] and only demonstrated a single peak. Crystal structures are available to confirm the stereochemistry of some compounds and can be accessed through the CCDC database. Previous publications on the Mg/MeOH detosylation have demonstrated that no loss of chirality occurs during the reaction, and our observations agree with the literature findings.[4]

Computational Methods. Data from the computational analysis are reproduced in the Supporting Information. Using the crystal structure of **2** (CCDC 1998668),[24] all synthesized 1,2-bis-(tosylamides) were able to be constructed and edited in Avogadro[30,31] and optimized with MMFF94 in Avogadro for a conformational search using the Crest[32] tool in the xTB package. The extended semiempirical tight-binding model GFN2[33−35] was used with the xTB and Crest default parameters with the exception of **6**, where the Crest "-loose" setting was used due to the extremely high number of conformations. No conformational search was performed on structures with a crystal structure readily available, including **2**, which was acquired in this publication, or for the previously published structures available in the CCDC database,[24] including benzylmesylamide (KOYVID, CCDC 1200072)[36] and benzyltosylamide (PTSBZA01, CCDC 1010172).[37] For **16**, our recently published crystal structure for a methoxy-functionalized derivative (TUMBOV, CCDC 1990559)[38] was edited in the same way to produce conformations. The crest_best structure from the Crest conformational analysis or crystal structures, where available, were then chosen for further analysis by DFT. For further modifications (such as the removal of a tosyl group), the DFT-optimized structure (1,2-bis(tosylamide) for the generation of monotosylamide products and monotosylamides for the generation of primary amines) was modified in the same way as the crystal structures. A comparison of structures for **mono-2** from Crest and Confab[39] (after optimization with B3PW91-D3(BJ)/6-31G(d)) as well as previous benchmarks[40,41] indicated that this methodology does produce low energy conformations.

For DFT, functional and basis set choices was based on previous benchmark studies for all calculations,[19,42] and all calculations used the Grimme D3 dispersion correction with Becke−Johnson damping (D3BJ).[43] DFT optimizations on all neutral molecules were performed in Gaussian 09[44] using the B3PW91[45] functional and 6-31G(d) basis set in the gas phase (except *N*-benzylmethanesulfonamide and *N*-benzyl-4-methylbenzenesulfonamide, which were also optimized with the 6-31+G(d) basis set), followed by reoptimization with the implicit solvent model PCM using default solvent parameters for methanol, THF, or propylamine where indicated. All structures were checked to ensure that the default convergence criteria from both the geometry optimization and frequency calculations were met and that there were no negative vibrational frequencies. Single point calculations were performed in Gaussian 16[46] using the B3PW91 functional and 6-311+G(d,p) basis set with the default implicit solvent model PCM using default solvent parameters for methanol, THF, or propylamine where indicated. For the radical anion single points, the neutral geometry with the appropriate charge and multiplicity was used as the input with UB3PW91. Despite a previous benchmark[19] recommending the use of the 6-311+G(2df,p) basis set for single point calculations, we found no significant difference for the VEA calculation of benzylmesylamide (6-311+G(d,p) = 0.76 eV and 6-311+G(2df,p) = 0.75 eV). Therefore, we used the smaller basis set to reduce the computational time. LUMOs (lowest unoccupied molecular orbitals) and spin densities were generated using the Cubegen utility and viewed in VESTA.[47,48] All the optimized structures (Cartesian coordinates, xyz) were generated from Gaussian output files using Open Babel[49,50] and can be found in the Supporting Information. The VEA (vertical electron affinity) was calculated in solvent as VEA = E(geometry of the neutral compound in solvent) − E(geometry of the neutral compound as a radical anion in solvent). For the NMR calculation of **amine-6**, conformers for **amine-6** were generated by exporting the ChemDraw structure to ChemDraw3D, then exporting that to Avogadro[30,31] and optimizing under MMFF94. Confab[39] in Openbabel[49,50] (energy cutoff = 7 kcal·mol^{-1}) was used to generate 16 conformers, which were optimized under B3LYP/6-31G(d) in Gaussian 09.[44] All the optimized conformers contained intramolecular hydrogen bonding between the nitrogen atoms with exception of the highest energy conformer, which contained intramolecular hydrogen bonding to H2 and H3 from both nitrogens. The two lowest-energy conformers and the higher energy H2 and H3 hydrogen bonded conformers were subjected to a gas-phase optimization and NMR calculation with GIAO using the SMD solvent model with $CHCl_3$, as described in the CHESIRE database recommendations[51,52] (mPW1PW91/6-311+G(2d,p)/SMD-($CHCl_3$)//B3LYP/6-311+G(2d,p)). The data were corrected using linear regression and the suggested scaling factors (slope of −1.0933 and intercept of 31.9088). Only the conformer with the highest R^2 value is reported, and the final optimized structure (xyz) can be found in the Supporting Information. Where a carbon had rotameric resonances, the strongest resonance was used for Figure S2 and Table S1.

*The Synthesis of (2R,2′R)-1,1′-Ditosyl-2,2′-biaziridine ((R,R)-**1**).* The experimental procedures to the synthesis of biaziridine **1** are presented here, as there were amendments to the procedures compared to those published in ref 11, including the scale-up.

*Dimethyl (4R,5R)-2,2-Dimethyl-1,3-dioxolane-4,5-dicarboxylate (**S1**).*[11] A reaction mixture containing (*R*,*R*)-tartaric acid (53.1 g, 354 mmol), toluenesulfonic acid (0.2 g, 1 mmol), MeOH (20 mL), and reagent-grade DMP (94 mL) was stirred under an air atmosphere with heating at reflux using a Vigreux column as an air condenser until the suspension formed a dark red solution (~1 h). To the mixture was added cyclohexane (220 mL). The Vigreux column was wrapped in aluminum foil, and a short path distillation apparatus was connected to the top along with a 250 mL receiving flask. The temperature was slowly increased until a small trickle of solvent was observed to distill into the 250 mL round-bottom flask, and more DMP (50 mL) was added at 24 and 36 h (when it was observed that no further solvent was undergoing distillation). After 48 h, when no further solvent was collected, the solution was cooled, and DMP (3 mL) and K_2CO_3 (0.6 g) were added to the mixture. The mixture was stirred at rt for 30 min, and EtOAc was used to transfer the product to a separatory funnel. The organic phase was washed with water (5 × 250 mL) and brine (2 × 250 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* (high vacuum for 24 h) to yield the protected product **S1** (77.4 g, >99%) as a golden yellow oil.

*((4S,5S)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)dimethanol (**S2**).*[11] To a 2 L round-bottom flask containing freshly opened undried THF (139 mL) at 0 °C was added $LiAlH_4$ (16.3 g, 426 mmol) in air portion-wise over 1 h, and the gray suspension was allowed to stir for 10 min at 0 °C. The pure protected tartaric acid **S1** (46.6 g, 213 mmol)[a] was then placed in a 250 mL separatory funnel and added dropwise to the mixture with vigorous stirring such that the gas

https://doi.org/10.1021/acs.joc.1c00359
J. Org. Chem. 2021, 86, 9163−9180

formation dissipated between each drop. After addition, any residual oil within the separatory funnel was washed into the reaction with additional THF (10 mL). The solution was then warmed slowly to rt and stirred overnight to produce a thick yellow-gray slurry. Diethyl ether (1 L) was carefully added to the mixture. A Fieser quench was performed (16.26 mL H_2O, 16.26 mL 15% NaOH, 48.78 mL H_2O), and the solution was stirred for 1 h before being filtered by suction. The precipitate was washed with EtOAc (~2 L) until most of the yellow oil had eluted. The filtrate was dried ($MgSO_4$), filtered by gravity, and concentrated *in vacuo* (high vacuum for 48 h) to give the diol **S2** (34.02 g, 96%) as a viscous yellow oil.

*(4S,5S)-4,5-Bis(azidomethyl)-2,2-dimethyl-1,3-dioxolane (**S4**).*[11] To a 1 L round-bottom flask containing the diol **S2** (35.3 g, 218 mmol) in CH_2Cl_2 (654 mL) was added NEt_3 (68.0 mL, 488 mmol) in air at 0 °C in one portion, and the solution was stirred for 1 min. Methanesulfonyl chloride (37.0 mL, 478 mmol) was then added dropwise such that the temperature of the solution was maintained at 5−10 °C. After addition, the suspension was then stirred at 0 °C for 1 h before aq. citric acid (500 mL, 1 M) was added portion-wise. The solution was allowed to warm to rt with stirring over 24 h, then the layers were separated. The organic phase washed with water (3 × 200 mL) and brine (200 mL) and concentrated *in vacuo* (high vacuum for 48 h) to afford the crude mesylate **S3** (59.4 g) as a red solid.

To a solution of the crude mesylate **S3** (59.4 g) in anhydrous DMF (529 mL) was added NaN_3 (36.4 g, 560 mmol) portion-wise in air at rt. The suspension was then placed under N_2 and heated to 80 °C for 72 h, cooled to rt, and quenched with H_2O (50 mL). The suspension was poured into a separatory funnel. To the funnel was added diethyl ether (1 L) was added, followed by brine (300 mL), and the solution was left to separate for 30 min. The aqueous layer was separated and extracted with diethyl ether (2 × 250 mL), and the combined organic layers were washed with H_2O (14 × 250 mL) and brine (3 × 250 mL). The organic phase was concentrated *in vacuo* to furnish a red oil, which was dissolved in EtOAc (400 mL) and further washed with H_2O (6 × 500 mL) to remove the last remaining DMF. The organic phase was then concentrated *in vacuo* (high vacuum 48 h) to yield the azide **S4** (32.0 g, 69%) as a red oil.

*N,N′-(((4S,5S)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis-(methylene))bis(4-methylbenzenesulfonamide) (**S6**).*[11] To freshly opened undried THF (245 mL) at 0 °C in air was added $LiAlH_4$ (11.5 g, 303 mmol) portion-wise with stirring, and the suspension was allowed to stir for 10 min. The diazide **S4** (32.0 g, 151 mmol) was dissolved in THF (447 mL) and added dropwise to the gray suspension at 0 °C over 4 h in air using a 500 mL separatory funnel. Halfway through the addition of the azide **S4**, the thick reaction slurry required the careful addition of more reagent-grade THF (~100 mL) to keep the reaction stirring freely. After the completion of the addition, the golden yellow-gray suspension was warmed to rt and left to stir overnight. The reaction mixture was quenched with a Fieser quench (11.5 mL H_2O, 11.5 mL 15% NaOH, and 34.5 mL H_2O) and then filtered by vacuum filtration, and the solids were washed with THF (~2 L) until most of the yellow oil had eluted. The filtrate was dried (Na_2SO_4) and concentrated *in vacuo* (high vacuum for 24 h) to give the crude diamine **S5** (25.5 g) as a red oil, which contained some alkyl impurities and residual THF.

To a well-stirred solution of the crude amine **S5** (25.4 g) in reagent grade pyridine (308 mL) at 0 °C in air was added *p*-toluenesulfonyl chloride (60.4 g, 317 mmol) portion-wise, such that no gas evolution was observed. The red solution was warmed to rt, stirred for 72 h, then quenched with cold HCl (200 mL, 1 M aqueous) portion-wise, followed by brine (500 mL) and EtOAc (500 mL). After 1 h, two layers had formed and the aqueous layer was separated and extracted with EtOAc (2 × 250 mL); the combined organic phases were washed with cold HCl (~2 L, 1 M aqueous) until a wash with $CuSO_4$ (saturated aqueous solution) to the mixture remained blue, indicating the removal of most of the pyridine. The organic phase was then washed with brine (2 × 200 mL), dried (Na_2SO_4) and concentrated in a rotary evaporator to a thick red oil. The oil was redissolved in EtOAc (250 mL), washed with cold HCl (5 × 400 mL), then washed with brine (300 mL) to remove the last of the pyridine. Finally, concentration of the organic phase *in vacuo* (high vacuum for 24 h) afforded the ditosyl amine **S6** (38.6 g, 54% yield over 2 steps) as a thick red gum that could not be dried further.

Reaction note. Extreme care should be taken during the diazide addition to ensure that the reaction continuously stirs. If the reaction becomes difficult to stir, more THF can be slowly added, and the suspension can be allowed to mix for at least 30 min after all diazide dissolves. No significant increases in heat or gas evolution were observed during the reduction, even after repeating the reaction four times.

*N,N-((2S,3S)-2,3-Dihydroxybutane-1,4-diyl)bis(4-methoxybenzenesulfonamide) (**S7**).*[11] A suspension of the acetonide-protected tosyl amine **S6** (38.6 g, 82.3 mmol) in MeOH (380 mL) and HCl (95 mL, 1 M) was stirred into a vortex to ensure thorough mixing of the suspension, and the solution was heated at reflux for 2 h in air. After cooling to rt, the stir bar was removed and washed with CH_2Cl_2. Then, the solvent was concentrated on a rotary evaporator (to ~100 mL). To this suspension was added EtOAc (1 L), and the precipitated gum was dissolved with the aid of an ultrasonicator. The two layers were separated. The organic layer was washed with H_2O (200 mL), saturated aq. $NaHCO_3$ (2 × 300 mL), and finally H_2O (300 mL) and then dried (Na_2SO_4) and evaporated *in vacuo* (high vacuum for 48 h) to give the diol **S7** (32.5 g, 92%) as a tan solid that contained EtOAc and H_2O.

*(2R,2′R)-1,1′-Ditosyl-2,2′-biaziridine ((R,R)-**1**).* To a solution of the diol **S7** (15.2 g, 35.5 mmol) in pyridine (65 mL) was added MsCl (11.8 g, 103 mmol) dropwise at 0 °C, and the mixture was allowed to warm to rt overnight under nitrogen with magnetic stirring. The mixture was diluted with 1 M aq. HCl (300 mL) and EtOAc (500 mL). The aqueous phase was separated and extracted with EtOAc (3 × 250 mL). The combined organic fractions were washed with 1 M aq. HCl (2 × 500 mL), water (8 × 500 mL), and saturated aq. $NaHCO_3$ (2 × 100 mL). The organic solution was dried ($MgSO_4$), and the solvent was removed to afford the dimesylate **S8** (19.2 g) as a dark tan powder, which was used in the next step without further purification.

The crude dimesylate **S8** (19.2 g) was suspended in benzene (200 mL), and a 10% KOH solution (100 mL) was added slowly. The mixture was stirred vigorously at room temperature overnight, then diluted with EtOAc (400 mL) and water (100 mL). The separated aqueous phase was extracted with EtOAc (4 × 50 mL). The combined organic layers were washed with water (100 mL) and saturated aq. $NaHCO_3$ (4 × 50 mL) and dried ($MgSO_4$), and the solvent was removed to afford a crude residue. Flash chromatography (150 g silica, EtOAc/pet. spirits (30%)) of the residue afforded a highly crystalline major fraction, which was condensed and recrystallized from $CHCl_3$/pet. spirits to afford (*R,R*)-biaziridine (*R,R*)-**1** (9.18 g, 67% over two steps) as fluffy white crystals.

General Procedures. *General Procedure 1: Detosylation of 1,2-Bis(tosylamides) Using Mg Powder.* A round-bottom flask fitted with a septum containing the 1,2-bis(tosylamide) and magnesium powder (50 equiv) was placed under high vacuum for 1 h, then backfilled with argon.[b] Anhydrous MeOH (1 mL per 50 mg of Mg) was added under argon, and the flask was fitted with an argon balloon. The suspension was placed in an ultrasonicator at rt and sonicated for 45 min, with the flask being manually shaken every minute for the first 5 min to ensure thorough mixing. At the completion of the reaction, the water bath temperature was found to be 42−44 °C, and a gray suspension had formed. The suspension was poured over EtOAc with vigorous shaking to prevent a thick gel from forming, and the thick cloudy mixture was filtered through Celite 545 using a water aspirator and washed with EtOAc. Water was added to the mixture, the layers were separated, and the aqueous layer was extracted three times with EtOAc. The pooled organic fractions were then dried (Na_2SO_4).[c] After being concentrated *in vacuo*, the compounds were purified to afford the product as described in the individual procedures. All compounds, with the exception of **16** and **13**, were found to be contaminated with an unknown product (resonances at δ 1.26 ppm in the ^{1}H NMR and sometimes at δ 29.7 ppm in the ^{13}C NMR spectra of the contaminated compounds). This impurity could not be

https://doi.org/10.1021/acs.joc.1c00359
J. Org. Chem. 2021, 86, 9163−9180

removed by silica gel, alumina (neutral), or C18 silica gel chromatography; acid or base extractions; MeCN/hexanes extractions; recrystallization; filtration; or trituration. Purification procedures were attempted on both the free amine and HCl salt forms of the products.[d]

General Procedures 2a and ***2b****: Alkylation of 1,2-bis(tosylamides)*[e]*. General Procedure 2a.* To a stirred solution of the 1,2-bis(tosylamide), alkyl halide (6.0 equiv), and tetrabutylammonium iodide (0.3 equiv) in DMF (~11.6 mL per mmol 1,2-bis(tosylamide)) was added excess NaH (10.0 equiv) portion-wise in air. The vessel was placed under an atmosphere of N_2, and the the suspension was heated at 60 °C for the time specified. Reactions were carefully monitored by TLC analysis for starting material consumption. The solution was then cooled, quenched with H_2O, extracted, evaporated by rotary evaporation and compressed air (overnight as a gentle stream), and purified as identified in the individual procedures.

General Procedure 2b. To a stirred solution of 1,2-bis(tosylamide), alkyl halide (6.0 equiv), and tetrabutylammonium iodide (0.3 equiv) in DMF (~11.6 mL per mmol 1,2-bis(tosylamide)) was added fresh NaH (3.5 equiv) portion-wise in air. The vessel was placed under an atmosphere of N_2, and the suspension was heated at 60 °C for 3.5 h. The solution was immediately quenched with H_2O in one portion, extracted, evaporated by rotary evaporation and compressed air (overnight as a gentle stream), and purified as identified in the individual procedures.

General Procedure 3: N-Detosylation of Diamines with Na/Naphthalide.[53] To naphthalene (257 mg, 2.01 mmol) was added anhydrous DME (1.66 mL) under an atmosphere of Ar by first removing the septum and adding the solvent under a gentle Ar stream, followed by the addition of Na metal (52 mg, 2.3 mmol) in one portion. The solution was stirred for 2 h. The dark green solution was then added dropwise to a solution of the 1,2-bis(tosylamide) in DME (40 mg of 1,2-bis(tosylamide) per mL) at −78 °C until the dark green color persisted for 3−5 min. The reaction was then quenched with a few drops of H_2O, and the mixture was warmed to rt with stirring. Then, more H_2O was added to the mixture. The reaction mixture was extracted with CH_2Cl_2 (×2), and the pooled organic fractions were dried (Na_2SO_4) and evaporated *in vacuo*. The crude residue was analyzed by ^1H and ^{13}C NMR spectrometry.

General Procedure 4: Detosylation of diamines with SmI_2/H_2O/Pyrrolidine.[2] To a flask containing 1,2-diiodoethane (0.912 g, 3.24 mmol) in 25 mL of freshly distilled THF from a sodium/benzophenone still was added Sm[f] metal (0.710 g, 4.72 mmol) under N_2. The reaction mixture was then stirred at rt under N_2 until it turned dark blue (~5 h), indicating that SmI_2 had formed. The reaction mixture was added in one portion (20 equiv., 0.13 M) at rt to the neat tosyl amide. Thirty minutes after addition, H_2O (60 equiv) was added dropwise, followed by the dropwise addition of pyrrolidine (40 equiv). After stirring for a further 10 min, more H_2O was added to the brown mixture, and the aqueous phase was extracted with CH_2Cl_2 (×2). The combined organic fractions were dried (Na_2SO_4) and evaporated *in vacuo*. The crude residue was analyzed by ^1H and ^{13}C NMR spectrometry.

General Procedure 5: Deprotection of Diamines with Li/Ethylenediamine/Propylamine.[17] To a two-neck round-bottom flask, which was equipped with a condenser fitted with an argon balloon at the top and a rubber septum on the unused second flask neck, were added the tosyl amide (~0.084 mmol), *n*-propylamine (0.5 mL), and ethylenediamine (30 equiv, 2.5 mmol, 0.17 mL). The septum was removed briefly to purge the flask for 10 s, and the solution was stirred in an ice bath for 10 min under argon. To the solution was added Li metal (28 equiv), which was blotted with a paper towel to remove oil before weighing, in one portion by the removal and quick replacement of the septum. The reaction mixture was stirred until the solution turned dark blue and all the lithium was consumed, after which the reaction mixture was stirred for a further 20 min. The vessel was exposed to air, and the solution was poured over ice. The flask was rinsed with diethyl ether into the ice. After the ice had melted, diethyl ether was added to the mixture. The layers were separated, and the organic layer was washed with H_2O and brine, dried (Na_2SO_4), and evaporated *in vacuo*. The crude amine products were then purified by neutral aluminum oxide chromatography as identified in the individual procedures.

Syntheses of 1,2-Bis(tosylamides) and 1,2-Diamines. *N,N′-((2S,3S)-1,4-Diphenoxybutane-2,3-diyl)bis(4-methylbenzenesulfonamide) (****2****).* To a solution of phenol (1.57 g, 16.6 mmol) in THF (15.6 mL) was added KHMDS (16.2 mL, 16.2 mmol, 1.0 M in THF) dropwise at rt, and the resultant slurry was allowed to stir for 10 min. (*R*,*R*)-Biaziridine (*R*,*R*)-**1** (1.30 g, 3.31 mmol) in DMF (26.0 mL) was then added dropwise at rt over 2 h. More DMF (3.0 mL) was used to transfer the residual biaziridine (added dropwise over 5 min), then the solution was stirred for 24 h. The reaction was quenched with NH_4Cl (50 mL), and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, evaporated under a stream of compressed air overnight, and dried under high vacuum (1 h). The residue was then subjected to column chromatography (~35 g silica) with wet loading using CH_2Cl_2 and eluted with EtOAc/hexanes (20%). Fractions containing just the product and fractions containing the phenol/product mixture (by TLC analysis) were both separately concentrated *in vacuo*. Both fractions were then precipitated from boiling CH_2Cl_2/hexanes, cooled to −20 °C, filtered, dried in air (1 h), and dried under high vacuum (24 h) to afford the ring opened product **2** (1.80 g, 94%) as a white solid. The product was found to be unstable to high concentrations of TFA (50% v/v in CH_2Cl_2). mp 131−132 °C; TLC (EtOAc/hexanes (20%)) R_f = 0.27; $[\alpha_D^{25}]$ = +30.2 (c = 0.36, CH_2Cl_2); FTIR υ 3300 (br m), 2932 (w), 1598 (m), 1497 (m), 1460 (m), 1434 (m), 1337 (m), 1322 (m), 1290 (m), 1238 (s), 1149 (s), 1087 (s), 1057 (m), 1020 (w), 996 (w), 965 (w), 812 (m), 756 (s), 707 (s), 672 (s), 509 (m), 418 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 4H, H2′, H2″, H6′ and H6″), 7.25−7.19 (m, 8H, H3′, H3″ H5′, H5″, H3‴, H3⁗, H5‴, and H5⁗), 6.95 (t, *J* = 7.4 Hz, 2H, H4‴ and H4⁗), 6.62 (d, *J* = 7.6 Hz, 4H, H2‴, H2⁗, H6‴, and H6⁗), 5.10 (d, *J* = 6.1 Hz, 2H, NH), 3.96−3.82 (m, 6H, H1, H2, H3, and H4), 2.38 (s, 6H, $TsCH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5 (C1‴ and C1⁗), 143.9 (C4′ and C4″), 136.5 (C1′ and C1″), 129.8 (C5′, C5″, C6′ and C6″ or C5‴, C5⁗, C3⁗, and C3‴), 129.5 (C5′, C5″, C6′ and C6″ or C5‴, C5⁗, C3⁗, and C3‴), 127.3 (C2′, C2″, C6′, and C6″), 121.6 (C4‴ and C4⁗), 114.3 (C2‴, C2⁗, C6‴, and C6⁗), 66.3 (C1 and C4), 53.5 (C2 and C3), 21.6 ($TsCH_3$); MS (ESI−) 579 $[M - H]^-$; HRMS (ESI+) calcd for $C_{30}H_{33}N_2O_6S_2$ 581.1788, found 581.1780 $[M + H]^+$.

X-ray Crystal Growth. To a 2 mL vial containing ~5 mg of the compound was added CH_2Cl_2 (1.0 mL), and the product was sonicated to dissolution. To this mixture was then added MeOH (1.0 mL), and the solution shaken. The vial was then left open until the solvent had evaporated (~3 d), yielding clear white rod-like crystals.

*N,N′-((2R,3R)-1,4-Bis(2-iodophenoxy)butane-2,3-diyl)bis(4-methylbenzenesulfonamide) (****17****).*[11] To prepare the known **17**,[11] a modified procedure was developed. To a solution of 2-iodophenol (2.85 g, 13.0 mmol) in THF (10 mL) was added KHMDS (12.2 mL, 12.2 mmol, 1.0 M in THF) dropwise at rt,[g] and the slurry allowed to stir for 10 min. (*R*,*R*)-Biaziridine (*R*,*R*)-**1** (1.00 g, 2.56 mmol) in DMF (20 mL) was then added dropwise at rt, and the solution stirred for 24 h. The reaction was quenched with NH_4Cl (40 mL), and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (30 mL), dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The crude solid was subjected to silica gel chromatography (~20 g of silica) with wet loading using CH_2Cl_2 and eluted with EtOAc/hexanes (20%) to afford the product **17** (1.48 g, 70%) as a white solid.

*N,N′-((2R,3R)-1,4-Bis(phenylamino)butane-2,3-diyl)bis(4-methylbenzenesulfonamide) (****4****).*[11] To a solution of (*R*,*R*)-biaziridine (*R*,*R*)-**1** (22 mg, 0.057 mmol) in DMF (0.5 mL) was added 20 equiv of aniline[h] (0.12 mL, 1.3 mmol) in one portion, and then the reaction mixture was stirred for 24 h. The reaction was quenched with H_2O (10 mL), and the mixture was extracted with EtOAc (20 mL). The organic phase was separated; washed with brine (2 × 10 mL), water (3 × 10 mL), and brine (10 mL); and concentrated *in vacuo*. The oil

https://doi.org/10.1021/acs.joc.1c00359
J. Org. Chem. 2021, 86, 9163−9180

was evaporated under a stream of N_2 (~3 h). The resultant gum was dissolved in the minimum amount of $CHCl_3$ (<1.0 mL), precipitated by addition of hexanes (~150 mL), left to stand for 30 min, filtered by vacuum, and washed with hexanes (3 × 25 mL). The fluffy white solid was dissolved using $CHCl_3$ into a clean dry flask and concentrated *in vacuo* to yield the product **4** (24 mg, 72%)[I] as a clear colorless gum. Dissolving the gum with $CHCl_3$, precipitation with hexanes, and evaporation *in vacuo* gave the product as a white solid with ^{1}H NMR spectra that were identical to the gum.

Reaction Notes. On larger scale (244 mg), the reaction was incomplete after 24 h, and stirring for longer did not cause the reaction to go to completion. In this case, evaporation to a gum under a stream of N_2, followed by the addition of a second amount of DMF and aniline, allowed reaction to reach completion. After the above workup, precipitation was not feasible. Therefore, silica gel column chromatography (20 g of silica gel) with gradient elution using $CHCl_3$/hexanes (50%, 150 mL; 80%, 200 mL; 100%, 150 mL) gave a single spot by TLC analysis that was dissolved in $CHCl_3$, precipitated from hexanes, filtered, and evaporated *in vacuo*. The remaining column fractions that contained no aniline by TLC analysis (but multiple other spots) were subjected to further silica gel chromatography (30 g of silica gel) with elution using $CHCl_3$/hexanes (50%, 400 mL), followed by $CHCl_3$ (100%), until no further product was eluted. Fractions with a single spot by TLC were evaporated *in vacuo*, dissolved in $CHCl_3$, precipitated with hexanes, filtered, and evaporated *in vacuo*, then combined with the previous pure fractions to give **4** (161 mg, 45%) as a white solid. This reaction was not repeated on a large scale again due to this being the 10th step in the synthesis; hence, there was a lack of material to reoptimize the reaction on such a scale.

*N,N′-((3R,4R)-1,6-Diphenylhexane-3,4-diyl)bis(4-methylbenzenesulfonamide) (**3**).*[11] To prepare the known compound **3**,[11] a modified procedure was developed. A 50 mL two-neck flask containing $CuBrSMe_2$ (306 mg, 1.50 mmol) was equipped with an argon balloon that was attached to a Teflon tap and a septum on the spare neck. The flask was purged with argon for 5 s. Tetrahydrofuran (7.0 mL) was added to the flask, and the mixture was cooled to −40 °C (MeCN/$N_{2(l)}$). BnMgCl (7.6 mL, 15 mmol, 2.0 M in THF) was then added through the septum, and the mixture was stirred for 10 min. A solution of (*R*,*R*)-biaziridine (*R*,*R*)-**1** (398 mg, 1.00 mmol) in THF (7.0 mL) was added dropwise at −40 °C; any undissolved (*R*,*R*)-biaziridine **1** was dissolved with more THF (1.5 mL) and added to the reaction mixture dropwise. The flask was purged with argon for 5 s by removing the pierced septum and replacing it with a fresh septum, and the solution was stirred for 2 h at −40 °C. The reaction solution was warmed to rt, stirred overnight, quenched with NH_4Cl (20 mL), and extracted with EtOAc (150 mL). The organic layer was separated and further washed with NH_4Cl (4 × 50 mL) until the aqueous layer was no longer blue. The organic layer was dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The residual oily solid was recrystallized from boiling $CHCl_3$/hexanes (~30 mL) with vigorous stirring during precipitation and cooling (slowly cooled in the oil bath to rt) until a fine white precipitate had formed (~2 h). The flask was cooled to 0 °C in a freezer (15 min), and the white solid was filtered by vacuum filtration. The solid was eluted from the filter paper using CH_2Cl_2. The filtrate was evaporated and dried *in vacuo* to give the ring opened product **3** (436 mg, 75%) as a white solid.

4-Methoxybenzyl Chloride. This was synthesized by a modified procedure.[54,55] To 4-methoxybenzyl alcohol (3.12 g, 22.6 mmol) was added concentrated HCl (6.0 mL), and the reaction mixture was stirred at rt for 15 min. The mixture was transferred to a separatory funnel with the aid of pet. spirit (~10 mL). The layers were separated, and the aqueous layer was extracted with pet. spirit (20 mL). The combined organic fractions were washed with brine (20 mL) and dried (Na_2SO_4). After filtration and evaporation on a rotary evaporator, the oil was dried further under high vacuum (5 min) to give 4-methoxybenzyl chloride (2.93 g, 86%) as a clear oil. The sample was placed over K_2CO_3 and stored in a freezer at −20 °C for 24 h before use.

*N,N′-((2S,3S)-1,4-Bis(hexyloxy)butane-2,3-diyl)bis(4-methylbenzenesulfonamide) (**6**).* To a solution of hexanol (0.48 mL, 0.39 mmol) in THF (3.0 mL) was added NaHMDS (3.8 mL, 3.8 mmol, 1 M in THF) dropwise at rt, and the slurry allowed to stir for 10 min. (*R*,*R*)-Biaziridine (*R*,*R*)-**1** (303 mg, 0.772 mmol)[J] in DMF (3.0 mL) was then added dropwise at rt over 30 min. More DMF (0.5 mL) was used to transfer any residual biaziridine (added dropwise over 1 min). The solution was stirred for 19 h and then the reaction was quenched with NH_4Cl (10 mL). The aqueous reaction mixture was extracted with EtOAc (150 mL). The organic phase was separated and washed with brine (2 × 50 mL), NaOH (3 × 25 mL, 2.0 M), H_2O (50 mL), and finally brine (50 mL). The organic phase was dried (Na_2SO_4), filtered, and evaporated *in vacuo*, with the exception that a heat gun was used to aid in the evaporation of the residual hexanol under high vacuum, yielding the crude product as a clear amber oil. The residue was then subjected to silica gel chromatography (10 g of silica) by wet loading with CH_2Cl_2 and elution with acetone/hexanes (10%, 150 mL). The fractions containing the product were collected and subjected to further silica gel chromatography in the same way (20 g of silica), eluting with acetone/hexanes (10%, 250 mL) to afford the product **6** (211 mg, 46%) as a clear colorless oil. TLC (acetone/hexanes (20%)) R_f = 0.27; $[\alpha_D^{25}]$ = +12.7 (c = 1.1, CH_2Cl_2); FTIR υ 3271 (br, s), 2953 (m), 2928 (m), 2858 (m), 1598 (w), 1495 (w), 1442 (br m), 1377 (w), 1329 (m), 1306 (w), 1290 (w), 1185 (w), 1159 (s), 1116 (m), 1088 (s), 1020 (w), 1002 (w), 966 (w), 909 (w), 814 (m), 707 (w), 669 (s), 610 (w), 655 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, J = 8.3 Hz, 4H, H2′, H2″, H6′, and H6″), 7.29 (d, J = 8.1 Hz, 4H, H3′, H3″, H5′, and H5″), 5.17 (d, J = 6.7 Hz, 2H, NH), 3.55−3.44 (m, 2H, H2 and H3), 3.41−3.34 (m, 2H, $H1_a$ and $H4_a$), 3.30−3.14 (m, 6H, $H1_b$, $H4_b$, H1‴, and H1⁗), 2.43 (s, 6H, $TsCH_3$), 1.46−1.16 (m, 16H, H2‴, H3‴, H4‴, H5‴, H2⁗, H3⁗, H4⁗, and H5⁗), 0.90 (t, 6H, H6‴ and H6⁗); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 143.5 (C4′ and C4″), 137.0 (C1′ and C1″), 129.7 (C3′, C3″, C5′, and C5″), 127.3 (C2′, C2″, C6′, and C6″), 71.4 (C1‴ and C1⁗), 69.2 (C1 and C4), 53.7 (C2 and C3), 31.6 (hexyl CH_2), 29.4 (hexyl CH_2), 25.7 (hexyl CH_2), 22.6 (hexyl CH_2), 21.6 ($TsCH_3$), 14.0 (C6‴ and C6⁗); MS (ESI+) 597 (100%, $[M + H]^+$); MS (ESI−) 595 (100%, $[M - H]^-$); HRMS (ESI+) calcd for $C_{30}H_{49}N_2O_6S_2$ 597.3027, found 597.3028 $[M + H]^+$.

*4-Methyl-N-((R)-2-(phenylamino)-1-((R)-1-tosylaziridin-2-yl)-ethyl)benzenesulfonamide (**18**).*[11] Attempts at synthesizing the above compound **4** using our previously published procedure[11] with only 5 equiv of aniline (0.060 mL, 0.66 mmol) and (*R*,*R*)-biaziridine (*R*,*R*)-**1** (48 mg, 0.12 mmol) in 1.0 mL of DMF yielded a mixture of the di-ring opened product **4** and the mono-ring opened product **18**.[K] These products were unable to be completely separated by silica gel column chromatography and required PLC separation, eluting with $CHCl_3$ five times to yield the crude mono-ring opened product **18** (15 mg of crude). TLC ($CHCl_3$ (100%), two times) R_f = 0.36; PLC (100% $CHCl_3$, 5 times) R_f = 0.31; ^{1}H NMR ($CDCl_3$, 400 MHz) (crude)[L] δ 7.75 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.17−7.10 (m, 2H), 6.74 (t, J = 7.3 Hz, 1H), 6.44 (dd, J = 8.6, 0.9 Hz, 2H), 4.75−4.67 (m, 1H), 3.31−2.93 (m, 6H), 2.47 (s, 3H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) (crude)[M] δ 146.8, 145.3, 143.9, 136.4, 133.7, 130.0, 129.9, 129.3, 128.2, 127.1, 118.5, 113.2, 43.1, 42.1, 41.1, 40.8, 21.7, 21.6; MS (ESI+) 508 (100%, $[M + Na]^+$), 486 (64%, $[M + H]^+$; MS (ESI−) 484 (34%, $[M - H]^-$); HRMS (ESI+) calcd for $C_{24}H_{28}N_3O_4S_2$ 486.1521, found 486.1526 $[M + H]^+$.

Reaction Note. A second fraction from the PLC plate was found to contain the di-ring opened product **4** (24 mg, 33%), which was spectroscopically identical to product **4** from the above procedure. PLC (100% $CHCl_3$, 5 times) R_f = 0.19.

*N,N′-((2R,3R)-1,4-Di(piperidin-1-yl)butane-2,3-diyl)bis(N-ethyl-4-methylbenzenesulfonamide) (**15**).* In a similar modification as that for **4**, 20 equiv of piperidine (0.13 mL, 1.3 mmol) was added in one portion to a solution of (*R*,*R*)-biaziridine (*R*,*R*)-**1** (25 mg, 0.064 mmol) in DMF (0.5 mL), and the reaction mixture was stirred for 24 h. The reaction was quenched with H_2O (10 mL), and the mixture was extracted with EtOAc (20 mL). The organic phase was separated;

https://doi.org/10.1021/acs.joc.1c00359
J. Org. Chem. 2021, 86, 9163−9180

washed successively with brine (2 × 10 mL), H_2O (3 × 10 mL), and brine (10 mL); dried (Na_2SO_4); filtered; and concentrated *in vacuo*. The residue was then dissolved in EtOAc (20 mL) and subjected to a second aqueous washing using H_2O (5 × 5 mL) and brine (3 × 5 mL);. The organic phase was then dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Residual silicon grease was removed by dissolution in MeCN (20 mL) and washing with hexanes (50 × 3 mL). The MeCN layer was dried (Na_2SO_4), filtered, and evaporated *in vacuo* to yield product **5** (32 mg crude), which was of sufficient purity for the next step. Spectroscopic data were in agreement with our previous report of the product.[11] The published purification was found to be difficult and only small amounts of the material (5−10 mg) could be easily purified, allowing for **5** to be subjected to Mg/MeOH reduction conditions. Therefore, in a second step using the above impure material and following general procedure 2b without tetrabutylammonium iodide, the ring opened product **5** (32 mg, 0.056 mmol), iodoethane (0.03 mL, 0.4 mmol), and NaH (8.4 mg, 0.21 mmol, 60% w/w) in DMF (0.66 mL) were reacted and subsequently quenched with H_2O (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and subjected to silica gel chromatography (5 g of silica) by wet loading using CH_2Cl_2 and elution with EtOAc/hexanes (20%) to give **15** (10 mg, 26% across two steps) as a clear colorless gum. TLC (EtOAc/hexanes (20%)) R_f = 0.22; $[\alpha_D^{25}]$ = +65.6 (c = 0.49, CH_2Cl_2); FTIR υ 2932 (s), 2853 (w), 2790 (w), 1598 (w), 1495 (w), 1468 (w), 1450 (w), 1379 (w), 1334 (s), 1305 (m), 1290 (w), 1261 (w), 1183 (w), 1161 (s), 1106 (m), 1088 (m), 1040 (w), 1019 (w), 998 (w), 987 (w), 962 (w), 932 (w), 902 (w), 865 (w), 814 (w), 800 (w), 781 (w), 756 (w), 733 (w), 708 (w), 696 (w), 667 (w), 619 (m), 515 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) (mixture of rotamers)[n] δ 7.81 (d, J = 8.3 Hz, 4H, H2′, H6′, H2″, and H6″), 7.28 (d, J = 8.0 Hz, 4H, C3′, C5′, C3″, and C5″), 4.24 (dd, J = 10.2, 4.5 Hz, 2H, H2 and H3), 3.76−3.61 (m, 2H, H1a‴″, H1a‴″), 3.52−3.37 (m, 2H, $H1_b$‴″ and $H1_b$‴″), 2.93−2.82 (m, 2H, $H1_a$ and $H4_a$), 2.42 (s, 6H, $TsCH_3$), 2.37−2.10 (m, 8H, H2‴, H6‴, H2‴, and H6‴), 1.85 (d, J = 9.4 Hz, 2H, H1b and H4b), 1.53−1.23 (m, 12H, H3‴, H4‴, H5‴, H3‴, H4‴, and H5‴), 1.19 (t, J = 7.1 Hz, 6H, H2‴″ and H2‴″); ^{13}C NMR ($CDCl_3$, 101 MHz, ^{13}C DEPTQ-135) (mixture of rotamers)[o] δ 142.9 (C4′ and C4″), 138.1 (C1′ and C1″), 129.3 (C3′, C5′, C3″, and C5″), 127.8 (C2′, C6′, C2″, and C6″), 59.0 (C1 and C4), 54.6 (C2, C3, C2‴, C6‴, C2‴, and C6‴), 40.3 (br, C1‴″ and C1‴″), 26.3 (C3‴, C5‴, C3‴, and C5‴), 24.5 (C4‴ and C4‴), 21.5 ($TsCH_3$), 15.9 (C2‴″ and C2‴″); MS (ESI+) 619 (100%, $[M + H]^+$); HRMS (ESI+) calcd for $C_{32}H_{51}N_4O_4S_2$ 619.3352, found 619.3358 $[M + H]^+$.

*Di-tert-butyl ((2S,3S)-1,4-Diphenoxybutane-2,3-diyl)bis-(tosylcarbamate) (**13**).* To a reaction flask containing the 1,2-bis(tosylamide) **2** (358 mg, 0.617 mmol) and DMAP (82 mg, 0.67 mmol) were added NEt_3 (0.43 mL, 3.1 mmol) and CH_2Cl_2 (10 mL), and the mixture was stirred until a solution had formed. To the reaction mixture was added Boc_2O (0.71 mL, 3.1 mmol, gently warmed to a liquid) dropwise at rt, and the solution was stirred for 24 h with monitoring by TLC analysis to ensure the consumption of the 1,2-bis(tosylamide) starting material. The solution was then evaporated on a rotary evaporator, dissolved in EtOAc (50 mL), and washed with HCl (3 × 20 mL, 0.1 M), brine (20 mL), saturated aq. $NaHCO_3$ (20 mL), and brine (20 mL). The organic phase was dried (Na_2SO_4), filtered, and evaporated to a white solid on a rotary evaporator. The solid was redissolved in MeCN (50 mL) and washed with hexanes (3 × 200 mL) to remove the residual grease. The MeCN layer was dried (Na_2SO_4), filtered, evaporated *in vacuo* to a gum, dissolved in diethyl ether (∼2.0 mL), and re-evaporated under high vacuum (3 h) to yield the *N,N′*-di-Boc-protected 1,2-bis(tosylamide) **13** (482 mg) as a white solid that contained alkyl impurities. No further purification was required for subsequent detosylation by Mg/MeOH. mp 45−50 °C; TLC (EtOAc/hexanes (20%)) R_f = 0.71; $[\alpha_D^{25}]$ = −75.3 (c = 0.29, CH_2Cl_2); FTIR υ 2978 (w), 1721 (w), 1597 (w), 1494 (w), 1350 (m), 1236 (m) 1140 (s), 1085 (w), 882 (w), 810 (m), 668 (m), 572 (s), 545 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 8.3 Hz, 4H, H2′, H2″, H6′, and H6″), 7.36−7.16 (m, 8H, H3′, H3″, H5′, H5″, H3‴, H5‴, H3‴, and H5‴), 6.93 (t, J = 7.3 Hz, H4‴ and H4‴), 6.68 (d, J = 7.7 Hz, 4H, H2‴, H6‴, H2‴, and H6‴), 5.70 (s, 4H, H2 and H3), 4.41 (s, 2H, H1 and H4), 2.42 (s, 6H, $TsCH_3$), 1.39 (s, 18H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.2 (C1‴ and C1‴″), 150.9 (COOR), 144.1 (C4′ and C4″), 137.4 (C1′ and C″), 129.6 (C3‴, C5‴, C3‴, and C5‴), 129.2 (C2′, C2″, C6′, and C6″ or C3′, C3″, C5′, and C5″), 129.1 (C2′, C2″, C6′, and C6″ or C3′, C3″, C5′, and C5″), 121.4 (C4‴ and C4‴), 114.8 (C2‴, C6‴, C2‴, and C6‴), 85.3 ($C(CH_3)_3$), 67.6 (C1 and C4), 57.7 (C2 and C3), 28.1 ($C(CH_3)_3$), 21.7 ($TsCH_3$); MS (ESI+) 804 (100%, $[M + Na]^+$); HRMS (ESI+) calcd for $C_{40}H_{48}N_2O_{10}NaS_2$ 803.2686, found 803.2648 $[M + Na]^+$.

*N,N′-((2S,3S)-1,4-Diphenoxybutane-2,3-diyl)bis(N-benzyl-4-methylbenzenesulfonamide) (**9**).* Following general procedure 2b, benzyl bromide (0.37 mL, 3.1 mmol), 1,2-bis(tosylamide) **2** (293 mg, 0.504 mmol)[p], tetrabutylammonium iodide (63 mg, 0.17 mmol), and NaH (72 mg, 1.8 mmol, 60% w/w) were reacted in DMF (6.0 mL). The reaction was quenched with H_2O (50 mL), and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), evaporated *in vacuo*, and purified by silica gel chromatography (20 g of silica) using gradient elution with EtOAc/hexanes (10%, 400 mL then 20%, 200 mL) to give the *N*-benzyl-protected 1,2-bis(tosylamide) **9** as a white gum. Impure fractions were subjected to a second round of silica gel chromatography under the same conditions, and any product containing trace amounts of benzyl bromide (by TLC analysis) were concentrated *in vacuo* and heated under vacuum (heat gun) to remove the residual benzyl bromide. The combined fractions were dissolved in MeCN (50 mL), washed with hexanes (3 × 100 mL), filtered, and evaporated *in vacuo* to yield the target product **9** (205 mg, 52%) as a clear colorless gum. TLC (EtOAc/hexanes (20%)) R_f = 0.57; $[\alpha_D^{25}]$ = −31.8 (c = 1.7, CH_2Cl_2); FTIR υ 3090 (w), 3064 (w), 2951 (br), 1599 (m), 1496 (m), 1454 (w), 1325 (m), 1228 (s), 1090 (m), 1046 (w), 1026 (w), 917 (w), 885 (w), 856 (w), 838 (w), 801 (m), 775 (w), 735 (s), 654 (s), 602 (w), 578 (w), 540 (s), 509 (w), 458 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.3 Hz, 4H, H2′, H2″, H6′, and H6″), 7.30−7.22 (m, 8H, H3′, H3″, H5′, H5″, H2‴″, H2‴″, H6‴″, and H6‴″), 7.21−7.15 (m, 6H, H3‴″, H3‴″, H4‴″, H4‴″, H5‴″, and H5‴″), 7.15−7.10 (m, 4H, H3‴, H3‴, H5‴, and H5‴), 6.88 (t, J = 7.3 Hz, 2H, H4‴ and H4‴), 6.18 (d, J = 7.7 Hz, 4H, H2‴, H2‴, H6‴, and H6‴), 4.76 (d, J = 15.8 Hz, 2H, benzyl CH_2), 4.70−4.62 (m, 2H, H2 and H3), 4.20 (d, J = 15.8 Hz, 2H, benzyl CH_2), 3.83−3.71 (m, 4H, H1 and H4), 2.42 (s, 6H, $TsCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.1 (C1‴ and C1‴), 143.4 (C4′ and C4″), 137.0 (C1‴″ and C1‴″), 136.6 (C1′ and C1″), 129.5 (C3′, C3″, C5′, and C5″), 129.2 (C3‴, C3‴, C5‴, C5‴, C2‴″, C2‴″, C6‴″, and C6‴″), 128.6 (C3‴″, C3‴″, C5‴″, and C5‴″), 127.9 (C2′, C2″, C6′, and C6″), 127.8 (C4‴″ and C4‴″), 121.0 (C4‴ and C4‴), 114.0 (C2‴, C2‴, C6‴, and C6‴), 64.1 (C1 and C4), 60.8 (C2 and C3), 50.1 (benzyl CH_2), 21.6 ($TsCH_3$); MS (ESI+) 783 (13%, $[M + Na]^+$); HRMS (ESI+) calcd for $C_{44}H_{44}N_2NaO_6S_2$ 783.2539, found 783.2538 $[M + Na]^+$.

Following general procedure 2a[q], benzyl bromide (0.36 mL, 3.0 mmol), 1,2-bis(tosylamide) (295 mg, 0.508 mmol), tetrabutylammonium iodide (62 mg, 0.17 mmol), and NaH (216 mg, 5.40 mmol, 60% w/w) were reacted in DMF (6.0 mL) with heating for 3.5 h. The compound was purified using the above method to yield the product as a clear colorless gum (234 mg, 61%) that was spectroscopically identical to the product obtained via general procedure 2b.

*N,N′-((2S,3S)-1,4-Diphenoxybutane-2,3-diyl)bis(N-(4-methoxybenzyl)-4-methylbenzenesulfonamide) (**10**).* Following general procedure 2a, freshly prepared 4-methoxybenzyl chloride[r] (0.42 mL, 3.1 mmol), 1,2-bis(tosylamide) **2** (294 mg, 0.507 mmol), tetrabutylammonium iodide (62 mg, 0.17 mmol), and NaH (218 mg, 5.44 mmol, 60% w/w) were reacted in DMF (6 mL) for 3.5 h. The reaction was quenched with H_2O (10 mL), and the mixture was extracted with CH_2Cl_2 (3 × 100 mL), dried (Na_2SO_4), and evaporated in the usual way with the exception that dry N_2 was used instead of air. The residue was then subjected to silica gel chromatography (20 g of silica) by wet loading with CH_2Cl_2 and gradient elution with EtOAc/hexanes (10%, 300 mL, then 20% until

https://doi.org/10.1021/acs.joc.1c00359
J. Org. Chem. 2021, 86, 9163−9180

the product eluted) to yield an impure fraction containing both decomposition and the product. After being concentrated *in vacuo*, this residue was subjected to repeated PLC separation (~60 mg crude, five PLC plates) by loading the compound with $CHCl_3$ and eluting with $CHCl_3$/hexanes (70%). Each PLC plate was required to be eluted six times, after which fractions containing the product were carefully removed from surrounding impurities and sonicated in $CHCl_3$ (~50 mL), then filtered through Celite. The Celite pad was rinsed with more $CHCl_3$ (~50 mL). After the evaporation and concentration of the filtrate *in vacuo*, a thick yellow gum was obtained. To the gum was added $CHCl_3$ (1 mL), and the he sample was gently heated using a heat gun under vacuum to obtain the *N,N′*-dibenzyl 1,2-bis(tosylamide) **10** (183 mg, 43%) as a white solid. mp 48−54 °C; TLC (EtOAc/hexanes (20%)) R_f = 0.10; PLC ($CHCl_3$/hexanes (70%), six times) R_f = 0.37; $[\alpha_D^{25}]$ = −35.4 (c = 1.47, CH_2Cl_2); FTIR υ 2959 (w), 2835 (w), 1610 (w), 1598 (m), 1587 (w), 1512 (s), 1496 (m), 1478 (w), 1328 (m), 1304 (w), 1244 (s), 1158 (s), 1089 (m), 1032 (m), 863 (m), 813 (m), 753 (s), 691 (m), 657 (m), 573 (w), 550 (s), 509 (w), 407 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.3 Hz, 4H, H2′, H2″, H6′, and H6″), 7.24 (d, J = 8.2 Hz, 4H, H3′, H3″, H5′, and H5″), 7.18 (d, J = 8.6 Hz, 4H, H2‴, H2⁗, H6‴, and H6⁗), 7.13 (dd, J = 8.6, 7.4 Hz, 4H, H2‴, H2⁗, H6‴, and H6⁗), 6.88 (t, J = 7.4 Hz, 2H, H4‴ and H4⁗), 6.69 (d, J = 8.7 Hz, 4H, H3‴, H3⁗, H5‴, and H5⁗), 6.22 (d, J = 7.9 Hz, 4H, H3‴, H3⁗, H5‴, and H5⁗), 4.72 (d, J = 15.6 Hz, 2H, benzyl CH_2), 4.66−4.59 (m, 2H, H2 and H3), 4.14 (d, J = 15.6 Hz, 2H, benzyl CH_2), 3.83−3.66 (m, 10H, OCH_3, H1 and H4), 2.41 (s, 6H, $TsCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3 (C4‴ and C4⁗), 157.3 (C1‴ and C1⁗), 143.3 (C4′ and C4″), 136.8 (C1′ and C1″), 130.5 (C2‴, C2⁗, C6‴, and C6⁗), 129.4 (C3′, C3″, C5′, and C5″), 129.2 (C2‴, C2⁗, C6‴, and C6⁗), 129.0 (C1‴ and C1⁗), 127.9 (C2′, C2″, C6′, and C6″), 120.9 (C4‴ and C4⁗), 114.0 (C3‴, C3⁗, C5‴, and C5⁗), 113.9 (C3‴, C3⁗, C5‴, and C5⁗), 64.2 (C1 and C4), 60.7 (C2 and C3), 55.1 (OCH_3), 49.5 (benzyl CH_2), 21.5 ($TsCH_3$); MS (ESI+) 843 (13%, $[M + Na]^+$); MS (ESI−) 855 (20%, $[M + Cl]^-$); HRMS (ESI+) calcd for $C_{46}H_{48}N_2NaO_8S_2$ 843.2750, found 843.2734 $[M + Na]^+$.

*N,N′-((2S,3S)-1,4-Diphenoxybutane-2,3-diyl)bis(N-(4-fluorobenzyl)-4-methylbenzenesulfonamide) (**11**) and N-(4-Fluorobenzyl)-4-methyl-N-((2S,3S)-3-((4-methylphenyl)sulfonamido)-1,4-diphenoxybutan-2-yl)benzenesulfonamide (**19**).* Following general procedure 2a, 4-fluorobenzyl chloride (0.070 mL, 0.58 mmol), 1,2-bis-(tosylamide) **2** (52 mg, 0.090 mmol), tetrabutylammonium iodide (9.8 mg, 0.026 mmol), and NaH (22 mg, 0.55 mmol, 60% w/w)[s] were reacted in DMF (1 mL) for 4 h. The reaction was quenched with H_2O (1 mL), and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The obtained oil was subjected to silica gel chromatography (14 g of silica) by wet loading with CH_2Cl_2 and gradient elution with EtOAc/hexanes (2%, 150 mL; 5%, 100 mL; then 20%, 100 mL). Fractions containing the *N,N′*-dibenzyl product **11** by TLC analysis were combined, evaporated *in vacuo*, dissolved in MeCN (10 mL), and washed with hexanes (3 × 100 mL), and the resultant MeCN fraction was evaporated *in vacuo* to yield the *N,N′*-dibenzyl 1,2-bis(tosylamide) **11** (59 mg, 82%) as a clear colorless gum. TLC (EtOAc/hexanes (20%)) R_f = 0.69; $[\alpha_D^{25}]$ = −33.5 (c = 2.8, CH_2Cl_2); FTIR υ 3071 (w), 3041 (w), 2957 (w), 2873 (w), 1601 (m), 1511 (s), 1496 (m), 1478 (w), 1400 (w), 1328 (m), 1305 (w), 1223 (s), 1156 (s), 1090 (m), 1048 (br), 1032 (w), 940 (w), 888 (w), 867 (w), 851 (w), 836 (w), 815 (w), 754 (m), 691 (m), 657 (m), 571 (w), 550 (m), 509 (w), 491 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.71 (d, J = 8.3 Hz, 4H, H2′, H2″, H6′, and H6″), 7.24−7.12 (m, 12H, H3‴, H3⁗, H5″, H5‴, H3′, H3″, H5′, H5″, H2‴, H2⁗, H6‴, and H6⁗), 6.91 (t, J = 7.4 Hz, 2H, H4‴ and H4⁗), 6.81 (t, J = 8.7 Hz, 4H, H3‴, H3⁗, H5‴, and H5⁗), 6.30 (d, J = 7.8 Hz, 4H, H2‴, H2⁗, H6‴, and H6⁗) 4.76−4.63 (m, 4H, C2, C3 and benzyl CH_2), 4.29 (d, J = 15.8 Hz, 2H, benzyl CH_2), 3.96−3.82 (m, 4H, H1 and H4), 2.40 (s, 6H, $TsCH_3$); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 162.4 (d, $^1J_{CF}$ = 247.0 Hz, C4‴ and C4⁗), 157.2 (C1‴ and C1⁗), 143.5 (C4′ and C4″), 136.9 (C1′ and C1″), 132.6 (d, $^4J_{CF}$ = 3.0 Hz, C1‴ and C1⁗), 130.9 (d, $^3J_{CF}$ = 8.1 Hz, C2‴, C2⁗, C6‴, and C6⁗), 129.5 (C3″, C3‴, C5‴, and C5⁗ or C3′, C3″, C5′, and C5″) 129.4 (C3‴, C3⁗, C5‴, and C5⁗ or C3′, C3″, C5′, and C5″), 127.8 (C2′, C2″, C6′, and C6″), 121.3 (C4‴ and C4⁗), 115.3 (d, $^2J_{CF}$ = 21.3 Hz, C3‴, C3⁗, C5‴, and C5⁗), 114.0 (C2‴, C2⁗, C6‴, and C6⁗), 64.8 (C1 and C4), 60.8 (C2 and C3), 49.7 (benzyl CH_2), 21.5 ($TsCH_3$); MS (ESI+) 819 (34%, $[M + Na]^+$); HRMS (ESI+) calcd for $C_{44}H_{43}N_2O_6F_2S_2$ 797.2531, found 797.2529.

After the elution of the *N,N′*-dibenzyl product **11** (see above procedure), fractions containing a small amount of the monobenzyl product **19** were collected and evaporated *in vacuo* to yield the crude *N*-benzyl 1,2-bis(tosylamide) **19** (5.6 mg of crude, 5.1 mg of the product[t], 8% yield,) as a yellow gum that contained a 4-fluorobenzyl chloride impurity. The isolated *N*-benzyl 1,2-bis(tosylamide) **19** was 91% pure by mass and was therefore used in the next step without further purification. TLC (EtOAc/hexanes (20%)) R_f = 0.63; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.73 (d, J = 8.3 Hz, 2H), 7.64 (d, J = 8.3 Hz, 2H), 7.33 (dd, J = 8.4, 5.5 Hz, 1H), 7.25−7.13 (m, 10H), 7.04 (t, J = 8.7 Hz, 1H), 6.93−6.88 (m, 2H), 6.83 (t, J = 8.6 Hz), 6.55−6.51 (m, 2H), 6.45−6.40 (m, 2H), 5.29 (br s, 1H, NH), 4.51−4.38 (m, 2H), 4.21 (d, J = 15.6 Hz, 1H), 4.12−3.92 (m, 3H), 3.80−3.69 (m, 2H), 2.42−2.35 (m, 6H, $TsCH_3$); MS (ESI−) 687 (100%, $[M - H]^-$); HRMS (ESI−) calcd. for $C_{37}H_{36}N_2O_6FS_2$ 687.1999, found 687.1996 $[M - H]^-$.

*N-Benzyl-N-((2S,3S)-3-((N-(4-fluorobenzyl)-4-methylphenyl)-sulfonamido)-1,4-diphenoxybutan-2-yl)-4-methylbenzenesulfonamide (**12**).* Following general procedure 2a, benzyl bromide (0.10 mL, 0.84 mmol), the crude *N*-benzyl 1,2-bis(tosylamide) **19** (89 mg, 0.13 mmol)[u], tetrabutylammonium iodide (18 mg, 0.050 mmol), and NaH (59 mg, 1.5 mmol, 60% w/w) in DMF (2.0 mL) were reacted for 3.5 h. The reaction was quenched with H_2O (1.0 mL), and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was subjected to silica gel chromatography (18 g of silica) by wet loading with CH_2Cl_2 and gradient elution with $CHCl_3$/hexanes (10%, 100 mL; 20%, 200 mL; 30%, 200 mL; then 50%, 200 mL) to furnish 1,2-bis(tosylamide) **12** (77 mg, 76%) as a white solid.[v] mp 55−57 °C; TLC ($CHCl_3$/hexanes (50%)) R_f = 0.40; $[\alpha_D^{25}]$ = −38.3 (c = 0.26, CH_2Cl_2); FTIR υ 3064 (w), 3032 (w), 2952 (w), 2925 (w), 1704 (m), 1509 (w), 1496 (m), 1478 (w), 1455 (w), 1329 (m), 1305 (w), 1292 (w), 1238 (m), 1224 (m), 1156 (s), 1111 (w), 1089 (m), 1044 (w), 1031 (w), 1014 (w), 917 (w), 884 (w), 859 (w), 837 (w), 814 (m), 753 (m), 727 (m), 691 (m), 656 (m), 601 (w), 569 (w), 547 (s), 494 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.73 (dd, J = 12.1, 8.3 Hz, 4H, H2′, H2″, H6′, and H6″), 7.28−7.10 (m, 15H, H3′, H3″, H5′, H5″, H3‴, H3⁗, H5‴, H5⁗, H2⁗, C6⁗, H2⁗, H3⁗, H4⁗, H5⁗, and H6⁗), 6.93−6.87 (m, 2H, H4‴ and H4⁗), 6.84−6.78 (m, 2H, H3⁗ and H5⁗), 6.30−6.22 (m, 4H, H2‴, H2⁗, H6‴, and H6⁗), 4.81−4.63 (m, 4H, 4-fluorobenzyl CH_2, benzyl CH_2, H2, and H3), 4.27 (apr. dd, J = 15.7, 5.1 Hz, 2H, 4-fluorobenzyl CH_2 and benzyl CH_2), 3.91−3.78 (m, 4H, H1 and H4), 2.43−2.39 (m, 6H, $TsCH_3$); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 162.4 (d, $^1J_{CF}$ = 246.8 Hz, C4⁗), 157.2 (C1‴ and C1⁗), 143.4 (C4′ and C4″), 136.89 (C1′ or C1″), 136.85 (C1′ or C1″) 132.6 (C1⁗), 130.9 (d, $^3J_{CF}$ = 8.2 Hz, C2⁗ and C6⁗), 129.5 (C3′ and C5′, or C3″ and C5″, or C3‴ and C5‴, or C3⁗ and C5⁗, or C2⁗, C4⁗, and C6⁗), 129.46 (C3′ and C5′, or C3″ and C5″, or C3‴ and C5‴, or C3⁗ and C5⁗, or C2⁗, C4⁗, and C6⁗), 129.3 (C3′ and C5′, or C3″ and C5″, or C3‴ and C5‴, or C3⁗ and C5⁗, or C2⁗, C4⁗, and C6⁗), 129.24 (C3′ and C5′, or C3″ and C5″, or C3‴ and C5‴, or C3⁗ and C5⁗, or C2⁗, C4⁗, and C6⁗), 129.17 (C3′ and C5′, or C3″ and C5″, or C3‴ and C5‴, or C3⁗ and C5⁗, or C2⁗, C4⁗, and C6⁗), 128.6 (C3⁗ and C5⁗), 127.9 (C2′ and C6′ or C2″ and C6″), 127.8 (C2′ and C6′ or C2″ and C6″), 121.2 (C4‴ or C4⁗), 121.1 (C4‴ or C4⁗), 115.3 (d, $^2J_{CF}$ = 21.3 Hz, C3⁗ and C5⁗), 114.1 (C2‴ and C6‴ or C2⁗ and C6⁗), 114.0 (C2‴ and C6‴ or C2⁗ and C6⁗), 64.6 (C1 or C4), 64.5 (C1 or C4), 61.0 (C2 or C3), 60.7 (C2 or C3), 50.3 (benzyl CH_2 or 4-fluororobenzyl CH_2), 49.6 (benzyl CH_2 or 4-fluororobenzyl CH_2), 21.5 ($TsCH_3$); MS (ESI+) 801 (40%,

https://doi.org/10.1021/acs.joc.1c00359
J. Org. Chem. 2021, 86, 9163−9180

$[M + Na]^+$); HRMS (ESI+) calcd for $C_{44}H_{44}FN_2O_6S_2$ 779.2610, found 779.2625 $[M + H]^+$.

*N,N′-((2S,3S)-1,4-Diphenoxybutane-2,3-diyl)bis(N-ethyl-4-methylbenzenesulfonamide) (**8**).* Following general procedure 2b without tetrabutylammonium iodide, 1,2-bis(tosylamide) **2** (51 mg, 0.088 mmol), iodoethane (0.045 mL, 0.56 mmol), and NaH (13 mg, 0.53 mmol, 60% w/w) were reacted in DMF (1.0 mL). The reaction was quenched with H_2O (10 mL), and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The residue was dissolved in EtOAc (50 mL), washed with H_2O (5 × 10 mL) and brine (10 mL), dried (Na_2SO_4), filtered, and evaporated *in vacuo*. Residual grease was then removed by dissolving the residue with sonication in MeCN (30 mL) and washing with hexanes (3 × 100 mL). The MeCN layer was then filtered and evaporated *in vacuo* to yield *N,N′*-diethyl 1,2-bis(tosylamide) **8** (55 mg, 99%) as a clear colorless gum. $[\alpha_D^{25}]$ = +7.6 (c = 1.2, CH_2Cl_2); FTIR υ 3064 (w), 3031 (w), 2977 (w), 2937 (w), 2878 (w), 1599 (m), 1589 (m), 1497 (m), 1478 (w), 1383 (w), 1363 (w), 1335 (s), 1305 (m), 1291 (w), 1240 (s), 1185 (m), 1160 (s), 1088 (m), 1051 (w), 1020 (w), 1003 (w), 982 (w), 930 (w), 839 (w), 815 (w), 775 (m), 755 (m), 719 (m), 692 (m), 650 (m), 554 (m), 509 (m); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.81 (d, J = 8.3 Hz, 4H, H2′, H6′, H2″, and H6″), 7.29−7.16 (m, 8H, H3′, H5′, H3″, H5″, H3‴, H5‴, H3⁗, and H5⁗), 6.94 (t, J = 7.4 Hz, 2H, H4‴ and H4⁗), 6.65 (dd, J = 8.7, 0.9 Hz, 4H, H2‴, H6‴, H2⁗, and H6⁗), 4.75 (s, 2H, H2 and H3), 4.21−4.08 (m, 4H, H1 and H4), 3.65−3.46 (m, 4H, H1⁗ and H1⁗⁗), 2.40 (s, 6H, $TsCH_3$), 1.11 (t, J = 7.1 Hz, 6H, H2⁗ and H2⁗⁗); ^{13}C NMR ($CDCl_3$, 126 MHz) δ (mixture of rotamers)[w] 157.6 (C1‴ and C1⁗), 143.3 (C4′ and C4″), 138.2 (C1′ and C1″), 129.53 (C3′, C5′, C3″, and C5″ or C3‴, C5‴, C3⁗, and C5⁗), 129.50 (C3′, C5′, C3″, and C5″ or C3‴, C5‴, C3⁗, and C5⁗), 127.8 (C2′, C6, C2″ and C6″), 121.4 (C4‴ and C4⁗), 114.3 (C2‴, C6‴, C2⁗ and C6⁗), 67.1 (C1 and C4), 57.8 (br s, C2 and C3), 41.5 (br s, C1⁗ and C1⁗⁗), 21.5 ($TsCH_3$), 14.7 (C2⁗ and C2⁗⁗); MS (ESI+) 659 (62%, $[M + Na]^+$); HRMS (ESI+) calcd for $C_{34}H_{41}N_2O_6S_2$ 637.2400, found 637.2402 $[M + H]^+$ and calcd for $C_{34}H_{40}N_2NaO_6S_2$ 659.2220, found 659.2223 $[M + Na]^+$.

*N,N′-((2S,3S)-1,4-Diphenoxybutane-2,3-diyl)bis(N,4-dimethylbenzenesulfonamide) (**7**).* Following general procedure 2b without tetrabutylammonium iodide, 1,2-bis(tosylamide) **2** (51 mg, 0.088 mmol), iodomethane (0.03 mL, 0.5 mmol), and NaH (13 mg, 0.32 mmol, 60% w/w) were reacted in DMF (1.0 mL). The reaction was quenched with H_2O (10 mL), and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The solid was then precipitated from boiling CH_2Cl_2/hexanes (2.0 mL of CH_2Cl_2), filtered, washed with hexanes (50 mL), and eluted from the filter paper using CH_2Cl_2. The CH_2Cl_2 filtrate was evaporated *in vacuo* to yield the *N,N′*-dimethyl 1,2-bis(tosylamide) **7** (189 mg, 90%) as a yellow solid. mp 110−111 °C; $[\alpha_D^{25}]$ = +42.4 (c = 1.0, CH_2Cl_2); FTIR υ 3347 (br s), 3030 (w), 2891 (w), 1597 (m), 1587 (m), 1496 (m), 1466 (m), 1449 (m), 1388 (w), 1362 (w), 1334 (s), 1304 (w), 1290 (w), 1240 (s), 1214 (m), 1167 (s), 1148 (s), 1115 (m), 1083 (m), 1034 (m), 1020 (m), 999 (m), 908 (s), 844 (m), 812 (m), 799 (w), 772 (m), 756 (s), 708 (m), 682 (s), 652 (s), 621 (w), 601 (s), 548 (s), 553 (s), 507 (s), 442 (w), 424 (w); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, J = 8.2 Hz, 4H, H2′, H2″, H6′, and H6″), 7.33 (d, J = 8.1 Hz, 4H, H3′, H3″, H5′, and H5″), 7.18 (t, J = 8.0 Hz, 4H, H3‴, H5‴, H3⁗, and H5⁗), 6.91 (t, J = 7.4 Hz, 2H, H4‴ and H4⁗), 6.48 (d, J = 7.9 Hz, 4H, H2‴, H6‴, H2⁗, and H6⁗), 4.63−4.54 (m, 2H, H2 and H3), 4.19 (apr. dd, J = 10.7, 3.4) 2H, $H1_a$ and $H4_a$), 4.09 (dd, J = 10.7, 3.4 Hz, 2H, $H1_b$ and $H4_b$), 2.46 (s, 6H, $TsCH_3$), 2.97 (s, 6H, NCH_3); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 157.6 (C1‴ and C1⁗), 143.5 (C4′ and C4″), 135.7 (C1′ and C1″), 129.6 (C3′, C5′, C3″, and C5″), 129.4 (C3‴, C5‴, C3⁗, and C5⁗), 128.0 (C2′, C6′, C2″, and C6″), 121.3 (C4‴ and C4⁗), 114.3 (C2‴, C6‴, C2⁗, and C6⁗), 66.7 (C1 and C4), 55.6 (C2 and C3), 30.8 (NCH_3), 21.5 ($TsCH_3$); MS (ESI+) 631 (100%, $[M + Na]^+$), 609 (9%, $[M + H]^+$); HRMS (ESI+) calcd for $C_{32}H_{36}N_2O_6NaS_2$ 631.1907, found 631.1909 $[M + Na]^+$.

*N,N′-((3R,4R)-1,6-Diphenylhexane-3,4-diyl)bis(N-ethyl-4-methylbenzenesulfonamide) (**14**).* Following general procedure 2b without tetrabutylammonium iodide and with 9 equiv of the alkyl iodide, 1,2-bis(tosylamide) **3** (50 mg, 0.079 mmol), iodoethane (0.060 mL, 0.075 mmol), and NaH (13 mg, 0.32 mmol, 60% w/w) were reacted in DMF (1.0 mL). The reaction was quenched with H_2O (5.0 mL), and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give an oily residue. The residue was dissolved in EtOAc (30 mL), washed with H_2O (4 × 10 mL) and brine (2 × 10 mL), dried (Na_2SO_4), evaporated *in vacuo*, dissolved in MeCN (30 mL), washed with hexanes (5 × 50 mL), and concentrated *in vacuo* to give the *N,N′*-diethyl 1,2-bis(tosylamide) **14** (46 mg, 84%) as a golden yellow gum. $[\alpha_D^{25}]$ = +23.6 (c = 1.2, CH_2Cl_2); FTIR υ 3085 (w), 3062 (w), 3027 (w), 2938 (w), 2873 (w), 2361 (w), 2335 (w), 1599 (w), 1496 (w), 1454 (w), 1398 (w), 1381 (w), 1336 (s), 1305 (m), 1290 (w), 1154 (s), 1120 (m), 1087 (m), 1019 (w), 1004 (w), 986 (w), 929 (w), 816 (w), 801 (w), 750 (w), 731 (m), 701 (m), 666 (m), 622 (m), 589 (m), 552 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ[x](mixture of rotamers) 7.79 (d, J = 8.3 Hz, 4H, H2′, H6′, H2″, and H6″), 7.31 (d, J = 8.0 Hz, 4H, H3′, H5′, H3″ and H5″), 7.28−7.20 (m, 4H, H3‴ and H5‴ and H3⁗ and H5⁗), 7.20−7.13 (m, 2H, H4‴ and H4⁗), 7.05−6.98 (m, 4H, H2‴ and H6‴ and H2⁗ and H6⁗), 4.09 (t, J = 5.2 Hz, 2H, H3 and H4), 3.35 (q, J = 7.1 Hz, 4H, H1‴ and H1⁗), 2.51−2.32 (m, 10H, $TsCH_3$, H1 and H6), 2.10−1.92 (m, 2H, $H2_a$ and $H5_a$), 1.68 (br s, 2H, $H2_b$ and $H5_b$), 1.24 (t, 6H, H2‴ and H2⁗); ^{13}C NMR ($CDCl_3$, 101 MHz, ^{13}C DEPTQ-135) δ[y](mixture of rotamers) 143.4 (C4′ and C4″), 141.2 (C1‴ and C1⁗), 137.7 (br s, C1′ and C1″), 129.6 (C3′, C5′, C3″ and C5″), 128.5 (C3‴ and C5‴ and C3⁗ and C5⁗ or C2‴ and C6⁗ and C2⁗ and C6‴), 128.2 (C3‴ and C5⁗ and C3⁗ and C5‴ or C2‴ and C6⁗ and C2⁗ and C6‴), 127.6 (C2′, C6′, C2″ and C6″), 126.1 (C4‴ and C4⁗), 62.1 (br, C3 and C4), 41.1 (br, C1‴ and C1⁗), 33.9 (C1 and C6), 32.0 (C2 and C5), 21.5 ($TsCH_3$), 15.8 (C2‴ and C2⁗); MS (ESI+) 655 (100%, $[M - Na]^+$); HRMS (ESI+) calcd for $C_{36}H_{44}N_2NaO_4S_2$ 655.2650, found 655.2640 $[M + Na]^+$.

*(3S,3′S)-4,4′-Ditosyl-3,3′,4,4′-tetrahydro-2H,2′H-3,3′-bibenzo[b][1,4]oxazine (**16**).*[11] To synthesize the known **16**, a modified procedure was developed. A screw-cap pressure-sealed vial containing a magnetic stir bar, ring opened intermediate **17** (0.905 g, 1.09 mmol), CsOAc (2.782 g, 14.49 mmol), and anhydrous CuI (0.824 g, 4.33 mmol) was purged with a stream of N_2 for 5 min, and DMSO[z] (7.2 mL) added under a stream of N_2. The vial was sealed and heated at 110 °C for 3 d and then left to cool to rt. The vial was opened to the atmosphere, the reaction was quenched with saturated aq. NH_4Cl solution (50 mL), and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic phases were dried (Na_2SO_4), filtered through a pad of Celite, and concentrated *in vacuo* to give the crude product, which was recrystallized from CH_2Cl_2/hexanes (50%, ∼ 6 mL) by slow evaporation over 3 d at −20 °C. After filtration, drying in air, and further drying *in vacuo*, the product **16** (392 mg, 62%) was isolated as a white solid.

*4-Methyl-N-((S)-2-phenoxy-1-((S)-4-tosyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)ethyl)benzenesulfonamide (**20**).* Following the above procedure for compound **16** using the ring opened product **17** (0.998 g, 1.20 mmol), anhydrous CuI (0.914 g, 4.80 mmol), CsOAc (3.36 g, 17.50 mmol), and wet DMSO (7.2 mL) produced a mixture of monocyclized and dicyclized products by crude ^{1}H NMR. After the same aqueous extraction as the above procedure, these products could be separated with extreme difficulty by silica gel chromatography (17 g of silica) by wet loading with CH_2Cl_2 and elution with CH_2Cl_2 (100%). Careful TLC analysis with all TLC plates side-by-side allowed the visualization of both products due to their close R_f values. The dicyclic product **16** (197 mg, 34%) was observed to elute first, with spectra identical to those reported. TLC (CH_2Cl_2 (100%), two times) R_f = 0.94. The monocyclic product **20**[a1] (65 mg, 11%) was a white gum and eluted immediately after the dicyclic product **16**. The product **20** contained EtOAc and acetone that could not be dried further from the gum. TLC (CH_2Cl_2 (100%), two times) R_f = 0.89; $[\alpha_D^{25}]$ = −89.0 (c = 1.0, CH_2Cl_2); FTIR υ 3313 (br s), 364 (w), 3040

https://doi.org/10.1021/acs.joc.1c00359
J. Org. Chem. 2021, 86, 9163−9180

(w), 2960 (w), 2923 (w), 2888 (w), 1598 (m), 1490 (s), 1454 (w), 1401 (w), 1338 (m), 1305 (w), 1291 (w), 1239 (m), 1186 (w), 1163 (s), 1124 (w), 1089 (m), 1068 (w), 1019 (w), 1009 (w), 985 (w), 964 (w), 909 (m), 890 (m), 862 (w), 813 (m), 755 (m), 729 (m), 707 (m), 691 (m), 663 (m), 614 (w) 571 (m), 563 (m), 546 (m), 510 (w); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, J = 8.3 Hz, 2H, H2′ and H6′ or H2″ and H6″), 7.42 (d, J = 8.2 Hz, 2H, H2′ and H6′ or H2″ and H6″), 7.33−7.15 (m, 7H, H3′, H5′, H3″, H5″, H3‴, H5‴, and H6‴), 6.99 (t, J = 7.3 Hz, 2H, H4‴ and H7‴), 6.88 (d, J = 8.0 Hz, 2H, H2‴ and H5 or H6‴, or H7‴, or H8‴), 6.79−6.64 (m, 2H, H5‴, H6‴, H7‴, or H8‴), 5.38 (d, J = 6.3 Hz, 1H, NH), 4.40 (d, J = 9.6 Hz, 1H, H3‴), 4.28 (dd, J = 10.3, 2.8 Hz, 1H, $H2_a$), 4.11 (dd, J = 10.2, 2.4 Hz, 1H, $H2_b$), 4.02 (d, J = 12.1 Hz, 1H, $H2_a$‴), 3.43−3.35 (m, 1H, H1), 2.92 (dd, J = 12.1, 2.6 Hz, 1H, $H2_b$‴), 2.44 (s, 3H, $TsCH_3$), 2.36 (s, 3H, $TsCH_3$); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.0 (C1‴), 145.4 (C8a‴), 144.8 (C4′ or C4″), 143.3 (C4′ or C4″), 136.5 (C1′ and C1″ or C4a‴), 134.3 (C1′ and C1″ or C4a‴), 130.1 (C3′ and C5′, or C3″ and C5″, or C2‴ and C6‴), 129.8 (C3′ and C5′, or C3″ and C5″, or C2‴ and C6‴), 129.6 (C3′ and C5′, or C3″ and C5″, or C2‴ and C6‴), 127.3 (C2′ and C6′ or C2″ and C6″), 127.1 (C2′ and C6′ or C2″ and C6″), 126.1 (C7‴), 125.2 (C3‴ and C5‴), 121.7 (C4‴), 121.33 (C5‴, C6‴ or C8‴), 121.26 (C5‴, C6‴ or C8‴), 117.2 (C5‴, C6‴ or C8‴), 114.7 (C2‴ and C6‴), 67.8 (C2), 61.7 (C2‴), 53.8 (C3‴), 52.0 (C1), 21.6 ($TsCH_3$); MS (ESI +) 579 (53%, $[M + H]^+$); HRMS (ESI+) calcd for $C_{30}H_{30}N_2NaO_6S_2$ 601.1438, found 601.1438 $[M + Na]^+$.

*tert-Butyl ((S)-2-Phenoxy-1-((S)-4-tosyl-3,4-dihydro-2H-benzo-[b][1,4]oxazin-3-yl)ethyl)(tosyl)carbamate (**21**).* To a solution of 1,2-bis(tosylamide) **20**[b1] (36 mg, 0.62 mmol), DMAP (6.9 mg, 0.56 mmol), and NEt_3 (0.04 mL, 0.3 mmol) in CH_2Cl_2 (1 mL) was added Boc_2O (0.065 mL, 0.28 mmol, gently heated) dropwise, and the solution was stirred for 20 h. The reaction was mixture diluted with EtOAc (30 mL) and washed with $NaHCO_3$ (2 × 10 mL), brine (10 mL), NH_4Cl (2 × 10 mL), and brine again (10 mL). The organic phase was dried (Na_2SO_4), filtered, and evaporated *in vacuo*, redissolved in EtOAc, washed further with HCl (3 × 5 mL, 0.1 M), dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The residue was dissolved in MeCN (20 mL) and washed with hexanes (3 × 100 mL) to remove residual grease. The MeCN layer was dried (Na_2SO_4), filtered, and evaporated *in vacuo* to yield the *N*-Boc-1,2-bis-(tosylamide) **21**[c1] (42 mg, 99%) as a gum, which solidified to a white solid after repeated evaporation from $CHCl_3$ (3 × 1 mL) under high vacuum. mp 159−161 °C; $[\alpha_D^{25}]$ = +51.0 (c = 0.71, CH_2Cl_2); FTIR υ 2985 (w), 2926 (w), 2898 (w), 1725 (m), 1598 (w), 1587 (w), 1490 (m), 1477 (m), 1456 (w), 1395 (s), 1357 (w), 1328 (w), 1291 (m), 1256 (m), 1237 (s), 1169 (s), 1156 (m), 1090 (w), 1061 (w), 1044(w), 1035 (w), 1022 (w), 995 (m), 928 (w), 905 (w), 883 (w), 846 (w), 813 (m), 799 (w), 775 (w), 752 (s), 707 (w), 688 (m), 670 (m), 653 (m), 604 (m), 592 (w), 574 (s), 559 (w), 544 (s); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.06 (d, J = 8.1 Hz, 1H, H5‴), 7.93 (d, J = 8.2 Hz, 2H, H1′ and H6′ or H1″ and H6″), 7.46 (d, J = 8.2 Hz, 2H, H1′ and H6′ or H1″ and H6″), 7.31−7.18 (m, 6H, H3′, H5′, H3″, H5″, H3‴, and H5‴), 7.15−7.10 (m, 1H, H7‴), 7.02 (t, J = 7.5 Hz, 1H, H6‴), 6.94 (t, J = 7.3 Hz, 1H, H4‴), 6.89−6.82 (m, 3H, H1‴, H6‴ and H8‴), 5.13 (d, J = 9.8 Hz, 1H, H3‴), 4.93−4.84 (m, 1H, H1), 4.52 (t, J = 8.5 Hz, 1H, $H2_a$), 4.28 (dd, J = 9.0, 5.9 Hz, 1H, $H2_b$), 4.02 (d, J = 12.0 Hz, 1H, H2a‴), 3.11 (d, J = 11.3 Hz, $H2_b$‴), 2.43 (s, 3H, $TsCH_3$), 2.38 (s, 3H, $TsCH_3$), 1.36 (s, 9H, O*t*Bu); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.2 (C1‴), 150.8 (COOR), 146.3 (C8a‴), 144.3 (C4′ or C4″), 143.7 (C4′ or C4″), 137.9 (C1′ or C1″), 135.1 (C1′ or C1″), 129.9 (C3′ and C5′ or C3″ and C5″), 129.4 (C3′ and C5′, or C3″ and C5″, or C3‴ and C5‴), 128.9 (C3′ and C5′, or C3″ and C5″, or C3‴ and C5‴), 128.5 (C1′ and C6′ or C1″ and C6″), 127.4 (C1′ and C6′ or C1″ and C6″), 127.1 (C5‴), 126.7 (C7‴), 121.8 (C4a‴), 121.6 (C6‴), 121.3 (C4‴), 117.3 (C8‴), 114.8 (C1‴ and C6‴), 85.2 (-$\underline{C}(CH_3)_3$), 65.9 (C2), 61.9 (C2‴), 55.1 (C1), 52.1 (C3‴), 28.0 (O*t*Bu), 21.6 (2 × $TsCH_3$); MS (ESI+) 701 (100%, $[M + Na]^+$); HRMS (ESI+) calcd for $C_{35}H_{38}N_2NaO_8S_2$ 701.1967, found 701.1981 $[M + Na]^+$.

X-ray Crystal Growth. The product (∼30 mg) was dissolved in CH_2Cl_2/hexanes (50%, 50 mL) and allowed to evaporate to dryness to yield clear colorless cube crystals.

1-Propoxyethan-1-ol. Following general procedure 5, Li metal (17 mg, 2.4 mmol) was added to a solution of 1,2-bis(tosylamide) **2** (44 mg, 0.076 mmol) in ethylenediamine (0.17 mL, 2.5 mmol) and propylamine (0.5 mL). The solution turned dark blue and was stirred for a further 20 min, then quenched over ice. The reaction mixture was diluted with H_2O (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried (Na_2SO_4) and evaporated *in vacuo* to give 1-propoxyethan-1-ol (7.3 mg crude) as a crude gum that contained some decomposition, and further purification was not attempted.

Reaction Notes. Attempts at reducing the quantity of Li/ethylenediamine in the solution resulted in an incomplete reaction, with the major product still being 1-propoxyethan-1-ol by ^{1}H NMR analysis. Therefore, no further attempts were made to obtain the deprotected diamine.

*(2S,3S)-1,4-Diphenoxy-2,3-di(N-tert-butoxycarbonylamino)-butane (**amine-13**).* Following general procedure 1, impure **13** (449 mg, 0.574 mmol) and Mg powder (698 mg, 28.7 mmol) were sonicated in MeOH (14.0 mL). After the completion of the reaction, the suspension was poured over EtOAc (100 mL) and filtered through Celite. The filtrate was washed with H_2O (20 mL), and the aqueous phase was separated and back-extracted with EtOAc (3 × 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in MeCN (20 mL), washed with hexanes (3 × 100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to an oil. Re-evaporation from diethyl ether (2 × 10 mL), followed by drying on high vacuum (∼1 h), afforded the deprotected **amine-13** (245 mg, 90%) as a white solid. The product was found to be unstable to silica gel chromatography and mildly acidic workups. mp 84−86 °C; $[\alpha_D^{25}]$ = −66.7 (c = 0.28, CH_2Cl_2); FTIR υ 3369 (br s), 2977 (w), 2930 (w), 1684 (s), 1599 (w), 1514 (m), 1498 (m), 1365 (w), 1289 (s), 1237 (s), 751 (s), 690 (s), 559 (br), 507 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.19 (m, 4H, H3‴, H5‴, H3‴ and H5‴), 6.96 (t, J = 7.3 Hz, 2H, H4‴ and H4‴), 6.68 (d, J = 7.7 Hz, 4H, H2‴, H6‴, H2‴, and H6‴), 5.41 (br s, 2H, NH), 4.35 (br s, 2H, H2 and H3), 4.13−4.02 (m, 2H, H1 and H4), 1.45 (s, 18H, O*t*Bu); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5 (C1‴ and C1‴), 156.5 (COOR), 129.7 (C3‴, C5‴, C3‴, and C5‴), 121.4 (H4‴ and H4‴), 114.5 (H2‴, H6‴, H2‴, and H6‴), 79.9 (C2′ and C2″), 67.5 (C1 and C4), 51.4 (C2 and C3), 28.5 (O*t*Bu); MS (ESI+) 473 (48%, $[M + H]^+$), 495 (11%, $[M + Na]^+$); HRMS (ESI+) calcd for $C_{26}H_{36}N_2O_6Na$ 495.2478, found 495.2471 $[M + Na]^+$.

Attempted N-Boc Deprotection. All subsequent *N*-Boc deprotections produced a mixture of products with the use of TFA, HCl and thermal conditions. These deprotections gave broad ^{1}H NMR resonances that were unable to be further purified, indicating likely decomposition. HRMS ESI was employed to examine the possible products, which were assigned to a mixture of the following products: mono-Boc deprotection, *N*-*t*-butylation, urea formation, and subsequent combinations of these. Previously, we have been able to perform this deprotection with concentrated HCl under microwave conditions in a joint *N*-Boc deprotection and urea cleavage reaction; this is the suggested method to acces primary amines from the *N*,*N*′-di-Boc-protected **amine-13** above.[28]

*(2S,3S)-N^2,N^3-Dibenzyl-1,4-diphenoxybutane-2,3-diamine (**amine-9**).* Following general procedure 1, *N*,*N*′-dibenzyl 1,2-bis(tosylamide) **9** (234 mg, 0.308 mmol) and Mg powder (379 mg, 15.6 mmol) were sonicated in MeOH (7.5 mL). The reaction mixture was poured over EtOAc (100 mL) and filtered through Celite. The filtrate was washed with H_2O (20 mL) and back-extracted with EtOAc (3 × 50 mL). The combined organic fractions were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the deprotected **amine-9** (126 mg, 90%) as a yellow gum. The product was stable for more than 3 months in a desiccator, although it was observed to decompose during acidic workups and completely decompose during silica gel chromatography. $[\alpha_D^{25}]$ = −27.3 (c = 1.3, CH_2Cl_2); FTIR υ

https://doi.org/10.1021/acs.joc.1c00359
J. Org. Chem. 2021, 86, 9163−9180

3331 (br s), 3062 (w), 3028 (w), 2926 (br s), 2872 (br s), 1599 (m), 1587 (w), 1496 (s), 1454 (w), 1300 (w), 1242 (s), 1172 (w), 1153 (w), 1079 (w), 1034 (w), 882 (w), 817 (w), 753 (s), 692 (s), 510 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.19 (m, 14H, H3′, H5′, H3″, H5″, H2‴, H3‴, H4‴, H5‴, H6‴, H2⁗, H3⁗, H4⁗, H5⁗, and H6⁗), 6.94 (t, J = 7.3 Hz, 2H, H4′ and H4″), 6.87 (d, J = 8.0 Hz, 4H, H2′, H2″, H6′, and H6″), 4.18 (dd, J = 9.7, 3.8 Hz, 2H, $H1_a$ and $H4_a$), 4.04 (dd, J = 9.7, 3.9 Hz, 2H, $H1_b$ and $H4_b$), 3.93 (d, J = 13.1 Hz, 2H, benzyl CH_2), 3.80 (d, J = 13.2 Hz, 2H, benzyl CH_2), 3.20 (s, 2H, H2 and H3), 2.06 (br, 2H, NH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.6 (C1′ and C1″), 140.2 (C1‴ and C1⁗), 129.4 (C3′, C3″, C5′ and C5″), 128.4 (benzyl Ar−C), 128.2 (benzyl Ar−C), 127.0 (benzyl Ar−C), 120.9 (C4′ and C4″), 114.5 (C2′, C2″, C6′, and C6″), 66.7 (C1 and C4), 57.3 (C2 and C3), 51.9 (benzyl CH_2); MS (ESI+) 453 (100%, $[M + H]^+$); HRMS (ESI+) calcd for $C_{30}H_{33}N_2O_2$ 453.2542, found 453.2553 $[M + H]^+$.

(2S,3S)-N²,N³-Bis(4-methoxybenzyl)-1,4-diphenoxybutane-2,3-diamine (***amine-10***). Following general procedure 1, 1,2-bis-(tosylamide) **10** (183 mg, 0.222 mmol) and Mg powder (273 mg, 11.2 mmol) were sonicated in MeOH (5.4 mL). After the completion of the reaction, the suspension was poured over EtOAc (100 mL) and filtered through Celite. The filtrate was washed with H_2O (20 mL), and the aqueous phase was separated and back-extracted with EtOAc (3 × 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to give **amine-10** (108 mg, 94%) as a white gum. The product was stable to be storaged in a desiccator for >3 months, although it decomposed during mildly acidic workups. Complete decomposition was observed during attempts to deprotect the 4-methoxybenzyl with trifluoroacetic acid and during purification with silica gel chromatography. $[\alpha_D^{25}]$ = −52.2 (c = 0.72, CH_2Cl_2); FTIR υ 3335 (br s), 3061 (w), 3030 (w), 2997 (w), 2931 (w), 2834 (w), 1611 (w), 1599 (m), 1586 (w), 1511 (m), 1463 (m), 1301 (w), 1243 (s), 1173 (w), 1107 (w), 1079 (w), 1035 (m), 883 (w), 817 (br s), 754 (m), 692 (m), 511 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.29−7.24 (m, 4H, H3′, H3″, H5′, and H5″), 7.23−7.19 (m, 4H, H1‴, H1⁗, H6‴, and H6⁗), 6.97−6.92 (m, 2H, H4′ and H4″), 6.88−6.84 (m, 4H, H2′, H2″, H6′, and H6″), 6.83−6.79 (m, 4H, H3‴, H3⁗, H5‴, and H5⁗) 4.19−4.11 (m, 2H, $H1_a$ and $H4_a$), 4.05−3.99 (m, 2H, $H1_b$ and $H4_b$), 3.86 (apr. d, J = 12.8 Hz, 2H, benzyl CH_2), 3.77 (s, 6H, OCH_3), 3.73 (apr. d, J = 12.9 Hz, 2H, benzyl CH_2), 321−3.13 (m, 2H, H2 and H3), 1.95 (br s, 2H, NH); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.7 (C1′ and C1″ or C4″ and C4‴), 158.6 (C1′ and C1″ or C4″ and C4‴), 132.6 (C1‴ and C1⁗), 129.4 (C3′, C3″, C5′, and C5″ or C1‴, C1⁗, C6‴, and C6⁗), 129.3 (C3′, C3″, C5′, and C5″ or C1‴, C1⁗, C6‴, and C6⁗), 120.8 (C4′ and C4″), 114.6 (C2′, C2″, C6′, and C6″), 113.8 (C3‴, C3⁗, C5‴, and C5⁗), 67.1 (C1 and C4), 57.3 (C2 and C3), 55.2 (OCH_3), 51.5 (benzyl CH_2); MS (ESI+) 513 (100%, $[M + H]^+$); HRMS (ESI+) calcd for $C_{32}H_{37}N_2O_4$ 513.2753, found 513.2750 $[M + H]^+$.

(2S,3S)-N²,N³-Bis(4-fluorobenzyl)-1,4-diphenoxybutane-2,3-diamine (***amine-11***). Following general procedure 1, 1,2-bis-(tosylamide) **11** (71 mg, 0.089 mmol) and Mg powder (111 mg, 4.58 mmol) were sonicated in MeOH (2.15 mL). After the completion of the reaction, the suspension was poured over EtOAc (100 mL) and filtered with Celite. The filtrate was washed with H_2O (20 mL), and the aqueous phase separated and back-extracted with EtOAc (3 × 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to give **amine-11** (33 mg, 76%) as a white gum, which upon standing for 1 h turned to a white solid.[d1] The product was able to be stored in a desiccator for more than 3 months. Complete decomposition was observed during purification with silica gel chromatography, and partial decomposition observed only when a high concentration of the hydrochloride salt was neutralized in acid or base extractions (see the section below for details). The compound was found to be stable to neutral alumina but was not able to be purified by this method, and insolubility in most solvents suitable for reverse phase (C18) chromatography made this technique unusable. mp 42−44 °C; $[\alpha_D^{25}]$ = −33.4 (c = 0.52, CH_2Cl_2); FTIR υ 3281 (br s), 3065 (w), 3040 (w), 2926 (br s), 2850 (w), 2821 (w), 1600 (s), 1586 (w), 1510 (s), 1496 (s), 1417 (w), 1302 (w), 1243 (s), 1221 (s), 1173 (w), 1155(w), 1095 (w), 1079 (w), 1036 (w), 1016 (w), 834 (w), 825 (br), 754 (m), 692 (m), 510 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.32−7.22 (m, 8H, H3′, H3″, H5′, H5″, H3‴, H3⁗, H5‴, and H5⁗), 6.99−6.91 (m, 6H, H4′, H4″, H2‴, H2⁗, H6‴, and H6⁗), 6.89−6.82 (m, 4H, H2′, H2″, H6′, and H6″), 4.15 (dd, J = 9.5, 4.4 Hz, 2H, $H1_a$ and $H4_a$), 4.03 (dd, J = 9.6, 4.4 Hz, 2H, $H1_b$ and $H4_b$), 3.89 (d, J = 13.1 Hz, 2H, benzyl CH_2), 3.76 (d, J = 13.2 Hz, 2H, benzyl CH_2), 3.22−3.11 (m, 2H, H2 and H3), 2.04 (br s, 2H, NH); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 161.93 (d, $^1J_{CF}$ = 244.6 Hz, C1‴ and C1⁗), 158.6 (C1′ and C1″), 136.08 (d, $^4J_{CF}$ = 2.8 Hz, C4‴ and C4⁗), 129.69 (d, $^3J_{CF}$ = 8.1 Hz, C2‴, C2⁗, C6‴, and C6⁗), 129.5 (C3′, C3″, C5′ and C5″), 121.0 (C4′ and C4″), 115.15 (d, $^2J_{CF}$ = 21.3 Hz, C3‴, C3⁗, C5‴, and C5⁗), 114.5 (C2′, C2″, C6′ and C6″), 67.0 (C1 and C4), 57.3 (C3 and C4), 51.3 (benzyl CH_2); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −115.80 (s); MS (ESI+) 489 (100%, $[M + H]^+$); HRMS (ESI+) calcd for $C_{30}H_{31}F_2N_2O_2$ 489.2354 found 489.2362 $[M + H]^+$.

(2S,3S)-N²-Benzyl-N³-(4-fluorobenzyl)-1,4-diphenoxybutane-2,3-diamine (***amine-12***). Following general procedure 1, 1,2-bis-(tosylamide) **12** (76.7 mg, 0.0985 mmol) and Mg powder (124 mg, 5.10 mmol) were sonicated in MeOH (2.5 mL). After the completion of the reaction, the suspension was poured over EtOAc (100 mL) and filtered through Celite. The filtrate was washed with H_2O (20 mL), and the aqueous phase separated and back-extracted with EtOAc (3 × 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to afford **amine-12** (47 mg, 98%) as a white gum. $[\alpha_D^{25}]$ = +126.6 (c = 1.9, CH_2Cl_2); FTIR υ 3063 (w), 3030 (w), 2926 (m), 2871 (w), 2855 (w), 1599 (m), 1587 (w), 1508 (w), 1496 (s), 1463 (w), 1465 (w), 1242 (s), 1222 (w), 1172 (w), 1154 (w), 1079 (w), 1035 (m), 822 (br s), 753 (s), 692 (m), 509 (w); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.33−7.22 (m, 11H, H3′, H3″, H5′, H5″, H2‴, H6‴, H2⁗, H3⁗, H4⁗, H5⁗, and H6⁗), 6.99−6.92 (m, 4H, H4′, H4″, H3‴, and H5‴), 6.89−6.844 (m, 4H, H2′, H2″, H6′, and H6″), 4.20−4.13 (m, 2H, $H1_a$ and $H4_a$), 4.07−4.00 (m, 2H, $H1_b$ and $H4_b$), 3.96−3.87 (m, 2H, 4-F-PhC$\underline{H}_2$ and PhC$\underline{H}_2$), 3.83−3.73 (m, 2H, 4-F-PhC$\underline{H}_2$ and PhC$\underline{H}_2$), 3.22−3.14 (m, 2H, H2 and H3) 2.11 (br, 2H, NH); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 161.9 (d, $^1J_{CF}$ = 244.7 Hz, C4⁗), 158.6 (C1′ and C1″), 140.3 (C1‴), 136.0 (d, $^4J_{CF}$ = 2.7 Hz, C1‴), 129.7 (d, $^3J_{CF}$ = 8.1 Hz, C2‴ and C6⁗), 129.5 (C3′, C3″, C5′ and C5″), 128.4 (benzyl Ar−C), 128.1 (benzyl Ar−C), 127.0 (benzyl Ar−C), 120.9 (C4′ and C4″), 115.1 (d, $^2J_{CF}$ = 21.2 Hz, C3‴ and C5⁗), 114.4 (C2′, C2″, C6′ and C6″), 66.9 (C1 or C4), 66.6 (C1 or C4), 57.4 (C2 or C3), 57.2 (C2 or C3), 52.0 (4-F-PhC$\underline{H}_2$ or PhC$\underline{H}_2$), 51.2 (4-F-PhC$\underline{H}_2$ or PhC$\underline{H}_2$); MS (ESI+) 471 (100%, $[M + H]^+$); HRMS (ESI+) calcd for $C_{30}H_{32}FN_2O_2$ 471.2448, found 471.2449 $[M + H]^+$.

(2S,3S)-N²,N³-Diethyl-1,4-diphenoxybutane-2,3-diamine (***amine-8***). Following general procedure 1, 1,2-bis(tosylamide) **8** (27 mg, 0.042 mmol) and Mg powder (61 mg, 2.5 mmol) were sonicated in MeOH (1.2 mL). After the completion of the reaction, the suspension was poured over EtOAc (50 mL) and filtered through Celite. The filtrate was washed with H_2O (10 mL), and the aqueous phase separated and back-extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to give **amine-8** (12 mg, 80%) as a clear gum. The compound was found to decompose during acidic workups.[e1] $[\alpha_D^{25}]$ = +7.6 (c = 1.2, CH_2Cl_2); FTIR υ 3327 (br s), 3061 (w), 3039 (w), 2964 (m), 2922 (m), 2870 (w), 2850 (w), 1775 (w), 1599 (s), 587 (m), 1516 (s), 1516 (s), 1464 (m), 1382 (w), 1344 (w), 1300 (w), 1242 (s), 1172 (w), 1153 (w), 1123 (w), 1079 (w), 1035 (m), 947 (w), 881 (w), 816 (w), 753 (s), 691 (m), 509 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.31−7.23 (m, 4H, ArH), 6.99−6.92 (m, 6H, ArH), 4.16 (dd, J = 9.6, 4.0 Hz, 2H, $H1_a$ and $H4_a$), 4.02 (dd, J = 9.6, 4.0 Hz, 2H, $H1_b$ and $H4_b$), 3.11 (s, 4H, H2 and H3), 2.91−2.78 (m, 2H, $H1_a$‴ and $H1_a$⁗), 2.74−2.62 (m, $H1_b$‴ and $H1_b$⁗), 2.07 (br, 2H, NH), 1.13 (t, J = 7.1 Hz, 6H, H2‴ and H2⁗); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 158.8 (C1′ and C1″), 129.5 (ArC), 120.9 (ArC), 114.6 (ArC), 66.8 (C1 and C4), 58.1 (C2 and C3), 42.3 (C1‴ and C1⁗), 15.6 (C2‴ and C2⁗); MS (ESI+) 329 (100%, $[M + H]^+$); HRMS

https://doi.org/10.1021/acs.joc.1c00359
J. Org. Chem. 2021, 86, 9163−9180

(ESI+) calcd for $C_{20}H_{27}N_2NaO_2$ 351.2048, found 351.2041 $[M + H]^+$.

(2S,3S)-1,4-Bis(hexyloxy)butane-2,3-diamine (***amine-6***). Following general procedure 5, Li metal (17.1 mg, 2.46 mmol) was added portion-wise to a solution of 1,2-bis(tosylamide) **6** (50.0 mg, 0.08375 mmol) in ethylenediamine (0.17 mL, 2.55 mmol) and *n*-propylamine (0.5 mL). The dark blue solution was poured over crushed ice (caution! gas evolution) and allowed to melt, then diethyl ether (20 mL) added to the solution. The diethyl ether was washed with water (2 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was subjected to neutral aluminum oxide chromatography (16 g of alumina) by dry loading the product (1 g of alumina) using $CHCl_3$ and eluting with acetone/hexanes (3%, 100 mL; 5%, 150 mL; and 10%, 200 mL). The product was unable to be visualized by TLC analysis through UV light or with stains ($KMnO_4$, CAM, ninhydrin, and iodine/silica gel). Therefore, all fractions from the column chromatography were evaporated separately with compressed air over 3 d. The first fractions contained an unknown oil (δ 1.26 by ^{1}H NMR), and later fractions contained the product as a clear oil mixture (~20 mL after acetone/hexanes (5%) was used). The product was dissolved in $CHCl_3$, concentrated *in vacuo*, redissolved and evaporated from $CHCl_3$ (2 × 50 mL), and dried under high vacuum (48 h). $CDCl_3$ was added (2 × 1 mL) to aid in the evaporation of acetone. This gave **amine-6** (7.3 mg, 30% crude) as a clear yellow gum that still contained trace amounts of acetone and silicon grease and could not be further purified. $[\alpha_D^{25}]$ = +6.9 (c = 0.35, CH_2Cl_2); FTIR υ 3300 (br s), 2958 (s), 2928 (s), 2855 (s), 1744 (w), 1668 (w), 1466 (m), 1378 (w), 1262 (w), 111 (s), 799 (w); ^{1}H NMR ($CDCl_3$, 400 MHz) (mixture of rotamers) δ 3.61−3.31 (m, 6H, H1, H2, H3 and H4), 2.24 (br s, 4H, NH_2), 1.70−1.47 (m, 4H, H1′ and H1″), 1.45−1.16 (m, 16H, H2′, H2″, H3′, H3′′, H4′, H4′′, H5′, and H5′′), 0.98−0.76 (m, 6H, H6′ and H6″); ^{13}C NMR ($CDCl_3$, 101 MHz, ^{13}C DEPTQ-135) (mixture of rotamers)[f1] δ 71.6 (C1 and C4), 71.5 (C1′ and C1″), 31.7 (C2 and C2″ or C4′ and C4″), 29.7/29.6/29.5 (C4′ and C4″ or C2 and C2″), 25.0/25.8 (C3′ and C3″), 22.6 (C5′ and C5″), 14.0 (C6′ and C6″); MS (ESI+) 289 (87%, $[M + H]^+$); HRMS (ESI+) calcd for $C_{16}H_{37}N_2O_2$ 289.2855, found 289.2861 $[M + H]^+$.

(3R,4R)-N^3,N^4-Diethyl-1,6-diphenylhexane-3,4-diamine (***amine-14***). Following general procedure 1, 1,2-bis(tosylamide) **14** (46 mg, 0.073 mmol) and Mg powder (87 mg, 3.6 mmol) were sonicated in MeOH (1.8 mL). After the completion of the reaction, the suspension was poured over EtOAc (25 mL) and filtered through Celite. The filtrate was washed with H_2O (10 mL), and the aqueous phase separated and back-extracted with H_2O (2 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*, and the residue was dissolved in MeCN (~50 mL) assisted by sonication and heat due to its low solubility. The MeCN solution was washed with hexanes (3 × 50 mL) and concentrated *in vacuo* to give **amine-14** (19 mg crude, 81% crude) as a white gum that contained an unknown impurity. $[\alpha_D^{25}]$ = −6.75 (c = 0.62, CH_2Cl_2); FTIR υ 3266 (br s), 3085 (w), 3061 (w), 3026 (w), 2963 (m), 2930 (m), 2862 (br), 1770 (w), 1725 (w), 1688 (w), 1602 (m), 1496 (s), 1454 (w), 1380 (w), 1335 (w), 1287 (s), 1261 (w), 1201 (w), 1155 (br s), 1088 (s), 863 (s), 799 (s), 720 (s), 700 (w); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39−7.13 (m, 10 H, ArH), 3.00−2.60 (m, 8H, alkyl H), 2.12−1.90 (m, 4H, alkyl H), 1.26−1.12 (m, 6H, H1′ and H1″); ^{13}C NMR ($CDCl_3$, 101 MHz,) δ 140.5 (C4‴ and C4⁗), 128.7 (ArC), 128.4 (ArC), 126.5 (ArC), 58.6 (C3 and C4), 41.1 (alkyl CH_2), 32.2 (alkyl CH_2), 31.2 (alkyl CH_2), 13.8 (C1′ and C1″); MS (ESI+) 325 (100%, $[M + H]^+$); HRMS (ESI+) calcd for $C_{22}H_{33}N_2$ 325.2644, found 325.2646 $[M + H]^+$.

(3S,3′S)-3,3′,4,4′-Tetrahydro-2H,2′H-3,3′-bibenzo[b][1,4]oxazine (***amine-16***). General procedure 1 was adapted to the following method:[g1] to a flask containing finely powdered 1,2-bis(tosylamide) **16**[11] (155 mg, 0.268 mmol) waere added Mg powder (649.1 mg, 26.71 mmol) and THF/MeOH (25%, 17.3 mL). The flask was sonicated with vigorous shaking and rotated by hand every 30 s until the full dissolution of the white solid was observed. Then, sonication was continued for a total of 45 min. The reaction mixture was poured into EtOAc (100 mL) with vigorous shaking, then water (10 mL) was addedwith vigorous shaking. The mixture was filtered through Celite, the layers were separated, and the aqueous layer was back-extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4),[h1] filtered, and concentrated *in vacuo*. The residue was dissolved in MeCN (20 mL) and washed with hexanes (3 × 100 mL), and the MeCN layer was dried (Na_2SO_4) and concentrated *in vacuo* to give the deprotected **amine-16** (56 mg, 78%) as a yellow gum. $[\alpha_D^{25}]$ = −227.5 (c = 0.10, CH_2Cl_2); FTIR υ 3399 (m), 2881 (w), 1608 (m), 1500 (s), 1275 (m), 1207 (m), 1112 (w), 1044 (w), 743 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.84−6.75 (m, 4H, H6, H6′, H8 and H8′), 6.70−6.60 (m, 4H, H5, H5′, H7 and H7′), 4.26−4.11 (m, 4H, $H2_a$, $H2_a'$, $H2_b$, and $H2_b'$), 3.90 (br s, 2H, NH), 3.51 (s, 2H, H3 and H3′); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 144.0 (C8a and C8a′), 132.5 (C4a and C4a′), 122.0 (C6 and C6′), 119.1 (C7 and C7′), 117.0 (C8 and C8′) 116.1 (C5 and C5′), 65.6 (C2 and C2′), 50.8 (C3 and C3′); MS (ESI+) 269 (100%, $[M + H]^+$); HRMS (ESI+) calcd for $C_{16}H_{17}N_2O_2$ 269.1301, found 269.1290 $[M + H]^+$.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00359.

NMR spectra for all synthesized compounds, computational data, X-ray structure data, general reaction notes, and supplementary experimental data for modified procedures of known compounds (PDF)

Accession Codes

CCDC 1998667−1998668 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Paul A. Keller − *School of Chemistry and Molecular Bioscience, Molecular Horizons,, University of Wollongong and Illawarra Health and Medical Research Institute, Wollongong, NSW 2522, Australia;* orcid.org/0000-0003-4868-845X; Email: keller@uow.edu.au

Authors

Jayden J. Gaston − *School of Chemistry and Molecular Bioscience, Molecular Horizons,, University of Wollongong and Illawarra Health and Medical Research Institute, Wollongong, NSW 2522, Australia;* orcid.org/0000-0002-8107-1841

Andrew J. Tague − *School of Chemistry and Molecular Bioscience, Molecular Horizons,, University of Wollongong and Illawarra Health and Medical Research Institute, Wollongong, NSW 2522, Australia;* orcid.org/0000-0003-0561-4629

Jamie E. Smyth − *School of Chemistry and Molecular Bioscience, Molecular Horizons,, University of Wollongong and Illawarra Health and Medical Research Institute, Wollongong, NSW 2522, Australia*

Nicholas M. Butler − *School of Chemistry and Molecular Bioscience, Molecular Horizons,, University of Wollongong and Illawarra Health and Medical Research Institute, Wollongong, NSW 2522, Australia;* orcid.org/0000-0002-6479-7819

Anthony C. Willis − *School of Chemistry, The Australian National University, Canberra, ACT 2601, Australia*
Nico van Eikema Hommes − *Computer Chemistry Center, Department of Chemistry and Pharmacy, Friedrich-Alexander Universität Erlangen-Nürnberg, 91052 Erlangen, Germany*
Haibo Yu − *School of Chemistry and Molecular Bioscience, Molecular Horizons,, University of Wollongong and Illawarra Health and Medical Research Institute, Wollongong, NSW 2522, Australia;* orcid.org/0000-0002-1099-2803
Timothy Clark − *Computer Chemistry Center, Department of Chemistry and Pharmacy, Friedrich-Alexander Universität Erlangen-Nürnberg, 91052 Erlangen, Germany;* orcid.org/0000-0001-7931-4659

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c00359

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the Australian Government for the award of an Australian Government Research Training Program Award to J.G. We also thank the University of Wollongong, School of Chemistry and Molecular Bioscience, the Australian National University, and the Friedrich-Alexander Universität for their support.

■ ADDITIONAL NOTES

[a]Only a portion of the material from **S1** was used due to safety concerns over the amount of $LiAlH_4$. It is recommended that extreme care be taken during addition of the ester to the $LiAlH_4$ suspension, which causes significant hydrogen gas evolution.
[b]Care must be taken to ensure that fresh and unoxidized magnesium is used. The use of old magnesium was found to produce the starting material in the case of **16** and decomposition in other tosyl protected amines.
[c]The use of $MgSO_4$ as a drying agent gave low yields for **16**, possibly due to binding of the product to magnesium. Considering this result, all further compounds were dried with Na_2SO_4.
[d]Preliminary results show that amines from this reaction were sufficiently pure to be utilized in subsequent transformations.
[e]General procedure 2a was found to be inferior to general procedure 2b for alkylation due to the highly inconsistent yields caused by excess NaH, which promoted decomposition. The use of fresh NaH with molar equivalents promoted reaction consistency with smaller amounts of decomposition, and only general procedure 2b was utilized for subsequent alkylations after this discovery.
[f]Significant difficulties were encountered in this study due to low-quality Sm that required changing suppliers and attempting SmI_2 generation through various methods, a difficulty which has been previously addressed.[13] The method that is reported here worked for only one batch of old (years) Sm metal stored in a desiccator; a second fresh batch purchased under an argon sealed ampule, and used immediately, would not generate SmI_2 under any reported method.
[g]Performing the reaction at −10 °C as previously reported[11] led to decomposition and trace amounts of product. This was due to the reaction forming an unstirrable slurry at low temperatures from the precipitation of the potassium phenolate. All phenoxide and alkoxide ring openings were therefore performed at room temperature.
[h]A modification to the number of equivalents of aniline from our previous procedure was made due to formation of the mono-ring opened product. See the reported procedure for details.
[i]The product was unable to be *N*-alkylated with K_2CO_3 at rt, and only decomposition was observed by ^1H NMR analysis (>16 $TsCH_3$ resonances). Attempted tetra-ethylation using general procedure 2b with 5 equiv of NaH and 12 equiv of ethyl iodide did not afford the product, and significant decomposition was observed by ^1H NMR analysis.
[j]Repeating this procedure using 50 mg of (*R*,*R*)-biaziridine **1** gave the pure product as an amber oil in an 80% yield after aqueous workup with no chromatography and a purity identical to that of the large-scale reaction as analyzed by ^1H NMR spectroscopy.
[k]Stirring the reaction for longer than the time indicated (∼3 d) did not cause any of **18** to be further consumed, as monitored by ^1H NMR analysis.
[l]No ^1H NMR assignments were made from the crude sample
[m]No ^{13}C NMR assignments were made from the crude sample.
[n]A broad carbon resonance was observed for $NC\underline{H}_2CH_3$, which indicates that rotamers are present as identified in compound **8** and previously reported.[29] This explains why some ^1H NMR resonances appear broad.
[o]As identified in compound **8** and previously reported,[29] rotamers can be observed by NMR analysis within these diamine scaffolds. For **15**, a broad carbon resonance in the ^{13}C NMR spectra was observed for the $NC\underline{H}_2CH_3$, indicating that **15** is rotameric.
[p]Following this procedure using only 20 mg of 1,2-bis(tosylamide) and 2.5 equiv of NaH gave a 100% conversion as analyzed by ^1H NMR spectroscopy and $TsC\underline{H}_3$ integration. Following this procedure using 2.2 equiv of NaH with 300 mg of 1,2-bis(tosylamide) gave a ∼50% conversion as analyzed by ^1H NMR spectroscopy and $TsC\underline{H}_3$ integration, indicating that a greater excess of NaH is required on scaleup.
[q]Continued heating under general procedure 2a for 24 h resulted in complete decomposition, with only *N*-benzyl-4-methylbenzenesulfonamide being isolated. Stirring at room temperature under general procedure 2a gave the starting material and decomposition. The formation of *N*-benzyl-4-methylbenzenesulfonamide is discussed in the section on decomposition (see Section S7 of the Supporting Information).
[r]4-Methoxybenzyl alcohol was found to form by the hydrolysis of 4-methoxybenzyl chloride in the presence of H_2O and base. Furthermore, the benzyl alcohol impurity was inseparable from the target product by silica gel chromatography and recrystallization. By preparing fresh 4-methoxybenzyl chloride and storing crude reaction samples in a vacuum-sealed desiccator (to exclude water), it is possible to prevent the slow hydrolysis of the 4-methoxybenzyl chloride and remove the difficulty in purification.
[s]The use of 10 equiv of NaH (211.6 mg, 5.29 mmol, 60% w/w), 1,2-bis(tosylamide) (299 mg, 0.514 mmol), tetrabutylammonium iodide (59.9 mg, 0.162 mmol), and 4-fluorobenzyl chloride (0.37 mL, 3.1 mmol) in DMF (6.0 mL) with heating for 3.5 h provided mostly decomposition. However, the crude

https://doi.org/10.1021/acs.joc.1c00359
J. Org. Chem. 2021, 86, 9163−9180

monobenzyl that contained 4-fluorobenzyl chloride (112.5 mg crude, 29%, 101.8 mg of tosylamide) and the pure dibenzyl product (26%, 106.6 mg) were still isolated using the same purification.

[t]Mass and molar quantity were corrected based on the ^{1}H NMR spectroscopy analysis.

[u]Mass of the 1,2-bis(tosylamide) **19** was calculated by the analysis of the crude NMR spectrum compared with the spectrum of 4-fluorobenzyl chloride (9.3 mg, 0.065 mmol) that was present.

[v]No alkylation from the residual 4-fluorobenzyl chloride was observed by ^{1}H NMR analysis in crude reaction mixtures or after purification.

[w]As identified within similar compounds in previous reports,[29] rotamers can be observed by an analysis of NMR spectra within the diamine scaffolds. Two broad carbon resonances in the ^{13}C NMR spectrum were observed for the NCH (δ 57.8, H2 and H3) and N($\underline{C}H_2$)CH_3 (δ 41.5, H1‴ and H1⁗), indicating that the compound is rotameric.

[x]Alkyl proton resonances are broad due to the compound being rotameric, as identified in **8** and in previous reports.[29]

[y]All broad carbon resonances are due to the compound being rotameric, as identified in **8** and in previous reports.[29]

[z]Care should be taken to use anhydrous DMSO due incomplete cyclization and decomposition occurring with wet DMSO. See the reported procedure for details.

[a1]Due to similarities in the environments of aromatic carbons atoms and protons, the NMR assignments for compound **20** are ambiguous; however, some distinction between the cyclic and linear functionalities can be made that confirm the structure as presented. The *N*-Boc-protected derivative **21** was synthesized to allow for crystal formation and an absolute determination of the absolute structure by X-ray crystallography.

[b1]Due to similarities in the environments of aromatic carbons atoms and protons, the NMR assignments for compound **20** are ambiguous; however, some distinction between the cyclic and linear side can be made that confirm the structure as presented. The absolute confirmation of compound **20** therefore required X-ray crystallography, which was obtained from the *N*-Boc-protected derivative **21**.

[c1]The attempted removal of the *N*-tosyl protecting groups produced mixtures of compounds that could not be separated by chromatography.

[d1]Silicon grease could be removed from **amine-11** using a very dilute acid/base extraction process. **Amine-11** (11 mg) in diethyl ether (10 mL) was extracted with 5.0 M HCl (3 × 33 mL). The combined acidic extracts were basified with 10% NaOH to pH 12 and then extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were concentrated *in vacuo*, dissolved in MeCN (20 mL), which was assisted by heating and sonication, washed with hexanes (3 × 100 mL), dried (Na_2SO_4), filtered, and evaporated *in vacuo*. Careful cleaning of the glassware and the complete purification of the 1,2-bis(tosylamide) starting material makes the above procedure unnecessary. This procedure did not work on larger scales and led to more decomposition during acid/base extraction.

[e1]One of the three samples synthesized of **amine-8** resulted in decomposition upon standing in $CDCl_3$ for 24 h in an NMR tube. This was suspected to be due to residual HCl present in $CDCl_3$ in the "old" solvent. A fresh bottle of the NMR solvent was used for other samples of **amine-8**, and no decomposition was observed even after standing for a week in $CDCl_3$ in an NMR tube.

[f1]While the resonances for H2 and H3 were observed in the ^{1}H NMR spectrum, resonances for C2 and C3 were unable to be observed by an analysis of the ^{13}C NMR spectrum, possibly due to signal broadening from rotamers as experienced with compound **8** and reported previously in similar compounds.[29] All other data were in accordance with the presented structure, anda calculation of the ^{13}C NMR spectra using DFT gavea good correlation to experimental data (R^2 = 0.9935). The C2 and C3 resonances were calculated to be at 56.2 and 52.5 ppm, respectively. The carbon resonance assignments were made based upon the calculated chemical shifts by DFT (see Figure S1 and Table S2).

[g1]An adaptation of general procedure 1 was required due to the high insolubility of the cyclic 1,2-bis(tosylamide) **16** in MeOH. This was solved by using THF as a cosolvent in a 1:3 THF/MeOH ratio,[3] a twofold dilution of the 1,2-bis-(tosylamide), using 100 equiv of Mg powder (to maintain [Mg] = 50 mg mL^{-1}), and regular vigorous shaking of the flask by hand to ensure thorough mixing.

[h1]The use of $MgSO_4$ as a drying agent was found to give very low yields, likely due to binding of the product to $MgSO_4$. It is not recommended to attempt any of these procedures with the use of $MgSO_4$. Therefore, Na_2SO_4 should be employed.

REFERENCES

(1) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Thieme Publishing Group: Stuggart, Germany, 2005.

(2) Ankner, T.; Hilmersson, G. Instantaneous Deprotection of Tosylamides and Esters with SmI_2 /Amine/Water. *Org. Lett.* **2009**, *11* (3), 503−506.

(3) Nyasse, B.; Grehn, L.; Ragnarsson, U. Mild, Efficient Cleavage of Arenesulfonamides by Magnesium Reduction. *Chem. Commun.* **1997**, *1997* (11), 1017−1018.

(4) Pak, C. S.; Lim, D. S. Deprotection of 2-Pyridyl Sulfonyl Group from Pyridine-2-Sulfonamides by Magnesium in Methanol. *Synth. Commun.* **2001**, *31* (14), 2209−2214.

(5) Zaed, A. M.; Sutherland, A. Stereoselective Synthesis of the Bicyclic Guanidine Alkaloid (+)-Monanchorin. *Org. Biomol. Chem.* **2010**, *8* (19), 4394−4399.

(6) Kiso, Y.; Satomi, M.; Ukawa, K.; Akita, T. Efficient Deprotection of N^G -Tosylarginine with a Thioanisole−Trifluoromethanesulphonic Acid System. *J. Chem. Soc., Chem. Commun.* **1980**, *22*, 1063−1064.

(7) Liu, Q.; Ferreira, E. M.; Stoltz, B. M. Convergency and Divergency as Strategic Elements in Total Synthesis: The Total Synthesis of (−)-Drupacine and the Formal Total Synthesis of (±)-Cephalotaxine, (−)-Cephalotaxine, and (+)-Cephalotaxine. *J. Org. Chem.* **2007**, *72* (19), 7352−7358.

(8) Javorskis, T.; Orentas, E. Chemoselective Deprotection of Sulfonamides Under Acidic Conditions: Scope, Sulfonyl Group Migration, and Synthetic Applications. *J. Org. Chem.* **2017**, *82* (24), 13423−13439.

(9) Abdel-Aziz, A. A. M.; El Bialy, S. A. A.; Goda, F. E.; Kunieda, T. Enantioselective Synthesis of (1*S*,2*S*)-1,2-Di-*Tert*-Butyl and (1*R*,2*R*)-1,2-Di-(1-Adamantyl)Ethylenediamines. *Tetrahedron Lett.* **2004**, *45* (43), 8073−8077.

(10) Kuroki, T.; Katsuki, T. Synthesis of a New Chiral Auxiliary, (1*R*, 2*R*, 3*R*, 6*R*)-3,6-Dimethylcyclohexane-1,2-Diamine. *Chem. Lett.* **1995**, *24* (5), 337−338.

(11) Bailey, S. J.; Wales, S. M.; Willis, A. C.; Keller, P. A. Ring-Opening and -Expansion of 2,2′-Biaziridine: Access to Diverse Enantiopure Linear and Bicyclic Vicinal Diamines. *Org. Lett.* **2014**, *16* (16), 4344−4347.

(12) Szostak, M.; Spain, M.; Procter, D. J. Determination of the Effective Redox Potentials of SmI_2, $SmBr_2$, $SmCl_2$, and Their

https://doi.org/10.1021/acs.joc.1c00359
J. Org. Chem. 2021, 86, 9163−9180

Complexes with Water by Reduction of Aromatic Hydrocarbons. Reduction of Anthracene and Stilbene by Samarium(II) Iodide−Water Complex. *J. Org. Chem.* **2014**, *79* (6), 2522−2537.
(13) Szostak, M.; Spain, M.; Procter, D. J. Preparation of Samarium(II) Iodide: Quantitative Evaluation of the Effect of Water, Oxygen, and Peroxide Content, Preparative Methods, and the Activation of Samarium Metal. *J. Org. Chem.* **2012**, *77* (7), 3049−3059.
(14) Miller, R. S.; Sealy, J. M.; Shabangi, M.; Kuhlman, M. L.; Fuchs, J. R.; Flowers, R. A. Reactions of SmI_2 with Alkyl Halides and Ketones: Inner-Sphere vs Outer-Sphere Electron Transfer in Reactions of Sm(II) Reductants. *J. Am. Chem. Soc.* **2000**, *122* (32), 7718−7722.
(15) Closson, W. D.; Ji, S.; Schulenberg, S. Mechanism of Sulfonamide Cleavage by Arene Anion Radicals. *J. Am. Chem. Soc.* **1970**, *92* (3), 650−657.
(16) Lee, G.; Youn, I.; Choi, E.; Lee, H.; Yon, G.; Yang, H.; Pak, C. Magnesium in Methanol (Mg/MeOH) in Organic Syntheses. *Curr. Org. Chem.* **2004**, *8* (13), 1263−1287.
(17) Garst, M. E.; Dolby, L. J.; Esfandiari, S.; Fedoruk, N. A.; Chamberlain, N. C.; Avey, A. A. Reductions with Lithium in Low Molecular Weight Amines and Ethylenediamine. *J. Org. Chem.* **2000**, *65* (21), 7098−7104.
(18) Andrieux, C. P.; Gelis, L.; Saveant, J. M. Outer-Sphere and Inner-Sphere Processes in Organic Chemistry. Reaction of Trifluoromethyl Bromide with Electrochemically Generated Aromatic Anion Radicals and Sulfur Dioxide Anion Radicals. *J. Am. Chem. Soc.* **1990**, *112* (2), 786−791.
(19) Borioni, J. L.; Puiatti, M.; Vera, D. M. A.; Pierini, A. B. In Search of the Best DFT Functional for Dealing with Organic Anionic Species. *Phys. Chem. Chem. Phys.* **2017**, *19* (13), 9189−9198.
(20) Lexa, D.; Saveant, J. M.; Schaefer, H. J.; Binh, S. K.; Vering, B.; Wang, D. L. Outer-Sphere and Inner-Sphere Processes in Reductive Elimination. Direct and Indirect Electrochemical Reduction of Vicinal Dibromoalkanes. *J. Am. Chem. Soc.* **1990**, *112* (17), 6162−6177.
(21) Chaban, V. V.; Prezhdo, O. V. Electron Solvation in Liquid Ammonia: Lithium, Sodium, Magnesium, and Calcium as Electron Sources. *J. Phys. Chem. B* **2016**, *120* (9), 2500−2506.
(22) Williams, D. B. G.; Lawton, M. Drying of Organic Solvents: Quantitative Evaluation of the Efficiency of Several Desiccants. *J. Org. Chem.* **2010**, *75* (24), 8351−8354.
(23) Armarego, W. L. F.; Chai, C. L. L. Purification of Organic Chemicals. In *Purification of Laboratory Chemicals*; Elsevier: Oxford, U.K., 2009; pp 88−444.
(24) Groom, C. R.; Bruno, I. J.; Lightfoot, M. P.; Ward, S. C. The Cambridge Structural Database. *Acta Crystallogr., Sect. B: Struct. Sci., Cryst. Eng. Mater.* **2016**, *72* (2), 171−179.
(25) *CrysAlis Pro*, ver. 1.171.37.2. Technologies, Oxford Diffraction/Agilent: Yarnton, U.K., 2018.
(26) Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. SIR 92 − a Program for Automatic Solution of Crystal Structures by Direct Methods. *J. Appl. Crystallogr.* **1994**, *27* (3), 435−435.
(27) Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. CRYSTALS Version 12: Software for Guided Crystal Structure Analysis. *J. Appl. Crystallogr.* **2003**, *36* (6), 1487−1487.
(28) Wales, S. M.; Willis, A. C.; Keller, P. A. The First Syntheses of Enantiopure 2,2′-Biindoline. *Chem. Commun.* **2010**, *46* (48), 9226.
(29) Kennedy, M. D.; Bailey, S. J.; Wales, S. M.; Keller, P. A. Enantiopure Trans −4,5-Disubstituted 2-Imidazolidinones via Copper(I)-Catalyzed Ring Opening of 1,1′-DiBoc-2,2′-Biaziridine with Grignard Reagents. *J. Org. Chem.* **2015**, *80* (11), 5992−5998.
(30) *Avogadro: An open-source molecular builder and visualization tool*, ver. 1.2.0. http://avogadro.cc/ (accessed 2019-10-23).
(31) Hanwell, M. D.; Curtis, D. E.; Lonie, D. C.; Vandermeersch, T.; Zurek, E.; Hutchison, G. R. Avogadro: An Advanced Semantic Chemical Editor, Visualization, and Analysis Platform. *J. Cheminf.* **2012**, *4* (1), 17.
(32) Pracht, P.; Bohle, F.; Grimme, S. Automated Exploration of the Low-Energy Chemical Space with Fast Quantum Chemical Methods. *Phys. Chem. Chem. Phys.* **2020**, *22* (14), 7169−7192.
(33) Pracht, P.; Caldeweyher, E.; Ehlert, S.; Grimme, S.A Robust Non-Self-Consistent Tight-Binding Quantum Chemistry Method for Large Molecules. *ChemRxiv*, June 26, 2019, ver. 1. DOI: 10.26434/chemrxiv.8326202.v1
(34) Grimme, S.; Bannwarth, C.; Shushkov, P. A Robust and Accurate Tight-Binding Quantum Chemical Method for Structures, Vibrational Frequencies, and Noncovalent Interactions of Large Molecular Systems Parametrized for All Spd-Block Elements (Z = 1−86). *J. Chem. Theory Comput.* **2017**, *13* (5), 1989−2009.
(35) Bannwarth, C.; Ehlert, S.; Grimme, S. GFN2-XTB - An Accurate and Broadly Parametrized Self-Consistent Tight-Binding Quantum Chemical Method with Multipole Electrostatics and Density-Dependent Dispersion Contributions. *J. Chem. Theory Comput.* **2019**, *15* (3), 1652−1671.
(36) Elmore, D. T.; Jones, J. H.; Raissi, M.; Prout, K. N-Benzylmethanesulfonamide. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1992**, *48* (7), 1331−1333.
(37) Yi-Ni, Y. PTSBZA01 : N-Benzyl-4-Methylbenzenesulfonamide. *CSD Comm.* **2014**, DOI: 10.5517/cc12x56c.
(38) Gaston, J. J.; Keller, P. A.; Willis, A. C. TUMBOV : (3*S*,3′*S*)-6,6′-Dimethoxy-4,4′-Ditosyl-3,3′,4,4′-Tetrahydro-2*H*,2′*H*-3,3′-Bibenzo[*b*][1,4]Oxazine. *CSD Comm.* **2020**, DOI: 10.5517/ccdc.csd.cc24tblx.
(39) O'Boyle, N. M.; Vandermeersch, T.; Flynn, C. J.; Maguire, A. R.; Hutchison, G. R. Confab - Systematic Generation of Diverse Low-Energy Conformers. *J. Cheminf.* **2011**, *3* (1), 8.
(40) Sharapa, D. I.; Genaev, A.; Cavallo, L.; Minenkov, Y. A Robust and Cost-Efficient Scheme for Accurate Conformational Energies of Organic Molecules. *ChemPhysChem* **2018**, *20* (1), 92−102, DOI: 10.1002/cphc.201801063.
(41) Řezáč, J.; Bím, D.; Gutten, O.; Rulíšek, L. Toward Accurate Conformational Energies of Smaller Peptides and Medium-Sized Macrocycles: MPCONF196 Benchmark Energy Data Set. *J. Chem. Theory Comput.* **2018**, *14* (3), 1254−1266.
(42) Rienstra-Kiracofe, J. C.; Tschumper, G. S.; Schaefer, H. F.; Nandi, S.; Ellison, G. B. Atomic and Molecular Electron Affinities: Photoelectron Experiments and Theoretical Computations. *Chem. Rev.* **2002**, *102* (1), 231−282.
(43) Grimme, S.; Ehrlich, S.; Goerigk, L. Effect of the Damping Function in Dispersion Corrected Density Functional Theory. *J. Comput. Chem.* **2011**, *32* (7), 1456−1465.
(44) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, rev. E.01; Gaussian, Inc.: Wallingford, CT, 2013.
(45) Becke, A. D. Density-functional Thermochemistry. III. The Role of Exact Exchange. *J. Chem. Phys.* **1993**, *98* (7), 5648−5652.
(46) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.;

https://doi.org/10.1021/acs.joc.1c00359
J. Org. Chem. 2021, 86, 9163−9180

Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian 16*, rev. C.01; Gaussian, Inc.: Wallingford, CT, 2016.

(47) Momma, K.; Izumi, F. VESTA 3 for Three-Dimensional Visualization of Crystal, Volumetric and Morphology Data. *J. Appl. Crystallogr.* **2011**, *44* (6), 1272−1276.

(48) Momma, K.; Izumi, F. *VESTA*, ver. 3.0; 2011. http://jp-minerals.org/vesta/en/ (accessed 2019-10-23).

(49) O'Boyle, N. M.; Banck, M.; James, C. A.; Morley, C.; Vandermeersch, T.; Hutchison, G. R. Open Babel: An Open Chemical Toolbox. *J. Cheminf.* **2011**, *3* (1), 33.

(50) *The Open Babel Package*, ver. 2.3.1.; 2011. http://openbabel.org (accessed 2019-10-23).

(51) Tantillo, D. J. *Chemical Shift Repository (CHESIRE)*. http://cheshirenmr.info/ (accessed 2020-08-31).

(52) Lodewyk, M. W.; Siebert, M. R.; Tantillo, D. J. Computational Prediction of 1H and 13C Chemical Shifts: A Useful Tool for Natural Product, Mechanistic, and Synthetic Organic Chemistry. *Chem. Rev.* **2012**, *112* (3), 1839−1862.

(53) Bergmeier, S.; Seth, P. E. A General Method for Deprotection of N-Toluenesulfonyl Aziridines Using Sodium Naphthalenide. *Tetrahedron Lett.* **1999**, *40*, 6181−6184.

(54) Rorig, K.; Johnston, J. D.; Hamilton, R. W.; Telinski, T. J. P-METHOXYPHENYLACETONITRILE. *Org. Synth.* **1956**, *36*, 50.

(55) Maraš, N. Nuceophilic substitution of a benzylic alcohol; 4-methoxybenzyl chloride. *ChemSpider* **2011**, No. 518.

https://doi.org/10.1021/acs.joc.1c00359
J. Org. Chem. 2021, 86, 9163−9180