2,6-Dichloro-9-thiabicyclo[3.3.1]nonane: A Privileged, Bivalent Scaffold for the Display of Nucleophilic Components

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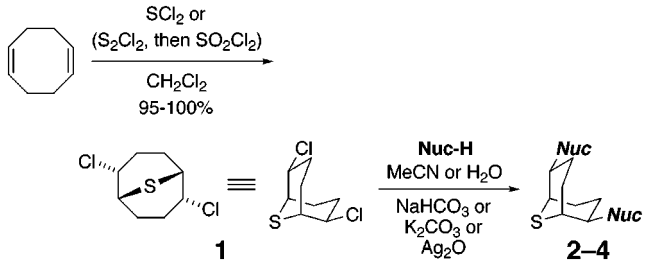
The title compound, the condensation product of sulfur dichloride and 1,5-cyclooctadiene, is a reliable acceptor of a wide variety of heteroatom nucleophiles, sometimes in reversible fashion. Optical resolution of the core structure has been achieved and preserved in succeeding transformations. The high reactivity and reliable stereochemical control afforded by this system illustrates the power of neighboring-group participation by the sulfur center.

Introduction

The transannular additions of SCl_2 to 1,5-cyclooctadiene (COD),[1−3] 1,5,9-cyclododecatriene,[4] and other cyclic and acyclic diolefins[3−6] were discovered more than 30 years ago. The resulting dihalosulfide products were reported to be substrates for facile and regiospecific substitution reactions, consistent with the expected anchimeric assistance provided by the sulfur center.[1,3−5,7−11] Because of our interest in creating "functional" molecules by using only a few of the very best reactions for modular assembly of reactive components,[12] the old reports on the special reactivity of these "mustard" compounds made them intriguing as potential scaffolds and connectors. Pursuit of these interests has confirmed our expectations and also led to substantial improvements in both the scope and the efficiency of the transformations.

The electrophilic addition of SCl_2 to certain cyclic and acyclic dienes provides an inexpensive[13] route to *anti*-dichlorosulfide structures of the mustard class.[1−5,14] In the majority of cases, competing polymerization pathways dominate, but the reaction parameters are nearly optimal for the addition of SCl_2 to a few cyclic polyenes and above all for 1,5-cyclooctadiene. Thus, COD and sulfur dichloride[15] give **1** in excellent yield at a variety of concentrations and scales in our hands (Scheme 1), but this reaction is successful only when SCl_2 is purified by careful distillation just before use. As an alternative, the sequential treatment of diene with sulfur monochloride (S_2Cl_2) followed by sulfuryl chloride (SO_2Cl_2) provides high yields in a robust and convenient process (Scheme 1).[16]

Scheme 1. Synthesis and Reactivity of 1



Extending the literature reports of halide substitution in this class of molecules,[1,11] we have found that a variety

(1) Weil, E. D.; Smith, K. J.; Gruber, R. J. *J. Org. Chem.* **1966**, *31*, 1669−1682.
(2) Lautenschlaeger, F. K. *Can. J. Chem.* **1966**, *44*, 2813−2817.
(3) Corey, E. J.; Block, E. *J. Org. Chem.* **1966**, *31*, 1663−1668.
(4) Lautenschlaeger, F. *J. Org. Chem.* **1968**, *33*, 2627−2633.
(5) Lautenschlaeger, F. *J. Org. Chem.* **1966**, *31*, 1679−1682.
(6) (a) Lautenschlaeger, F. *J. Org. Chem.* **1968**, *33*, 2620−2627. (b) McCabe, P. H.; Routledge, W. *Tetrahedron Lett.* **1976**, 85−86. (c) Komatsu, M.; Ogawa, H.; Mohri, M.; Ohshiro, Y. *Tetrahedron Lett.* **1990**, *31*, 3627−3630.
(7) Labows, J. N., Jr.; Landmesser, N. *J. Org. Chem.* **1975**, *40*, 3798−3800.
(8) (a) Tabushi, I.; Tamaru, Y.; Yoshida, Z.-I.; Sugimoto, T. *J. Am. Chem. Soc.* **1975**, *97*, 2886−2891. (b) For an early example of episulfonium rearrangements, see Marvel, C. S.; Weil, E. D. *J. Am. Chem. Soc.* **1954**, *76*, 61−69. (c) Novitskaya, N. N.; Kunakova, R. V.; Zaev, E. E.; Tolstikov, G. A.; Spirikhin, L. V. *Zh. Org. Khim.* **1975**, *11*, 1434−1440.
(9) Fort, R. C., Jr.; Stahl, M. H.; Sky, A. F. *J. Org. Chem.* **1987**, *52*, 2396−2399.
(10) Vincent, J. A. J. M.; Schipper, P.; deGroot, A.; Buck, H. M. *Tetrahedron Lett.* **1975**, 1989−1992.
(11) Compound **2c** and the analogous pyrollidine adduct have been reported to have anti-inflammatory activity: Tolstikov, G. A.; Krivonogov, V. P.; Galimov, B. I.; Iazareva, D. N.; Davydova, V. A.; Krivonogova, I. I.; Murinov, Y. U. *Khim.-Farm. Zh.* **1997**, *31*, 26−29.
(12) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.*, in press.
(13) For example, on a research scale (Aldrich Chemical Co.), 1 mol of 1,5-cyclooctadiene and SCl_2 costs approximately $4 and $0.82, respectively.
(14) (a) Tolstikov, G. A. *Sulfur Rep.* **1983**, *3*, 39−70. (b) Capozzi, G.; Modena, G.; Pasquato, L. In *The Chemistry of Sulfenic Acids and Their Derivatives*; Patai, S., Ed.; Wiley: Chichester, 1990; Chapter 10. Mustard structures of the type discussed here are also available from appropriate di-epoxides: Cope, A. C.; Fisher, B. S.; Funke, W.; McIntosh, J. M.; McKervey, M. A. *J. Org. Chem.* **1969**, *34*, 2231−2234. (c) For the accepted mechanism of sulfenyl halide additions to olefins, see Schmid, G. H.; Strukelj, M.; Dalipi, S.; Ryan, M. D. *J. Org. Chem.* **1987**, *52*, 2403−2407 and references therein. (d) McCabe, P. H.; deJenga, C. I.; Stewart, A. *Tetrahedron Lett.* **1981**, *22*, 3681−3682.
(15) Bishop, R. *Org. Synth.* **1992**, *70*, 120−128.
(16) The purity of the reagents in this case is not critical: S_2Cl_2 contains variable amounts of SCl_2 and may be used as received and after extended storage. The two-stage addition of S_2Cl_2 to olefins has been observed to give bis-2-chloroalkyl disulfides, which can be reduced to episulfides: (a) Lautenschlaeger, F.; Schwartz, N. V. *J. Org. Chem.* **1969**, *34*, 3991−3998. (b) Bombala, M. U.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3013−3016. (c) Abu-Yousef, I. A.; Hynes, R. C.; Harpp, D. N. *Tetrahedron Lett.* **1993**, *34*, 4289−4292. Our use of SO_2Cl_2 to provide an additional equivalent of active chlorine appears to be new.

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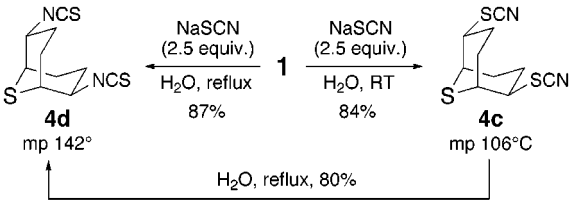
Table 1. Synthesis of Neutral Adducts of 1[a]

nucleophile	prod	yield (%)	nucleophile	prod	yield (%)
NH_3	**2a**	94	$PhNH_2$	**2g**	90
$MeNH_2$	**2b**	90	*p*-$MeC_6H_4SO_2NH_2$	**2h**	95
morpholine	**2c**	81	NaOMe	**3a**	71
adamantyl-NH_2	**2d**	97	NaOPh	**3b**	75
$PhCH_2NH_2$	**2e**	98	NaN_3	**4a**	96
$PhC(Me)HNH_2$	**2f**	71[b]	AgF	**4b**	95

[a] Compounds **2a**, **2b**, and **4a** were prepared in water; all other reactions were performed in acetonitrile. [b] Isolated as an equal mixture of diastereomers.

Scheme 2. Reactions of 1 with Thiocyanate



of heteroatom nucleophiles react with **1** in the presence of base at rt in acetonitrile to give disubstituted products **2**−**4** with retention of configuration (Scheme 1, Table 1). We have also come to appreciate that the substitution reactions of **1** can benefit from an aqueous environment, as described below. Primary amines, including adamantylamine and aniline, work well, but heterocyclic secondary amines such as carbazole, benzimidazole, and indazole are unreactive (see Chart 1 in the Experimental Section). The difluoride derivative **4b** is soluble in more solvents than **1** but is much less reactive. The potentially reversible nature of the substitution reaction is illustrated by Scheme 2. In water, sodium thiocyanate gives the thiocyanate adduct **4c** at rt and the isothiocyanate **4d** at reflux; purified **4c** cleanly isomerizes to **4d** when heated, presumably by ejection and re-addition of the nucleophile.[17]

Tertiary amines and pyridines add to **1** to give dicationic products **5** in high yields, which precipitate from the reaction mixture (Figure 1). As with other nucleophiles described above, substitution is rapid, occurs with retention, and gives disubstituted products exclusively, even when a deficiency of amine is employed. The relative reactivities of the nucleophiles depend on the solvent, as illustrated in Scheme 3. The addition of tertiary amines is irreversible in acetonitrile (the charged products precipitate), so the relatively poor base pyridine does not compete well with either quinuclidine or DABCO. In contrast, reversible substitution takes place in methanol, and the bis(pyridine) adduct **5c** is found to be by far the most stable. Compound **5c** likewise resists hydrolysis in water for more than 1 week at rt, whereas **5a** and **5b** are hydrolyzed in several hours to the known[1] dihydroxide adduct. An X-ray crystal structure of **5c** has been obtained (Experimental Section).[18,19]

While to date most of the above substitution reactions have been performed in acetonitrile, water can give

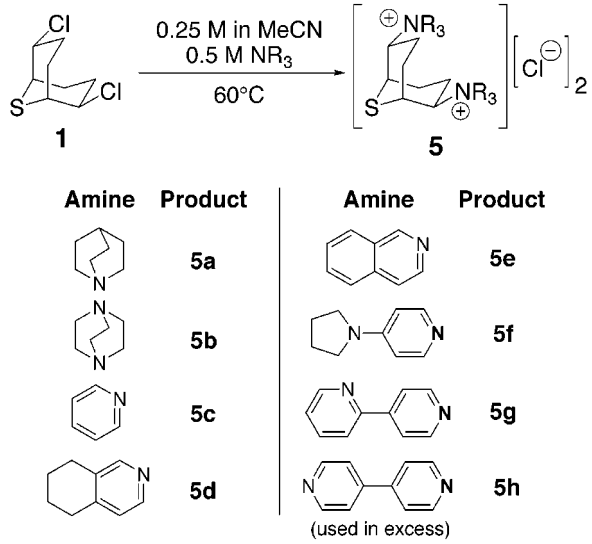


Figure 1. Addition of tertiary amines and pyridines to **1**. Isolated yields vary in the range of 50−80%, depending on the extent of precipitation of the products, and are not optimized; see Experimental Section.

superior results, even though the starting dichloride is not water-soluble. For example, the parent diamine **2a** is not a major product from the reaction of **1** with ammonia in methanol or acetonitrile solvents. Other routes, including hydrazinolysis of the bis(phthalimide) adduct and hydrolysis of the bis(trifluoroacetamide), also gave complex mixtures. The adduct of sodium bis(formyl)amide may be readily prepared, and its hydrolysis gives **2a** in 72% yield after precipitation from ether as the bis(hydrochloride) salt, but this route is cumbersome for large-scale synthesis. In contrast, **1** reacts with saturated aqueous ammonia rapidly at rt to afford **2a** in high yield; the methylamine adduct **2b** is similarly prepared (Table 1).

As previously reported,[7] we find that substitution is strongly inhibited when the sulfur atom of **1** is oxidized. When substitution is achieved, it occurs with inversion because of a switch in mechanism to direct S_N2.[7,9] For example, the sulfoxide **6** derived from **1**[20] is unreactive with NaN_3 at rt in DMF—the same conditions in which **1** reacts readily. Heating to 110 °C in DMF is required to force monosubstitution to give **7** (Scheme 4). The reaction stereochemistry was determined by condensation with dimethylacetylene dicarboxylate to give triazole **8** in high yield, which was characterized by X-ray crystallography, confirming that azide substitution had

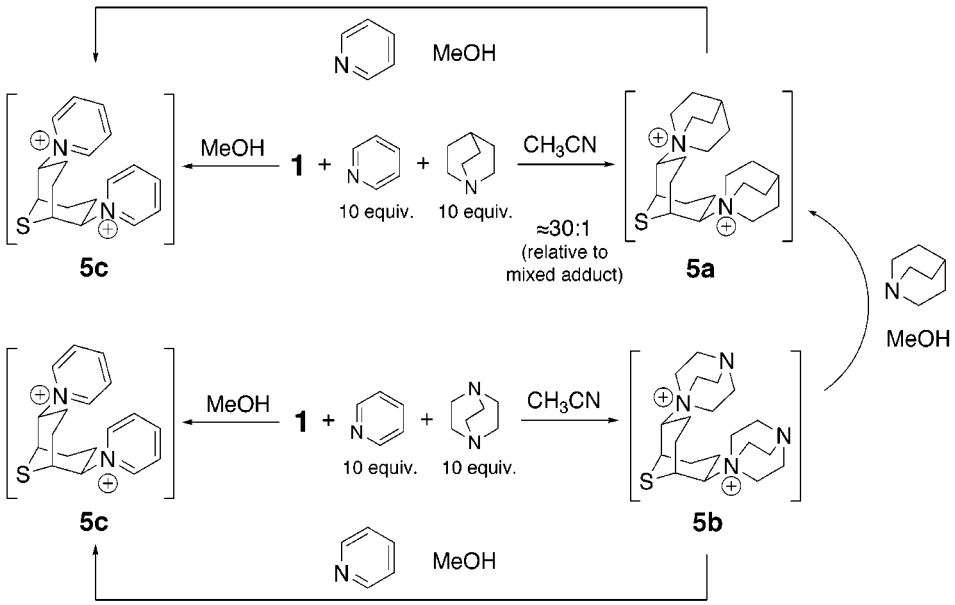
(17) Fava, A. In *The Chemistry of Organosulfur Compounds*; Kharasch, N., Meyers, C. Y., Eds.; Pergamon Press: New York, 1966; Vol. 2, pp 73−91.

(18) Crystallographic data (excluding structure factors) for structures **5c** and **8** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication Nos. CCDC 155115 and 155116, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, U.K. (fax: +44 1223 336033, or e-mail: deposit@ccdc.cam.ac.uk).

(19) Several factors could contribute to the stability of pyridine adduct **5c**. (a) Examination of space-filling models shows a less strained connection between the thiabicyclononane core and the pyridine as compared to DABCO or quinuclidine. NMe_3 and NEt_3 are unreactive toward **1**, just as they are relatively poor ligands for OsO_4. The greater reactivity of quinuclidine and DABCO in both contexts is at least partially due to steric factors, since NMe_3 and NEt_3 have larger cone angles. Note that the benzylamine and morpholine adducts (**2e** and **2c**, respectively) are more stable in methanol than the DABCO and quinuclidine compounds (**5b** and **5a**) even when protonated by excess HCl, perhaps also for steric reasons. (b) The pyridine adduct **5c** is likely to be better solvated by methanol than the DABCO or quinuclidine adducts, since the ammonium centers of the latter are shielded by hydrophobic methylene groups. (c) The relative kinetic reactivities of the nitrogen nucleophiles may be strongly dependent on solvent. For example, the stronger bases should be passivated to a greater degree by a protic medium such as methanol.

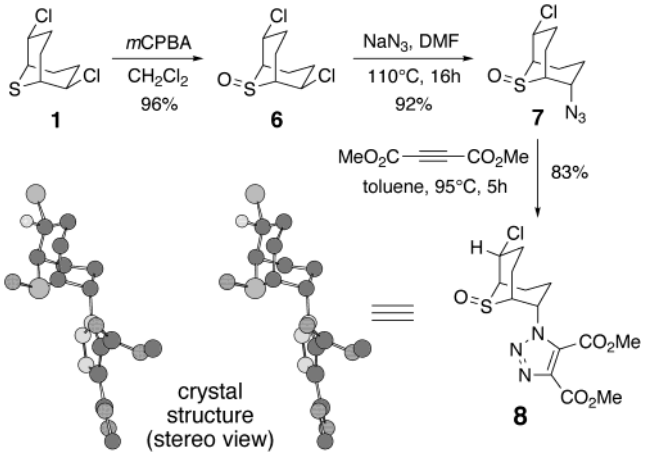
(20) McCabe, P. H.; de Jenga, C. I.; Stewart, A. *Tetrahedron Lett.* **1981**, *22*, 3679−3680.

Scheme 3. Competitions between Pyridine and Tertiary Amine Nucleophiles for 1 in Acetonitrile vs Methanol[a]



[a] All reactions were performed at rt; all yields are >95%.

Scheme 4. Proof of the Stereochemistry of Substitution Reactions

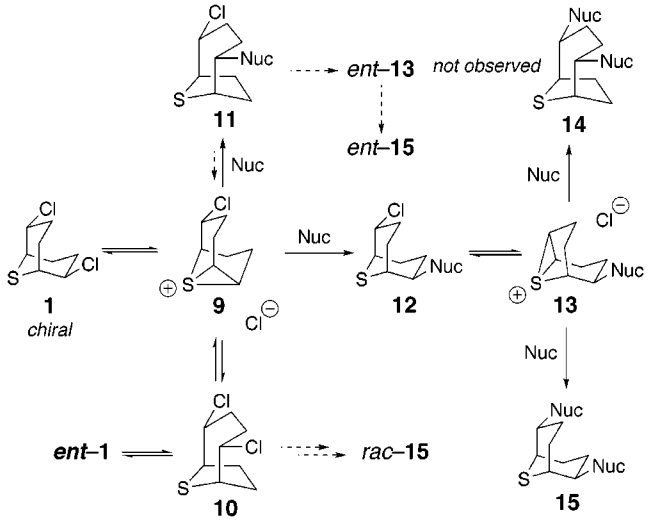


occurred with inversion at the site not blocked by the sulfoxide oxygen atom.[9,18,21] The corresponding sulfone does not react with NaN_3 even at 120 °C in DMF.

Scheme 5 shows the putative steps in substitution reactions of **1**, which is distinguished by the presence of episulfonium ions (e.g., **9** and **13**), the signature intermediates of neighboring-group participation in sulfur mustards.[10,22] Attack at either carbon of the episulfonium ring is possible,[23] but products of the general form **14** are not observed, presumably because the 9-thiabicyclo[4.2.1] skeleton (**10**, **11**, and **14**) is higher in energy than the analogous [3.3.1] form (**1**, **12**, and **15**).[24] Thus, although structure **10** is accessible, the overall substitution processes are stereospecific and highly, if not completely, regioselective for thermodynamic reasons.

Other observations allow further insights into the relative rates of various steps in the mechanistic scheme.

Scheme 5. Mechanistic Pathways for Substitution Reactions

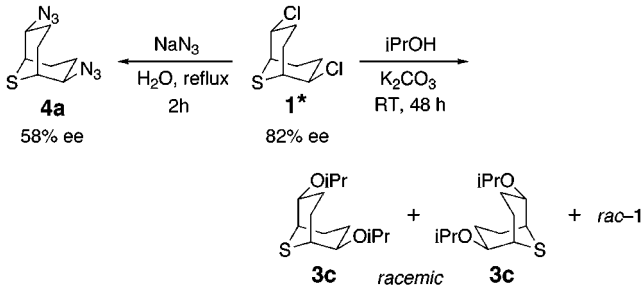


For example, in contrast to previous reports,[3,10] we do not observe monosubstitution of **1** by amine nucleophiles in acetonitrile, even when a deficiency of amine is employed. An equimolar mixture of **1** and morpholine gives an equimolar ratio of bis(adduct) **2c** and unreacted **1**. Likewise, phenethylamine in 1.5, 0.8, and 0.2 equiv with respect to **1** gives disubstituted adduct **2f** exclusively

(21) Thioethers may be readily converted to sulfilimes in an uncatalyzed reaction with chloramines (Marzinzik, A.; Sharpless, K. B. *J. Org. Chem.* **2001**, *66*, 594−596). As expected, the *N*-tosylsulfilimine derived from **1** behaves similarly to the sulfoxide, showing only S_N2 substitution by azide of a single chloride.

(22) For recent X-ray characterization of episulfonium (thiiranium) ions, see Destro, R.; Lucchini, V.; Modena, G.; Pasquato, L. *J. Org. Chem.* **2000**, *65*, 3367−3370. (a) Schmid, G. H. *Top. Sulfur Chem.* **1977**, *3*, 101−117. (b) Dittmer, D.; Patwardhan, B. H.; In *The Chemistry of the Sulphonium Group*; Stirling, C. J. M., Patai, S., Eds.; Wiley: New York, 1981; Part 1, pp 387−412. (c) Mueller, W. H. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 482−492. (d) Smit, W. A.; Zefirov, N. S.; Bodrikov, I. V.; Krimer, M. Z. *Acc. Chem. Res.* **1979**, *12*, 282−288. For specific examples, see (e) Tsushima, T.; Tanida, H. *J. Org. Chem.* **1980**, *45*, 3205−3211. (f) Yang, Y.-C.; Ward, J. R.; Luteran, T. *J. Org. Chem.* **1986**, *51*, 2756−2759. (g) Dohn, D. R.; Casida, J. E. *Bioorg. Chem.* **1987**, *15*, 115−124. (h) Hanessian, S.; Thavonekham, B.; DeHoff, B. *J. Org. Chem.* **1989**, *54*, 5831−5833. (i) Compain-Batissou, M.; Mesrari, L.; Anker, D.; Doutheau, A. *Carbohydr. Res.* **1999**, *316*, 201−205.

Scheme 6. Substitution Reactions of Enantiomerically Enriched 1



in each case, along with the corresponding amount of unreacted **1**. It is therefore apparent that the second substitution (**12**→**15** in Scheme 5) is much faster than the first (**1**→**12**), and thus, the rate and/or equilibrium constant for formation of episulfonium ion **13** is likely to be much greater than for the formation of **9**. One possible contributing factor is the difference in polarity of **1** vs the monosubstituted intermediate **12**. The calculated dipole moment[25] of **1** is quite small (0.81 D) because the internal C−Cl dipoles point in opposing directions. In contrast, a model structure for monosubstitution, **12** with Nuc = NH_2, is calculated to have a greater dipole moment (2.78 D), which is oriented in the direction of the polarized C−Cl bond, since NH_2 is substantially less electronegative than Cl. Such pre-existing polarization, not present in **1**, may assist the generation of the episulfonium ion intermediate (**13**). If this is correct, then when chloride and the substituting group differ less substantially in electronegativity, the first and second substitution events should occur with similar facility. This occurs with azide: the reaction of **1** with a deficiency of NaN_3 in DMF gives a mixture of mono- and disubstituted products,[26] and the calculated dipole moment of the monosubstituted compound (**12**, Nuc = N_3) is a relatively low 1.31 D. Note that the preferential disubstitution by tertiary amines is driven not by polarity but rather by the precipitation of dications **5** from acetonitrile.

In order to explain why a more polarized intermediate such as **12** would undergo neighboring-group participation at a greater rate than a nonpolar structure such as **1**, we emphasize entropic factors in the polar solvents typically employed. While polarized intermediates may be expected to be less reactive (in enthalpic terms) than nonpolarized structures in a polar solvent, the creation of an ion from a neutral species would be expected to incur a large entropic penalty by virtue of solvent shell organization in a polar medium. Such an entropic cost would be partially paid in direct proportion to the dipole moment of the neutral precursor to the ionization step.

The chirality of the system provides additional opportunities to probe reactivity. The enantiomers of C_2-symmetric dichloride **1**, diazide adduct **4a**, and bis-(isopropoxide) adduct **3c** can be separated by chiral HPLC (Chiralcel OB-H). Small amounts of each enantiomer of the first two compounds were isolated in this fashion using an analytical-scale column, apparently the first resolutions of structures of this type.[27] Enantiomerically enriched **1** (designated **1***) does not racemize after standing for 24 h at rt in chloroform or hexane solution; (+)-**4a** is likewise unchanged. Interestingly, substitution of enantiomerically enriched **1** (designated **1***) in 2-propanol at rt provides racemic **3c** and racemic starting material (**1**) when the reaction mixture is analyzed before completion, whereas reaction with azide in refluxing water gives **4a** with substantial retention of absolute configuration (Scheme 6).

These results highlight the importance of solvent when charged intermediates are generated.[28] The extent of racemization is determined by the relative reactivities of the available nucleophiles with episulfonium ion **9** (Scheme 5). In the tight ion pair in which **9** exists in 2-propanol, chloride can compete with the solvent, usually regenerating **1** but occasionally providing the meso structure **10**. Intermediate **9** is thereby accessed many times and is racemized via **10** before the irreversible capture by 2-propanol occurs. Azide substitution in water is different: while **1** is insoluble in water, the derived ion pair **9** is presumably created in the aqueous phase or the aqueous boundary layer around the organic solid and would therefore be expected to be significantly solvent-separated.[29] Combined with the greater nucleophilicity of azide, this makes the capture of **9** by azide the predominant pathway in water. The loss of some enantiomeric excess in the conversion of **1** to **4a** could be due to contributions of **10** or **11** to the reaction manifold, giving racemate and *ent*-**4a**, respectively.[30]

Condensation of racemic **1** with 2 equiv of (−)-brucine gives **16** as a ≈7:1 mixture of two diastereomers in 70% yield (Scheme 7), whereas (+)-phenethylamine adduct **4f** is formed as an approximately equal ratio of diastereomers. It is probable that some dynamic kinetic resolution of **1** with brucine occurs, but the rates of substitution vs epimerization of **1** under these conditions are not yet known. When isolated **16** is heated in refluxing water in

(23) It is noteworthy that nucleophilic attack on the episulfonium ion sulfur atom is not observed, although this pathway could contribute to the formation of small amounts of uncharacterized byproducts in some cases. Attack at sulfur under basic or neutral conditions irreversibly regenerates the olefin. Evidence exists that attack at the sulfur atom of some thiiranium ions, for nonpolarizable heteroatoms at least, is substantially slower than attack at carbon: Lucchini, V.; Modena, G.; Pasi, M.; Pasquato, L. *J. Org. Chem.* **1997**, *62*, 7018−7020. The direction of nucleophile addition to sulfur of thiiranium intermediates is a topic of some dispute. See Sølling, T. I.; Wild, S. B.; Radom, L. *Chem. Eur. J.* **2000**, *6*, 590−591. Modena, G.; Pasquato, L.; Lucchini, V. *Chem. Eur. J.* **2000**, *6*, 589−590.

(24) The calculated (MM2, Macromodel Version 5) difference in energy between isomers **1** and **10** is 4.9 kcal/mol.

(25) Calculated dipole moments were obtained by Dr. Fahmi Himo, using the density-functional method PWP91, with basis set IV in the ADF program. The following variations of structure **12** were also examined, Nuc = OH, 1.85 D; OAc, 2.45 D.

(26) Vanhessche, K.; Richardson, P., unpublished results.

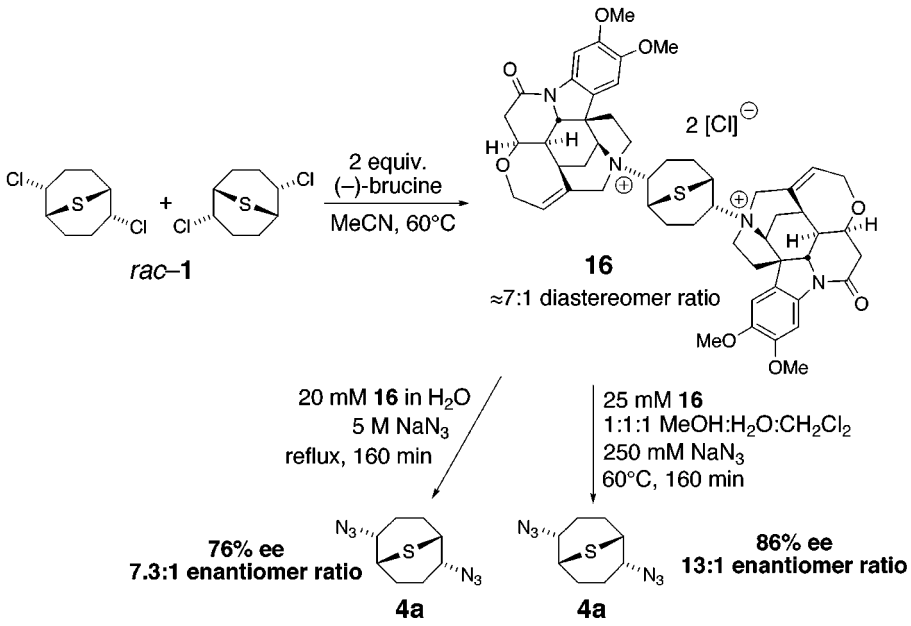
(27) The synthesis and ring opening of an enantiomerically enriched thiiranium ion has been reported: Lucchini, V.; Modena, G.; Pasquato, L. *J. Chem. Soc., Chem. Commun.* **1994**, 1565−1566.

(28) The following assumptions are applied. (i) The addition of 2-propanol and azide is irreversible under the conditions employed (both adducts are found to be stable in the presence of other nucleophiles). (ii) The formation of the bicyclo[3.3.1] skeleton is thermodynamically (and perhaps kinetically) more favorable than the bicyclo-[4.2.1] system.

(29) (a) For a theoretical treatment of the supportive role played by an aqueous medium in thiiranium ion formation and reactivity, see (a) Donovan, W. H.; White, W. E. *THEOCHEM* **1996**, *370*, 209−220. For examples of the importance of reaction medium in supporting thiiranium ion pairs, see (b) Sunko, D. E.; Jursic, B.; Ladika, M. *J. Org. Chem.* **1987**, *52*, 2299−2301. (c) Zefirov, N. S.; Sadovaya, N. K.; Novgorodtseva, L. A.; Achmedova, R. Sh.; Baranov, S. V.; Bodrikov, I. V. *Tetrahedron* **1979**, *35*, 2759−2765. (d) McManus, S. P.; Karaman, R. M.; Sedaghat-Herati, R.; Harris, J. M. *J. Org. Chem.* **1995**, *60*, 4764−4766.

(30) This analysis assumes that the dihydroxide adduct of **1** is not reversibly formed. This known[1] compound seems to resist substitution by azide and amine nucleophiles under neutral conditions, but further exploration of its chemistry is warranted.

Scheme 7. Substitution Reactions of 1 with Brucine



the presence of a large excess of sodium azide, substitution occurs with retention of enantiomeric excess to give **4a** in 76% ee (7.3:1 enantiomer ratio; Scheme 7). When the reaction is conducted under different conditions (60 °C in 1:1:1 H_2O:MeOH:CH_2Cl_2), the enantiomeric excess of the **4a** formed rises to 86% (13:1 ratio), suggesting either that brucine substitution is reversible and the two diastereomers react with azide at different rates or that the minor isomer of **16** decomposes to a greater extent during the substitution process.

In conclusion, the present work adds new examples to the pioneering studies of Weil, Corey and Block, and Lautenschlaeger et al. and highlights the remarkable powers of **1** as a platform for the diverse and reliable decoration of a saturated carbon framework. While much of the substitution chemistry discussed was done in acetonitrile solution for reasons of historical precedent, we believe that water will emerge as a superior solvent for this class of transformations, given its compatibility with reaction pathways that involve the generation of charged intermediates. Note that amines are shown here to be vastly superior to water as nucleophiles in capturing the episulfonium ions derived from **1**, resulting in clean substitution in aqueous solution. Such reactivity resembles the Schotten−Baumann acylation of amines by acid chlorides in aqueous base. The only requirement is that the nucleophile be at least marginally soluble in water so that it is available to react with the water-soluble episulfonium ion intermediate.

The potential reversibility of such reactions is demonstrated here by the racemization of enantiomerically enriched **1** (Scheme 6) and the conversions of **4c** to **4d** (Scheme 2), **5b** to **5a** to **5c** (Scheme 3), and **16** to **4a** (Scheme 7). SCl_2 (or S_2Cl_2 + SO_2Cl_2) functions as an S^{2+} equivalent, possessing reactivity analogous to two bromonium ions in one and giving adduct **1** in a single transformation, guided by thermodynamics via reversible addition−elimination steps. The substitution reactions of **1** can likewise be under thermodynamic control, depending on the nature of the nucleophile, the leaving group, and the solvent. We therefore regard the SCl_2 + COD system as being somewhat "metallic" in character, in analogy to metal−ligand bonding, which is often dominated by thermodynamic factors because facile mechanisms exist to speed the kinetics of ligand substitution.[31] Further exploration of these issues and the use of mustard electrophiles for the synthesis of combinatorial libraries, chiral ligands, and novel materials are subjects of ongoing interest in our laboratories and will be described in due course.

Experimental Section

General. All reactions were performed in air at rt with no precautions to exclude moisture, unless otherwise indicated. All reagents were purchased from standard commercial suppliers and used as received, except for SCl_2, which was doubly distilled before use. Unless otherwise noted, all chiral compounds were prepared as racemates. Enantiomerically enriched structures are represented by an arbitrary choice of absolute configuration, as no absolute configurations have been assigned. Optical rotations are given as an average with a standard deviation error range derived from three independent measurements. High-resolution mass spectrometry was performed by the Mass Spectrometry Facility at The Scripps Research Institute; elemental analyses were performed by Midwest Microlabs, Indianapolis, IN.

Synthetic Procedures and Characterization Data. 2,6-Dichloro-9-thiabicyclo[3.3.1]nonane (1). An alternative to the mole-scale synthesis of Bishop[15] is as follows. Sulfur monochloride (1.6 mL, 20 mmol) was added dropwise to a stirred solution of 1,5-cyclooctadiene (4.9 mL, 40 mmol) in dichloromethane (100 mL) at 0 °C. The reaction mixture was stirred for 1 h and then treated with sulfuryl chloride (1.6 mL, 20 mmol). After being stirred at 0 °C for 3.5 h, TLC analysis showed consumption of the starting diolefin. The organic reaction mixture was then washed 3× with brine; the organic phase was dried over $MgSO_4$; and finally, the solvent was evaporated at reduced pressure, providing **1** in 98% yield (8.3 g, 39.2 mmol) as a white solid. The enantiomers of **1** were resolved using a Chiralcel OB-H HPLC column, eluting with 98:2 hexane:2-propanol at 0.5 mL/min; retention times of 10.5 and 11.5 min. A total of 0.64 mg of the faster-eluting peak was collected and reanalyzed to confirm enantiomeric purity; $[\alpha]^{23}_D$ −124 ± 10 (*c* 1, EtOH).

(31) For an example of this type of reactivity, see Schmid, G. H.; Fitzgerald, P. H. *J. Am. Chem. Soc.* **1971**, *93*, 2547−2548.

2,6-Diamino-9-thiabicyclo[3.3.1]nonane (2a). A suspension of sulfide **1** (200 mg, 0.95 mmol) in 4 mL of aqueous ammonia was stirred for 7 h at rt. The organic aqueous suspension was extracted 4× with CH_2Cl_2. Evaporation of the organic layer gave 153 mg (0.89 mmol, 94% yield) of **2a** as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (bs, 4H), 1.57 (m, 2H), 1.87 (m, 2H), 2.07 (m, 2H), 2.36 (m, 2H), 2.45 (bs, 2H), 3.42 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.1, 31.9, 38.1, 53.4. HRMS (FAB$^+$) calcd for $C_8H_{14}NS$ (episulfonium ion from protonation and loss of NH_3) 156.0847; found, 156.0840.

2,6-Dimethylamino-9-thiabicyclo[3.3.1]nonane (2b). A suspension of sulfide **1** (200 mg, 0.95 mmol) in 4 mL of aqueous methylamine (40% w/w) was stirred for 16 h at rt. The organic aqueous suspension was extracted 4× with CH_2Cl_2. Evaporation of the organic layer gave 171 mg (0.86 mmol, 90% yield) of **2b** as a colorless liquid. Characterization data are presented in Supporting Information.

2,6-Dimorpholino-9-thiabicyclo[3.3.1]nonane (2c). To a stirred solution of **1** (500 mg, 2.36 mmol) in acetonitrile (8 mL) was added 2 equiv of morpholine (411 mg, 4.72 mmol) and 2 equiv of K_2CO_3 (655 mg, 4.73 mmol). The reaction was stirred overnight at rt, filtered to remove insoluble salts, and evaporated to give 495 mg (1.59 mmol, 67% yield) of **2c** as a slightly orange solid, mp 145−147 °C. Characterization data are presented in Supporting Information.

2,6-Diadamantylamino-9-thiabicyclo[3.3.1]nonane (2d). Preparation was performed as for **2c**, with 2 equiv of 1-adamantylamine (716 mg, 4.73 mmol). **2d** was obtained as a white solid (0.876 g, 1.99 mmol, 84% yield), mp 271 °C dec. Characterization data are presented in Supporting Information.

2,6-Dibenzylamino-9-thiabicyclo[3.3.1]nonane (2e). To a stirred solution of sulfide **1** (3.0 g, 17.4 mmol) in 65 mL of CH_3CN was added 3.81 mL (34.9 mmol, 2 equiv) of benzylamine and 4.82 g (34.9 mmol, 2 equiv) of K_2CO_3. The reaction was stirred for 16 h at rt. Filtration and evaporation provided 6.0 g (17.0 mmol, 98% yield) of **2e** as a crystalline, white solid, mp 99−100 °C. Characterization data are presented in Supporting Information.

2,6-Diphenethylamino-9-thiabicyclo[3.3.1]nonane (2f). Preparation was performed as for **2c**, with 2 equiv of phenethylamine (611 μL, 4.73 mmol). **2f** was obtained as a white solid (0.540 g, 1.42 mmol, 60% yield), mp 122−124 °C. Characterization data are presented in Supporting Information.

2,6-Dianilino-9-thiabicyclo[3.3.1]nonane (2g). Preparation was performed as for **2c**, with 2 equiv of aniline (431 μL, 4.73 mmol). **2g** was obtained as a white solid (0.752 g, 2.41 mmol, 98% yield), mp 222−223 °C. Characterization data are presented in Supporting Information.

2,6-Di-*p*-toluenesulfonamido-9-thiabicyclo[3.3.1]-nonane (2h). To a stirred solution of sulfide **1** (200 mg, 0.95 mmol) in 3.5 mL of CH_3CN was added 324 mg (2 equiv, 1.89 mmol) of *p*-toluenesulfonamide and 261 mg (2 equiv, 1.89 mmol) of K_2CO_3. The reaction was stirred for 16 h at rt. Filtration and evaporation gave 432 mg (0.90 mmol, 95% yield) of **2h** as a crystalline, white solid, mp 230−233 °C. Characterization data are presented in Supporting Information.

2,6-Dimethoxy-9-thiabicyclo[3.3.1]nonane (3a). 1 (500 mg, 2.36 mmol) was dissolved in a freshly prepared solution of NaOMe (using 164 mg of Na, 7.13 mmol, 3 equiv) in methanol (8 mL) and stirred overnight at rt. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2 and washed with brine 3×. The organic solution was dried over $MgSO_4$, and the solvent was evaporated to afford pure **3a** (339 mg, 2.13 mmol, 71% yield) as a slightly yellow oil. Characterization data are presented in Supporting Information.

2,6-Diphenoxy-9-thiabicyclo[3.3.1]nonane (3b). To a stirred solution of sulfide **1** (500 mg, 2.37 mmol) in 10 mL of CH_3CN was added 416 μL (2 equiv, 4.73 mmol) of phenol and 655 mg (2 equiv, 4.73 mmol) of K_2CO_3. The reaction was stirred for 16 h at rt. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2 and washed with brine 3×. The organic solution was dried over $MgSO_4$, and the solvent was evaporated to afford pure **3b** (578 mg, 2.13 mmol, 75% yield) as a white solid, mp 146−148 °C. Characterization data are presented in Supporting Information.

Racemization during Preparation of 2,6-Diisopropoxy-9-thiabicyclo[3.3.1]nonane (3c). Pure (+)-2,6-dichloro-9-thiabicyclo[3.3.1]nonane (**1***) was stirred in 2-propanol for 40 h in the presence of 2 equiv of K_2CO_3. Chiral HPLC analysis of the reaction mixture showed the production of racemic bis-(isopropoxide) adduct and *rac*-**1**.

2,6-Diazido-9-thiabicyclo[3.3.1]nonane (4a). Sodium azide reacts readily with **1** at rt in DMF solvent. However, the following aqueous-phase procedure at reflux provides better yields because of a more convenient workup. To a solution of NaN_3 (1.95, 30.0 mmol) in 20 mL of water was added 2.11 g (10.0 mmol) of sulfide **1**. The suspension was refluxed for 2 h and then cooled, and the suspended material was dissolved by the addition of CH_2Cl_2. The layers were separated, and the aqueous phase was extracted three more times with CH_2Cl_2. Evaporation of the combined organic layers gave 2.15 g (28.8 mmol, 96%) of **4a** as a transparent oil. Characterization data are presented in Supporting Information. Compound **4a** was resolved by HPLC on a Chiralcel OB-H column eluting with 5% iPrOH in hexane (0.5 mL/min). A total of 1.3 mg of each enantiomer was collected from 10 15-μL injections of a 33 mg/mL solution of the racemate. For the faster-eluting fraction, $[\alpha]^{23}_D$ −39.0 ± 1.2 (*c* 1.00, CH_2Cl_2).

2,6-Difluoro-9-thiabicyclo[3.3.1]nonane (4b). 1 (1.00 g, 4.74 mmol) and AgF (1.2 g, 9.48 mmol) were stirred at rt in acetonitrile solvent (16 mL) for 16 h. Filtration and evaporation of the solvent gave **4b** (800 mg, 4.50 mmol, 95% yield) as a pure, white solid. Characterization data are presented in Supporting Information.

2,6-Dithiocyano-9-thiabicyclo[3.3.1]nonane (4c). To a solution of sodium thiocyanate (4.8 g, 59.2 mmol) in 90 mL of water was added 5.0 g (23.7 mmol) of sulfide **1**. The suspension was stirred for 20 h at rt, and the mixture was extracted 4× with CH_2Cl_2. Evaporation of the organic solutions and recrystallization of the residue from methyl ethyl ketone gave 5.12 g (49.7 mmol, 84%) of **4c** as a crystalline, white solid, mp 106−107 °C. Characterization data are presented in Supporting Information.

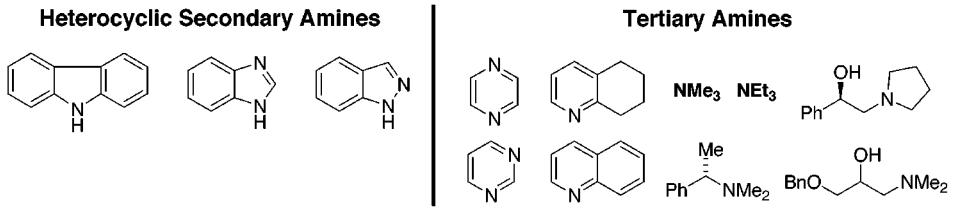
2,6-Diisothiocyano-9-thiabicyclo[3.3.1]nonane (4d). To a solution of sodium thiocyanate (253 mg, 3.13 mmol) in 5 mL of water was added 263 mg (1.25 mmol) of sulfide **1**. The suspension was refluxed for 20 h, and the mixture was extracted 4× with CH_2Cl_2. Evaporation of the organic layer and recrystallization from methyl ethyl ketone gave 278 mg (1.09 mmol, 87%) of **4d** as a crystalline, white solid, mp 142−143 °C. Characterization data are presented in Supporting Information.

Representative Procedure for Synthesis of Tertiary Amine and Pyridine Adducts (Figure 1). Sulfide **1** (1.00 g, 4.74 mmol) and quinuclidine (1.06 g, 9.5 mmol, 2 equiv) were heated at 60 °C in acetonitrile (20−30 mL) overnight. After being cooled to rt, the precipitate was collected and washed with cold acetonitrile or hexane to afford pure **5a** (1.09 g, 53%). For all adducts of this type, isolated yields varied between 50 and 80%, depending on the extent of precipitation. In each case, NMR showed the desired product to also constitute the large majority of the material remaining in the mother liquor, but we did not optimize yields by purification of the residue obtained by evaporation of the solvent. These salts may be purified by dissolution in water followed by precipitation of the PF_6 salt by addition of an aqueous solution of $NaPF_6$.

Characterization data for **5a**−**h** are presented in Supporting Information. The X-ray crystal structure of 2,6-dipyridinium-9-thiabicyclo[3.3.1]nonane dichloride (**5c**) is shown in Figure S1 of the Supporting Information.[18] Tertiary and heterocyclic amines that fail to give adducts of **1** are shown in Chart 1.

2,6-Dichloro-9-thiabicyclo[3.3.1]nonane 9-Oxide (6). To a stirred solution of sulfide **1** (25 g, 118 mmol) in 250 mL of CH_2Cl_2 was added 23.8 g (130 mmol, 1.1 equiv) of *m*-chloroperbenzoic acid at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and filtered. The filtrate was extracted consecutively with aqueous $Na_2S_2O_5$ and aqueous NaOH and

Chart 1. Nucleophiles that Fail to Add to 1



then dried over Na_2SO_4. Evaporation of the solvent gave 26 g (113 mmol, 96%) of **6** as a crystalline, white solid, mp 120−121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81 (m, 2H), 2.17 (m, 4H), 2.57 (m, 2H), 3.26 (bs, 1H), 3.31 (bs, 1H), 4.35 (m, 1H), 4.95 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.9, 20.8, 30.8, 52.2, 54.0, 56.0. HRMS (FAB$^+$) calcd for $C_{24}H_{20}N_2O_4SNa^+$ [(M + Na)$^+$], 455.1041; found, 455.1037.

2-Azido-6-chloro-9-thiabicyclo[3.3.1]nonane 9-Oxide (7). To a stirred solution of sulfoxide **6** (4.00 g, 176 mmol) in 70 mL of dimethylformamide was added 3.88 g (881 mmol) of sodium azide. The reaction mixture was stirred for 16 h at 120 °C and filtered. After removal of DMF under vacuum, the solid was eluted through a short silica column with 1% methanol in ethyl acetate. Evaporation of the solvent provided 3.78 g (162 mmol, 92%) of **7** as a crystalline, white solid, mp 83−84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78 (m, 2H), 2.12 (m, 4H), 2.49 (m, 1H), 2.75 (m, 1H), 3.18 (bs, 1H), 3.36 (bs, 1H), 4.31 (s, 1H), 4.93 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4, 19.9, 24.6, 30.0, 52.0, 52.8, 54.0, 62.5. HRMS (FAB$^+$) calcd for $C_8H_{12}ClN_3OSNa^+$ [(M + Na)$^+$], 256.0287; found, 256.0281.

1-(6-Chloro-9-oxo-9λ^4-thiabicyclo[3.3.1]non-2-yl)-1*H*-[1,2,3]triazole 4,5-Dicarboxylic Acid Dimethyl Ester (8). To a stirred solution of azide **7** (385 mg, 1.65 mmol) in 3.3 mL of toluene was added 257 mg (1.81 mmol) of dimethylacetylene dicarboxylate. The reaction mixture was stirred for 5 h at 95 °C and filtered through a short silica column (EtOAc). Evaporation of the solvent provided 570 mg (1.52 mmol, 92%) of **8** as a crystalline, pale yellow solid, mp 127−128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.99 (m, 2H), 2.34 (m, 2H), 2.58 (m, 2H), 2.70 (m, 1H), 2.80 (m, 1H), 3.31 (bs, 1H), 3.51 (bs, 1H), 3.93 (s, 3H), 3.95 (s, 3H), 4.93 (m, 1H), 5.57 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1, 21.1, 24.7, 29.3, 52.0, 52.3, 52.9, 53.6, 53.9, 60.9, 128.4, 140.5, 158.9, 160.4. HRMS (FAB$^+$) calcd for $C_{14}H_{18}ClN_3O_5SNa^+$ [(M + Na)$^+$], 398.0553; found, 398.0550.

2,6-Di-(−)-brucine-9-thiabicyclo[3.3.1]nonane Dichloride (16). 1 (2.00 g, 9.47 mmol) and (−)-brucine (7.51 g, 19.0 mmol) in 40 mL of acetonitrile were heated at 60 °C for 6 h. The reaction mixture was cooled, and the adduct **16** was isolated as an off-white solid by filtration and washing with cold acetonitrile (6.58 g, 70%), mp 182−183 °C. NMR shows the compound to be a mixture of diastereomers in approximately a 7:1 ratio; the peaks listed here are for the major diastereomer. ^{1}H NMR (600 MHz, CD_3OD): δ 1.51 (bd, J = 11.0, 2H), 1.81 (bd, J = 15.0, 2H), 2.19−2.31 (m, 4H), 2.67−2.70 (m, 6H), 2.82−2.93 (m, 4H), 2.94−3.07 (m, 4H), 3.43 (bs, 2H), 3.67 (bdd, J = 12.1, 7.3, 2H), 3.74 (s, 2H), 3.82 (m, 6H), 3.88 (s, 12H), 4.12−4.23 (m, 8H), 4.31 (dd, J = 0.14.3, 6.2, 2H), 4.40−4.42 (m, 2H), 4.46 (d, J = 12.1, 2H), 4.99 (bs, 2H), 6.53 (bs, 2H), 7.11 (s, 2H), 7.74 (s, 2H). ^{13}C NMR (150 MHz, CD_3OD): δ 24.0, 25.8, 26.3, 30.9, 31.2, 31.6, 32.5, 40.2, 43.5, 47.8, 48.7, 52.7, 56.6, 57.7, 60.9, 63.3, 65.0, 73.9, 79.1, 102.3, 108.4, 121.6, 137.3, 138.3, 148.2, 152.0, 171.3.

Azide Substitution of 16. Reactions were performed under nitrogen atmosphere using the concentrations of reagents specified in Scheme 7. The crude reaction mixtures were analyzed directly by chiral HPLC, and assignments were confirmed by co-injection of authentic samples of *rac*-**4a** and by GC/MS analysis. Conversion to **4a** is the dominant reaction, but yields were not determined. The major enantiomer formed is the faster-eluting one on HPLC, which is the (−)-enantiomer.

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Supporting Information Available: Characterization data for **2b**−**h**; **3a,b**; **4b**−**d**; and **5a**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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