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Toward the Synthesis of *Nuphar* Sesquiterpene Thioalkaloids: Stereodivergent Rhodium-Catalyzed Synthesis of the Thiolane Subunit

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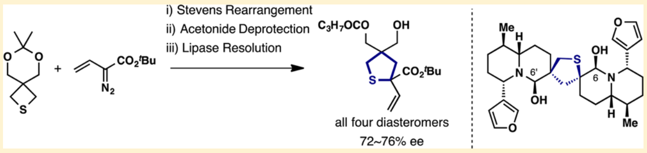
Supporting Information

ABSTRACT: A stereodivergent approach to the central thiolane subunit of *Nuphar* sesquiterpene thioalkaloids has been developed. This approach features a rhodium-catalyzed Stevens-type rearrangement in conjunction with an enzyme resolution reaction. Further elaboration into a polycyclic ring system via alcohol oxidation and ring-closing metathesis is also described.



INTRODUCTION

Nupharis rhizoma has been used as a tonic, diuretic, and a remedy for blood stasis syndrome in Chinese and Japanese traditional medicine. Various alkaloids have been isolated from the rhizome of *Nuphar japonicum* and *Nuphar pumilum* (T_{IMM}.) DC, including three types of dimeric sesquiterpene thioalkaloids (Figure 1). In 1965, Birnbaum corrected the structure of neothiobinupharidine (**3**),[1] first isolated by Achmatowicz a year earlier,[2] via X-ray crystallographic diffraction. In the 1970s, LaLonde carried out extensive structural elucidation of these dimeric sesquiterpene thioalkaloids, especially thiohemiaminal-type congeners, and also insightfully proposed their biogenesis from monomeric sesquiterpene alkaloids.[3] Despite their long history, the remarkable biological activities of these higher thioalkaloids were not discovered until the 2000s. Yoshikawa and co-workers found that 6-hydroxy group on the quinolizidine ring within hemithioaminal structure is essential for the potent antimetastatic and apoptosis-inducing activity. 6-Hydroxythiobinupharidine (**1b**), 6,6′-dihydroxythiobinupharidine (**1c**), and 6-hydroxythionuphlutine B (**2**) potently inhibited the invasion of the collagen matrix by B16 melanoma cells with an IC_{50} value of 29−360 nM in vitro.[4] In addition, 6-hydroxythiobinupharidine (**1b**) inhibited tumor growth in mice by more than 90% and induced apoptosis of human leukemia U973 cells in 1 h in vitro.[5] More recently, Gopas and co-workers reported that extracts of leaf and rhizome from *Nuphar lutea* inhibited the nuclear factor κB (NFκB) pathway. The active ingredient was identified as a mixture consisting primarily of the hydroxylated members 6-hydroxythionupharidine (**1b**) and 6-hydroxythionuphlutidine B (**2**).[6]

Despite numerous syntheses of the monomeric sesquiterpene alkaloids in the *Nuphar* alkaloid family,[7] only one synthesis of a dimeric sesquiterpene thioalkaloid has been reported to date, arguably due to the challenge in constructing the central 2,2,4,4-tetrasubstituted thiolane (tetrahydrothiophene) uniting the two quinolizidine units. On the foundation of the LaLonde biosynthetic hypothesis, Shenvi and co-workers reported an elegant total synthesis of neothiobinupharidine **3** featuring a late-stage biomimetic installment of the tetrahydrothiophene ring in 2013.[8]

Our goal was to develop a synthetic strategy allowing access to all four types of dimeric sesquiterpene alkaloids at varying oxidation states, especially members with the biologically essential 6-hydroxy group. A combination of the same monomeric amine precursor and all four diastereomers of a 2,2,4,4-tetrasubstituted thiolane should provide the complete diastereomeric series of sesquiterpene alkaloids **1**−**4**. We developed our synthesis plan in line with this analysis as depicted in Scheme 1. A straightforward ring-closing metathesis (RCM) disconnection, followed by amide cleavage of **5** led to piperidine **6** and tetrahydrothiophene **7**. Herein, we report a stereodivergent synthesis of the four diastereomers of 2,2,4,4-tetrasubstituted thiolane subunit **7**.

Substituted thiolanes themselves exhibit a broad spectrum of biological activity and are also used as versatile ligands in organic and organometallic chemistry.[9] Despite their useful properties, few examples of asymmetric syntheses of substituted thiolanes have been reported. Overman and Ponce reported stereocontrolled synthesis of substituted thiolanes by acid-promoted pinacol rearrangement of mercapto allylic alcohols with aldehydes or ketones.[10] The Jørgensen, Wang, and Xu groups have published enantioselective organocatalytic syntheses of substituted tetrahydrothiophenes by Michael−Michael or Michael−aldol cascade reactions.[11] However, no precedent for the enantioselective synthesis of tetrahydrothiophenes incorporating two tetrasubstituted carbon centers has been reported thus far.

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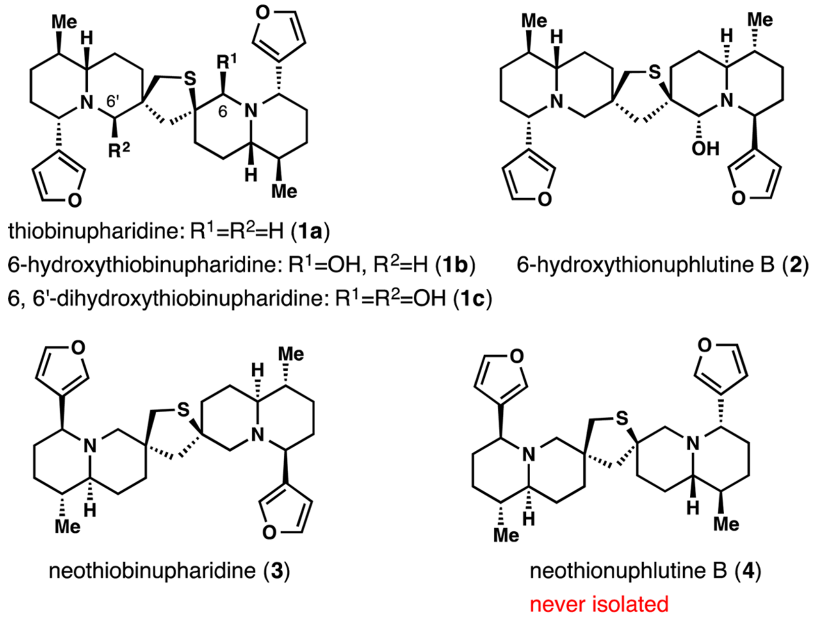


thiobinupharidine: R^1=R^2=H (**1a**)

6-hydroxythiobinupharidine: R^1=OH, R^2=H (**1b**)

6, 6'-dihydroxythiobinupharidine: R^1=R^2=OH (**1c**)

6-hydroxythionuphlutine B (**2**)

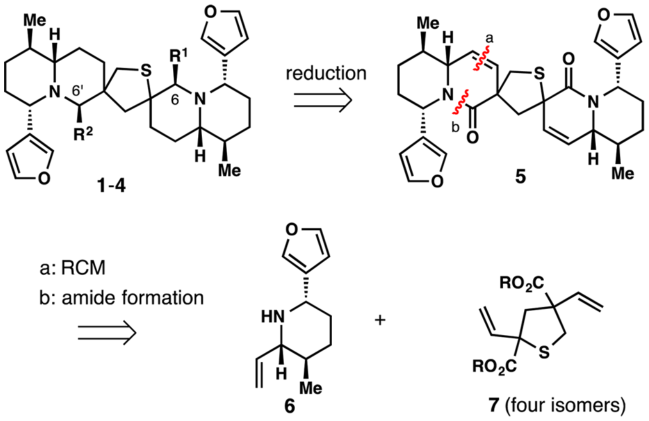
neothiobinupharidine (**3**)

neothionuphlutine B (**4**)

never isolated

Figure 1. Structures of dimeric sesquiterpene *Nuphar* thioalkaloids (1−4).

Scheme 1. Synthesis Plan for *Nuphar* Sesquiterpene Alkaloids 1−4

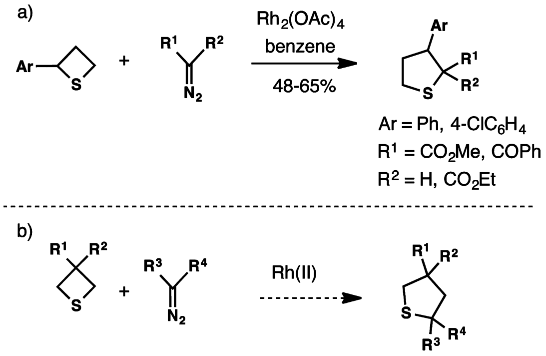


RESULTS AND DISCUSSION

Our first synthetic approach to 2,2,4,4-tetrasubstituted thiolanes involved a double functionalization of 2,4-disubstituted thiolane **8** (Scheme 2). The reaction of methyl 2-(bromomethyl)acrylate and methyl 2-mercaptoacetate afforded 2,4-dimethoxycarbonyl tetrahydrothiophene **8** in high yield (60% yield over two steps, dr 1.4:1) under basic conditions. However, in preliminary test experiments, attempted double enolization of diester **8** under various basic conditions (LDA or $LN(SiMe_3)_2$ in THF or diethyl ether at −78 °C, followed by trapping with Me_3SiCl, was unsuccessful, resulting mostly in untractable mixture of decomposition products.

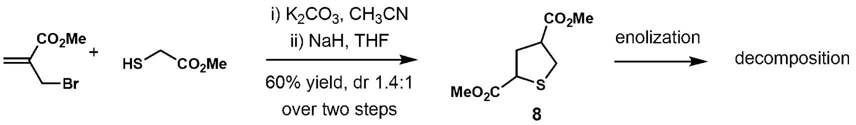
Failure to achieve clean double enolization of diester **8** prompted a change in approach. Thus, we turned our attention to an alternative based on Stevens rearrangement reaction. A literature search revealed a single precedent by the Nair group, who reported a few examples for tetrahydrothiophene formation from diethyl diazomalonate and thietane utilizing a rhodium-catalyzed Stevens rearrangement (Scheme 3a).[12] We postulated that the desired 2,2,4,4-tetrasubstituted thiolanes could be conveniently accessed by ring expansion from 3,3-disubstituted thietanes. Additionally, the expected lack of diastereoselectivity in the ring expansion reaction could provide a divergent approach to all four thiolane stereoisomers at the core of thioalkaloids **1**−**4**.

Scheme 3. Rhodium-Catalyzed Stevens Rearrangement: Precedence (a) and Plan (b)

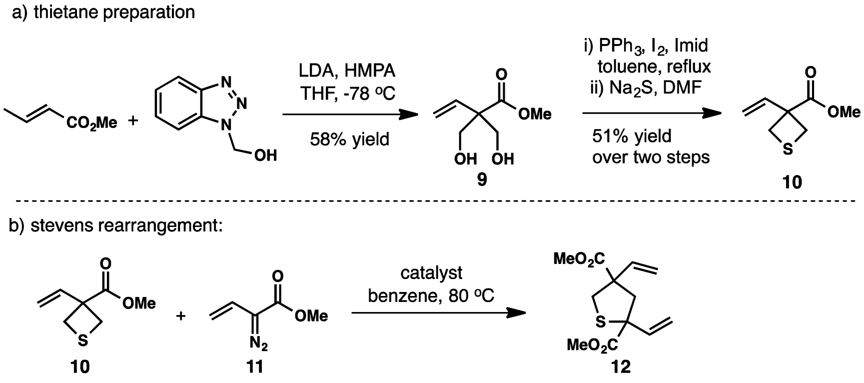


A double-aldol reaction of methyl crotonate with 1-hydroxymethylbenzotriazole, forming formaldehyde in situ, gave diol **9** in 58% yield (Scheme 4a).[13] Subsequent iodination and ring-closing substitution with sodium sulfide readily

Scheme 2. Synthesis of Thiolane 8

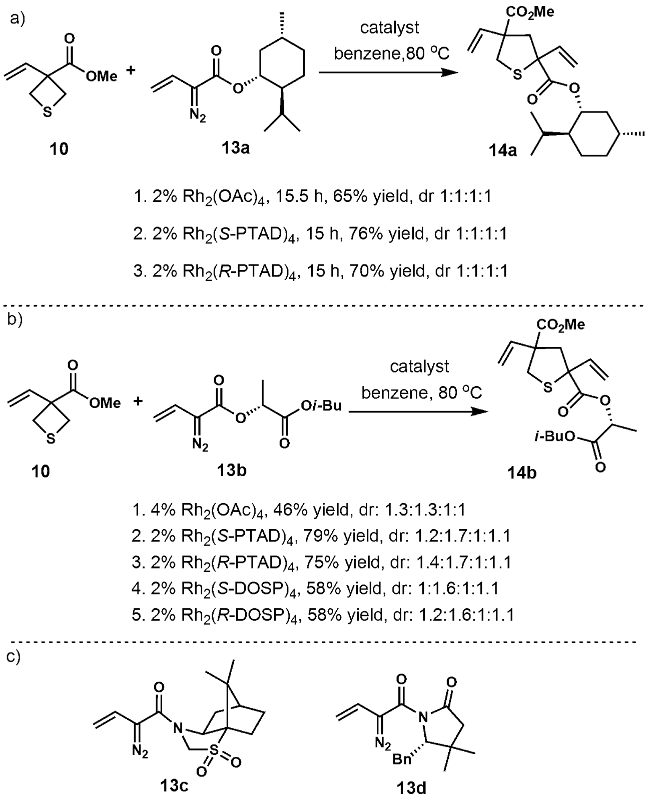


Scheme 4. Synthesis of Thietane 10 and Thiolane 12



1. 2% $Rh_2(OAc)_4$, 20 h, dr 1:1, 71% yield
2. 2% Rh_2(S-DOSP)$_4$, 14 h, dr 1:1, 50% yield, ee: 0%.
3. 2% Rh_2(S-PTAD)$_4$, 14 h, dr 1:1, 50% yield, ee: 0%.

Scheme 5. Studies of Diazo Compounds with Chiral Auxiliaries in Stevens Rearrangemnt



a)

1. 2% $Rh_2(OAc)_4$, 15.5 h, 65% yield, dr 1:1:1:1
2. 2% Rh_2(*S*-PTAD)$_4$, 15 h, 76% yield, dr 1:1:1:1
3. 2% Rh_2(*R*-PTAD)$_4$, 15 h, 70% yield, dr 1:1:1:1

b)

1. 4% $Rh_2(OAc)_4$, 46% yield, dr: 1.3:1.3:1:1
2. 2% Rh_2(*S*-PTAD)$_4$, 79% yield, dr: 1.2:1.7:1:1.1
3. 2% Rh_2(*R*-PTAD)$_4$, 75% yield, dr: 1.4:1.7:1:1.1
4. 2% Rh_2(*S*-DOSP)$_4$, 58% yield, dr: 1:1.6:1:1.1
5. 2% Rh_2(*R*-DOSP)$_4$, 58% yield, dr: 1.2:1.6:1:1.1

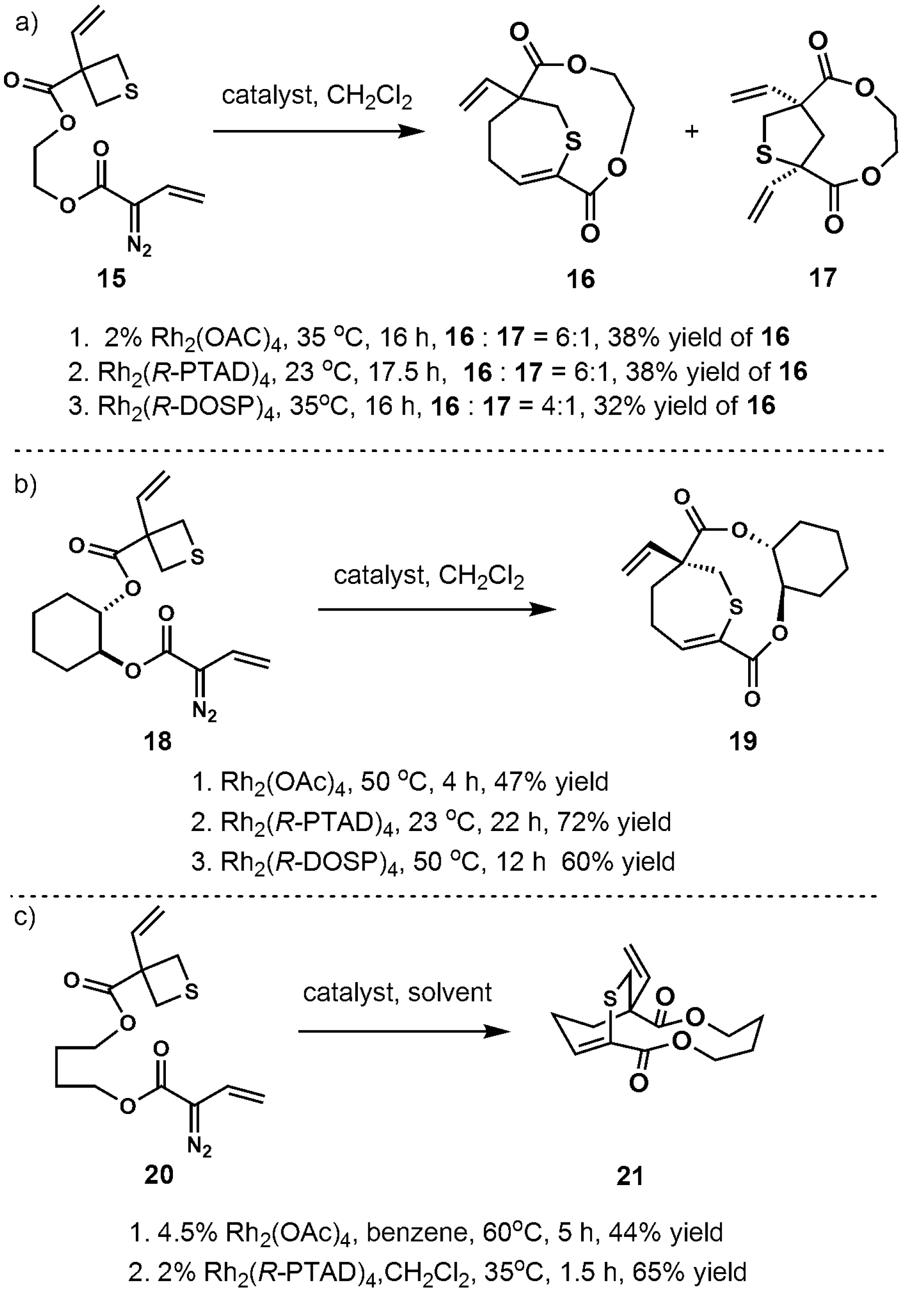
afforded thietane **10**. In the presence of 2% $Rh_2(OAc)_4$, the reaction of thietane **10** with methyl 2-diazo-3-butenoate **11** directly provided requisite thiolane **12** in 71% yield with a 1:1 diastereomeric ratio (Scheme 4b).[14] Of note, neither Rh_2(*S*-DOSP)$_4$ nor Rh_2(*S*-PTAD)$_4$ gave enantioenriched product.[15] Only trace amount of product could be obtained using CuOTf and (*S*,*S*)-2,2′-isopropylidenebis(4-phenyl-2-oxazoline) ligand. We did not observe the formation of cyclopropane products as far as could be concluded from ^{1}H NMR spectra of the crude mixture of products.

We next turned to chiral auxiliaries to effect asymmetric Rh-catalyzed Stevens-type ring expansion of 3,3-disubstituted thietanes. First, menthol derivative **13a** was prepared (Scheme 5a). The reaction of thietane **10** with **13a** was not diastereoselective even with chiral catalysts. The Davies group reported that the use of lactate as a chiral auxiliary showed remarkable asymmetric induction in cyclopropanation with rhodium(II) vinylcarbenoids.[16] This was rationalized by the interaction between the carbonyl oxygen of the chiral auxiliary and the carbenoid carbon. However, the reaction of **13b** with thietane **10** gave low diastereoselectivity with either achiral or chiral catalysts (Scheme 5b). Reduction of **14b** gave the corresponding diols in a 1.2−1.4:1 diastereomeric ratio in all cases. Diazo compounds **13c** and **13d** gave none of the expected thiolanes under the reaction conditions (Scheme 5c).

Since no selectivity was observed in the *inter*molecular Stevens-type rearrangement reaction, the intramolecular version was examined. We postulated that due to conformational constraints this type of approach could deliver useful levels of diastereoselectivity. When ethylene-tethered **15** was tested, thiepane **16** generated by a formal [1,4]-rearrangement was the major product, along with a trace amount of **17** as single diastereomer, somewhat validating the hypothesis but revealing a new problem of regiocontrol (Scheme 6a). Diester **18** derived from *trans*-1,2-cyclohexanediol was synthesized to effect a stricter conformational control (Scheme 6b). In the presence of Rh_2((*R*)-PTAD)$_4$, the reaction of **18** delivered **19** as a single diastereomer in 74% yield even at 23 °C. The relative configuration of **19** was unambiguously established by single crystal X-ray diffraction.[17] Elongating the tether did not lead to improvement in regiocontrol (Scheme 6c).

Desymmetrization is a powerful tool for the preparation of enatiomerically pure substrates.[18] Efficient desymmetrization of a prochiral carbon center in a racemic substrate would give two diastereomers with high enantiomeric excess. In line with this analysis, diol **25** was prepared in two steps via Stevens rearrangement of **22** with diazo ester **23** and subsequent removal of acetonide (Scheme 7a). Although the copper-catalyzed desymmetrization reaction gave 40% ee at best,[19] enzyme-mediated reaction afforded the desired diastereomers **26a** and **26b** with very good enantiometric excess after optimization. In the presence of Novozym 435, diastereomers **26a** and **26b** could be isolated in 91% combined yield with a nearly 1:1 diastereomeric ratio and 76% ee each (Scheme 7b). The relative configuration of **26a** was determined by NOE studies (see the Supporting Information for details). In addition, ***ent*-26a** and ***ent*-26b** could also be efficiently prepared using enzyme lipase AK. Thus, all four stereoisomers of

Scheme 6. Intramolecular Rearrangement Reaction of Thietane



thiolane **26** could be divergently accessed based on the choice of enzyme (Scheme 7c). Swern oxidation, Wittig reaction, and subsequent hydrolysis of ***ent*-26** provided two readily separable dienes **27a** and **27b** smoothly.

Our broader plans for the synthesis of *Nuphar* thioalkaloids call for a late-stage double ring-closing metathesis with a functionalized precursors containing the central thiolane nucleus. To assess compatibility of the RCM reaction with the cyclic sulfide group, diester *trans*-**12** was first advanced to bisallylic ether **28** in two steps by reduction with $LiAlH_4$ and *O*-allylation with allyl bromide and sodium hydride (Scheme 8). Gratifyingly, upon treatment with 5% of Grubbs II catalyst in benzene at 80 °C,[20] tricyclic substrate **29** was isolated in 87% yield, showing no indication of sulfur poisoning of the ruthenium catalyst.[21]

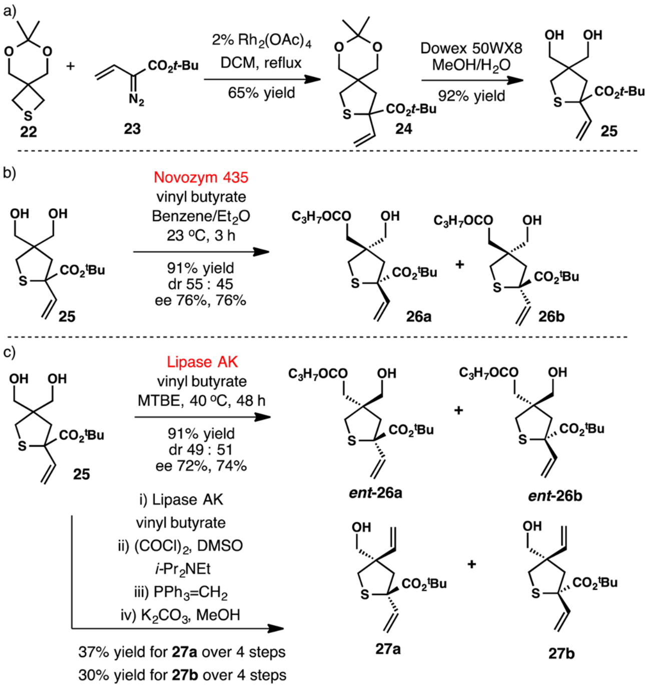
■ CONCLUSION

In conclusion, we have developed a feasible synthesis of all four stereoisomers of thiolane **26** basen on Stevens-type ring expansion of readily available thietanes to 2,2,4,4-tetrasubstituted thiolanes followed by enzyme-mediated desymmetrization reactions. Application of this general approach to the divergent total synthesis of diastereomeric *Nuphar* thioalkaloids is currently under investigation.

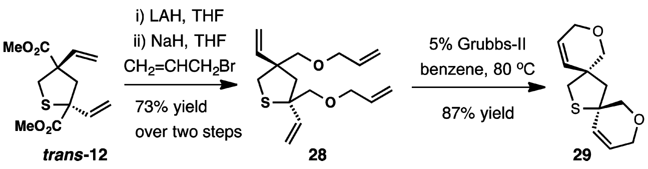
■ EXPERIMENTAL SECTION

General Information. All reactions were carried out under an inert atmosphere of dry argon in oven or flame-dried glassware, unless the reaction procedure states otherwise. Tetrahydrofuran (THF) and ether (diethyl ether) were distilled from sodium benzophenone in a continuous still under an atmosphere of argon. Dichloromethane, diisopropylamine, and triethylamine were distilled from calcium

Scheme 7. Enzyme-Mediated Desymmetrization of Diol



Scheme 8. Synthesis of Tricyclic Compound 29



hydride in a continuous still under an atmosphere of argon. Analytical thin-layer chromatography (TLC) was performed using precoated TLC plates with Silica Gel 60 F_{254} and visualized using combinations of UV, anisaldehyde, ceric ammonium molybdate (CAM), potassium permanganate, and iodine staining. Flash column chromatography was preformed using 40−63 mm silica gel as the stationary phase. Proton nuclear magnetic resonance spectra were recorded at 400, 500, and 600 MHz. Carbon nuclear magnetic resonance spectra were recorded at 100, 125, and 150 MHz on various NMR spectrometers. All chemical shifts were reported in δ units relative to tetramethylsilane. Optical rotations were measured on a polarimeter. High-resolution mass spectral data were obtained using ESI with TOF mass analyzer. Enantiomeric excess was determined by chiral HPLC analysis using a range of columns with a chiral stationary phase (250 mm × 4.6 mm, 4.6 μm particle size, ~1.0 mL/min flow rate). Compounds **14a,b** were prepared by a reported procedure.[22]

*Methyl 2,2-Bis(hydroxymethyl)but-3-enoate (**9**).* A solution of *n*-BuLi (46.2 mL, 2.25 M in hexanes, 0.104 mol) was added dropwise to a solution of *i*-Pr_2NH (14.8 mL, 10.7 g, 0.106 mol) in THF (100 mL) at −78 °C. After being stirred at this temperature for 30 min, hexamethylphosphoramide (17.4 mL, 0.100 mol) was added. The resultant mixture was stirred for further 30 min before methyl crotonate (2.1 mL, 19.8 mmol) was added. After being stirred for 30 min, a solution of 1-hydroxymethylbenzotriazole (8.95 g, 60.0 mmol) in THF (250 mL) was then added via syringe pump over 1 h. After being stirred for an additional 5 h, the reaction was quenched with a saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (eluent: 20−30% ethyl acetate in hexanes) to afford diol **9** (1.84 g, 11.5 mmol, 58%). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.74 (dd, *J* = 17.8, 11.1 Hz, 1H), 5.26 (d, *J* = 11.0 Hz, 1H), 5.15 (d, *J* = 17.8 Hz, 1H), 4.05 (d, *J* = 11.4 Hz, 2H), 3.86 (d, *J* = 11.4 Hz, 2H), 3.77 (s, 3H), 2.83 (brs, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 174.0, 133.9, 117.8, 66.3, 55.7, 52.4. HRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_7H_{12}O_4Na$ 183.0633, found 183.0622.

*Methyl 3-Vinylthietane-3-carboxylate (**10**).* Triphenylphosphine (0.314 g, 1.20 mmol) was added to a solution of iodine (0.305 g, 1.20 mmol) in toluene (4.0 mL) at 23 °C. After being stirred for 30 min, a solution of diol **9** (80.0 mg, 0.499 mmol) in toluene (1.0 mL) was added, followed by imidazole (81.7 mg, 1.20 mmol). The resultant mixture was then heated at 100 °C for 2.5 h. After cooling, the reaction mixture was diluted with hexanes, filtered, and rinsed with hexanes. The combined organic phase was concentrated, and the residue was purified by column chromatography on silica gel (eluent: 2% ethyl acetate in hexanes) to afford methyl 2,2-bis(iodomethyl)but-3-enoate (0.153 mg, 0.403 mmol, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.86 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.35 (d, *J* = 10.8 Hz, 1H), 5.25 (d, *J* = 17.6 Hz, 1H), 3.77 (s, 3H), 3.74 (d, *J* = 10.3 Hz, 2H), 3.58 (d, *J* = 10.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 169.0, 136.0, 118.6, 53.1, 52.3, 12.6. The diiodide was directly used to the next step without further characterization.

A solution of the above diiodide (0.142 g, 0.374 mmol) and $Na_2S\cdot 9H_2O$ (0.101 g, 0.421 mmol) in DMF (1.6 mL) was heated at 100 °C for 14 h. After cooling, the reaction mixture was diluted with water and extracted with diethyl ether. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (eluent: 2% ethyl acetate in hexanes) to afford thietane **10** (37.2 mg, 0.235 mmol, 63% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.06 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.28 (d, *J* = 10.6 Hz, 1H), 5.27 (d, *J* = 17.2 Hz, 1H), 3.76 (s, 3H), 3.71 (d, *J* = 9.6 Hz, 2H), 3.25 (d, *J* = 9.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 174.0, 138.1, 115.2, 54.9, 52.6, 33.1. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_7H_{10}O_2S$ 158.0402, found 158.0405.

*Dimethyl 2,4-Divinyltetrahydrothiophene-2,4-dicarboxylate (**12**).* To a solution of thietane **10** (31.6 mg, 0.200 mmol) and $Rh_2(OAc)_4$ (1.8 mg, 4.07 μmol) in benzene (1.5 mL) was added a solution of diazo **11** (50.4 mg, 0.400 mmol) in benzene (0.8 mL) via syringe pump over 0.5 h at 80 °C. The resultant mixture was stirred for a further 20 h. After cooling, the solvent was removed, and the residue was purified by column chromatography on silica gel (eluent: 5−10% ethyl acetate in hexanes) to afford tetrahydrothiophene **12** (36.4 mg, 0.142 mmol, dr 1:1, 71% yield). For characterization, *trans*-**12** could be partially separated as a pure diastereomer, while *cis*-**12** was isolated with *trans*-**12** as 2.3:1 mixture. *trans*-**12**. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.98 (dd, *J* = 16.8, 10.3 Hz, 1H), 5.91 (dd, *J* = 17.5, 10.6 Hz, 1H), 5.42 (dd, *J* = 16.8, 0.7 Hz, 1H), 5.22−5.17 (m, 3H), 3.73 (s, 3H), 3.66 (s, 3H), 3.54 (dd, *J* = 11.1, 1.2 Hz, 1H), 3.03 (d, *J* = 11.1 Hz, 1H), 2.86 (d, *J* = 13.5 Hz, 1H), 2.75 (dd, *J* = 13.5, 1.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 173.2, 172.8, 138.1, 137.3, 116.5, 115.8, 62.9, 61.1, 53.1, 52.3, 46.1, 39.0. HRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{12}H_{16}O_4SNa$ 279.0667, found 279.0661. *cis*-**12**. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.06 (dd, *J* = 17.1, 10.4 Hz, 1H), 5.96 (dd, *J* = 17.5, 10.6 Hz, 1H), 5.29 (d, *J* = 17.1 Hz, 1H), 5.20−5.15 (m, 2H), 5.13 (d, *J* = 10.4 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.53 (dd, *J* = 11.3, 1.1 Hz, 1H), 3.42 (dd, *J* = 13.7, 1.1 Hz, 1H), 2.99 (d, *J* = 11.3 Hz, 1H), 2.13 (d, *J* = 13.7 Hz, 1H).

General Procedure for the Preparation of Diazo Esters 15, 18, and 20. *2-[(tert-Butyldimethylsilyl)oxy]ethyl 2-Diazo-3-oxobutanoate (**S1**).* A solution of 2-[(*tert*-butyldimethylsilyl)oxy]ethanol (0.910 g, 5.16 mmol) and 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (0.734 g, 5.16 mmol) in toluene (6 mL) was heated at reflux for 2.5 h. After cooling, the solvent was removed, and the residue was directly used for the next step.

4-Acetamidobenzenesulfonyl azide (*p*-ABSA, 1.36 g, 5.68 mmol) and NEt_3 (1.1 mL, 7.74 mmol) were added sequentially to a solution of above crude ester in CH_3CN (10 mL). After the solution was stirred overnight, the solvent was removed, and the residue was purified by column chromatography on silica gel (eluent: 5−10% ethyl acetate in hexanes) to afford diazo **S1** (1.21 g, 4.42 mmol, 82% yield over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.34−4.28 (m, 2H), 3.87−3.81 (m, 2H), 2.48 (s, 3H), 0.88 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 190.1, 161.4, 66.4, 61.0, 28.2, 25.7, 18.2, −5.4. LRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{12}H_{22}N_2O_4SiNa$ 309, found 309.

*2-[(tert-Butyldimethylsilyl)oxy]ethyl 2-Diazobut-3-enoate (**S2**).* Sodium borohydride (0.175 g, 4.61 mmol) was added to a solution of diazoketone **S1** (1.10 g, 3.84 mmol) in a mixture of CH_2Cl_2 and MeOH (1:1, 8 mL) at 0 °C. After the solution was stirred at the same temperature for 1 h, the resulting mixture was quenched with cold water and extracted with CH_2Cl_2. The combined organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was directly used for the next step.

Triethylamine (2.1 mL, 15.4 mmol) and $POCl_3$ (0.54 mL, 5.76 mmol) were added sequentially to a solution of above crude alcohol in CH_2Cl_2 (9 mL) at 0 °C. The resultant mixture was allowed to stir at 23 °C overnight. The reaction mixture was carefully quenched with water at 0 °C and extracted with dichloromethane. The combined organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (eluent: 9% ethyl acetate in hexanes) to afford product **S2** (0.645 g, 0.239 mmol, 62% yield over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.17 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.12 (dd, *J* = 11.0, 0.9 Hz, 1H), 4.87 (dd, *J* = 17.4, 0.9 Hz, 1H), 4.38−4.19 (m, 2H), 3.94−3.71 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 120.4, 107.5, 66.3, 61.3, 25.8, 18.3, −5.39, −5.40. LRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{12}H_{22}N_2O_3SiNa$ 293, found 293.

*1-Vinylcyclobutanecarboxylic Acid (**S3**).* LiOH·H_2O (0.106 g, 2.53 mmol) was added to a solution of thietane **10** (0.133 g, 0.842 mmol) in a mixture of THF−H_2O (4/1, 10 mL). After being stirred at 23 °C for 10 h, the reaction mixture was acidified with 1 M aqueous solution of HCl and extracted with diethyl ether. The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated to afford acid **S3** (0.120 g, 0.839 mmol, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.26 (brs, 1H), 6.08 (dd, *J* = 17.3, 10.6 Hz, 1H), 5.37 (d, *J* = 17.3 Hz, 1H), 5.35 (d, *J* = 10.6 Hz, 1H), 3.73 (d, *J* = 9.6 Hz, 2H), 3.32 (d, *J* = 9.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 180.2, 137.5, 116.0, 54.9, 33.0. HRMS-EI (*m*/*z*): [M]$^+$ calcd for $C_6H_8O_2S$ 144.0245, found 144.0244.

*2-(2-Diazobut-3-enoyloxy)ethyl 1-Vinylcyclobutanecarboxylate (**15**).* TBAF (1.0 M, 1.5 mL, 1.5 mmol) was added to a solution of diazo **S2** (0.270 g, 1.00 mmol) in THF (10 mL) at 23 °C. After being stirred for 2 h, the reaction mixture was quenched with water and extracted with dichloromethane. The combined organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (eluent: 30% ethyl acetate in hexanes) to afford 2-hydroxyethyl 2-diazobut-3-enoate (**S4**) (0.111 g, 0.711 mmol, 76% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 6.17 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.14 (d, *J* = 11.0 Hz, 1H), 4.88 (d, *J* = 17.4 Hz, 1H), 4.40−4.34 (m, 2H), 3.90−3.84 (m, 2H), 2.03 (brs, 1H). **S4** was directly used for the next step without further characterization due to its instability.

EDCI (0.146 g, 0.760 mmol) and DMAP (12.4 mg, 0.102 mmol) were added sequentially to a solution of alcohol **S4** (0.111 g, 0.711 mmol) and acid **S3** (79.4 mg, 0.509 mmol) in CH_2Cl_2 (5 mL) at 23 °C. After being stirred for 16 h, the reaction mixture was quenched with water and extracted with CH_2Cl_2. The combined organic phase was washed with water, brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (eluent: 10% ethyl acetate in hexanes) to afford product **15** (0.126 g, 0.448 mmol, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.14 (dd, *J* = 17.4, 11.0 Hz, 1H), 6.05 (dd, *J* = 17.4, 10.6 Hz, 1H), 5.29 (d, *J* = 10.6 Hz, 1H), 5.28 (d, *J* = 17.4 Hz, 1H), 5.14 (d, *J* = 11.0 Hz, 1H), 4.88 (d, *J* = 17.4 Hz, 1H), 4.49−4.35 (m, 4H), 3.71 (d, *J* = 9.8 Hz, 2H), 3.28 (d, *J* = 9.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 173.3, 137.9, 120.0, 115.5, 107.9, 63.0, 62.3, 55.0, 33.1. HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{12}H_{14}N_2O_4SNa$ 305.0572, found 305.0578.

*8-Vinyl-3,6-dioxa-12-thiabicyclo[6.3.2]tridec-1(11)-ene-2,7-dione (**16**).* $Rh_2(OAc)_4$ (1.8 mg, 4.07 μmol) was added to a solution of diazo ester **15** (28.2 mg, 0.100 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was heated to 35 °C for 16 h. After cooling, the solvent was removed, and the residue was purified by column chromatography on silica gel (eluent: 25% ethyl acetate in hexanes) to afford product **16** (9.6 mg, 0.448 mmol, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.32 (t, *J* = 7.3 Hz, 1H), 5.68 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.15 (d, *J* = 10.7 Hz, 1H), 5.09 (d, *J* = 17.5 Hz, 1H), 4.93 (ddd, *J* = 14.3, 9.9, 1.5 Hz, 1H), 4.79 (ddd, *J* = 12.7, 2.9, 1.5 Hz, 1H), 4.25 (ddd, *J* = 14.3, 2.9, 1.9 Hz, 1H), 4.17 (ddd, *J* = 12.7, 9.9, 1.9 Hz, 1H), 3.46 (dd, *J* = 11.7, 2.2 Hz, 1H), 3.04 (dddd, *J* = 13.2, 11.1, 8.7, 7.2 Hz, 1H), 2.77 (d, *J* = 11.7 Hz, 1H), 2.57 (dddd, *J* = 13.6, 11.0, 8.1, 2.2 Hz, 1H), 2.45 (dddd, *J* = 13.2, 8.1, 7.3, 1.1 Hz, 1H), 1.77 (ddd, *J* = 13.6, 8.8, 1.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 174.2, 168.4, 139.8, 137.0, 128.7, 115.5, 65.7, 65.1, 51.2, 33.2, 32.8, 25.3. HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{12}H_{14}O_4SNa$ 277.0511, found 277.0520.

(1S,2S*)-2-(Diazobut-3-enoyloxy)cyclohexyl 1-Sinylcyclobutanecarboxylate (**18**).* EDCI (0.120 g, 0.628 mmol) and DMAP (12.8 mg, 0.105 mmol) were added sequentially to a solution of (1*S**,2*S**)-2-hydroxycyclohexyl 2-diazobut-3-enoate (**S5**) (0.110 g, 0.523 mmol) and acid **S3** (90.5 mg, 0.628 mmol) in CH_2Cl_2 (5 mL) at 23 °C. After being stirred for 24 h, the reaction mixture was quenched with water and extracted with CH_2Cl_2. The combined organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (eluent: 10% ethyl acetate in hexanes) to afford product **18** (96.2 mg, 0.263 mmol, 55% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.12 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.96 (dd, *J* = 17.4, 10.5 Hz, 1H), 5.22 (d, *J* = 17.4 Hz, 1H), 5.20 (d, *J* = 10.5 Hz, 1H), 5.10 (d, *J* = 11.0 Hz, 1H), 4.98−4.88 (m, 2H), 4.84 (d, *J* = 17.4 Hz, 1H), 3.65−3.61 (m, 2H), 3.29−3.23 (m, 2H), 2.14−2.04 (m, 2H), 1.80−1.73 (m, 2H), 1.51−1.32 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 173.0, 138.0, 120.3, 115.3, 107.5, 74.7, 74.4, 55.2, 33.4, 33.1, 30.5, 30.0, 23.5, 23.4. HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{16}H_{20}N_2O_4SNa$ 359.1041, found 359.1040.

*Tetrahydrothiophene **19**.* Rh_2(*R*-PTAD)$_4$ (1.7 mg, 1.08 μmol) was added to a solution of diazo ester **18** (18.1 mg, 53.8 μmol) in CH_2Cl_2 (5.4 mL). The reaction mixture was stirred at 23 °C for 22 h. Then the solvent was removed, and the residue was purified by column chromatography on silica gel (eluent: 25% ethyl acetate in hexanes) to afford product **19** (11.9 mg, 38.6 μmol, 72% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.19 (t, *J* = 7.1 Hz, 1H), 5.64 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.15−5.08 (m, 1H), 5.08 (d, *J* = 10.7 Hz, 1H), 5.00 (d, *J* = 17.5 Hz, 1H), 4.59−4.52 (m, 1H), 3.54 (d, *J* = 12.7 Hz, 1H), 3.21−3.10 (m, 1H), 2.55−2.46 (m, 2H), 2.40 (d, *J* = 12.7 Hz, 1H), 2.31−2.24 (m, 1H), 1.91−1.74 (m, 4H), 1.71−1.61 (m, 1H), 1.49−1.30 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm): 174.3, 171.9, 153.2, 140.4, 129.3, 115.0, 85.2, 77.3, 52.2, 33.7, 31.6, 31.5, 30.5, 24.8, 24.1, 24.0. HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{16}H_{20}O_4SNa$ 331.0980, found 331.0988.

*4-(2-Diazobut-3-enoyloxy)butyl 1-Vinylcyclobutanecarboxylate (**20**).* EDCI (87.8 mg, 0.458 mmol) and DMAP (7.4 mg, 6.07 μmol) were added sequentially to a solution of 4-hydroxybutyl 2-diazobut-3-enoate (**S6**) (56.2 mg, 0.305 mmol) and acid **S3** (66.0 mg, 0.458 mmol) in CH_2Cl_2 (6 mL) at 23 °C. After being stirred for 13 h, the reaction mixture was quenched with water and extracted with CH_2Cl_2. The combined organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (eluent: 10% ethyl acetate in hexanes) to afford product **20** (60.2 mg, 0.194 mmol, 64% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.15 (dd, *J* = 17.4, 11.0 Hz, 1H), 6.06 (dd, *J* = 17.3, 10.6 Hz, 1H), 5.29 (d, *J* = 10.6 Hz, 1H), 5.28 (d, *J* = 17.3 Hz, 1H), 5.12 (d, *J* = 11.0 Hz, 1H), 4.87 (d, *J* = 17.4 Hz, 1H), 4.27−4.16 (m, 4H), 3.71 (d, *J* = 9.7 Hz, 2H), 3.27 (d, *J* = 9.7 Hz, 2H), 1.78−1.71 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 173.5, 138.2, 120.3, 115.4, 107.6, 64.8, 64.4, 55.0, 33.2, 25.4, 25.2. HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{14}H_{18}N_2O_4SNa$ 333.0885, found 333.0887.

*10-Vinyl-3,8-dioxa-14-thiabicyclo[8.3.2]tridec-1(13)-ene-2,9-dione (**21**).* $Rh_2(R\text{-PTAD})_4$ (1.4 mg, 0.909 μmol) was added to a solution of diazo ester **20** (14.1 mg, 45.4 μmol) in CH_2Cl_2 (4.5 mL). The reaction mixture was heated to 35 °C for 1.5 h. After cooling, the solvent was removed, and the residue was purified by column chromatography on silica gel (eluent: 25% ethyl acetate in hexanes) to afford product **21** (8.3 mg, 38.6 μmol, 65% yield). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.30 (t, *J* = 7.3 Hz, 1H), 5.62 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.07 (d, *J* = 10.7 Hz, 1H), 5.01 (d, *J* = 17.4 Hz, 1H), 4.53 (ddd, *J* = 10.8, 7.5, 2.9 Hz, 1H), 4.41 (ddd, *J* = 11.6, 7.6, 2.4 Hz, 1H), 4.20 (ddd, *J* = 10.8, 6.4, 3.6 Hz, 1H), 3.81 (ddd, *J* = 11.6, 7.3, 2.0 Hz, 1H), 3.58 (dd, *J* = 12.0, 1.9 Hz, 1H), 3.18–3.07 (m, 1H), 2.60 (d, *J* = 12.0 Hz, 1H), 2.55–2.47 (m, 2H), 2.01–1.80 (m, 4H), 1.77–1.70 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm): 174.2, 166.2, 152.0, 141.3, 127.8, 114.8, 67.8, 65.0, 51.6, 32.8, 30.4, 27.1, 25.7, 24.9. HRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{14}H_{18}O_4SNa$ 305.0824, found 305.0813.

*tert-Butyl 8,8-Dimethyl-3-vinyl-7,9-dioxa-2-thiaspiro[4.5]decane-3-carboxylate (**24**).* A solution of *tert*-butyl 2-diazobut-3-enoate (**23**) (1.01 g, 6.00 mmol) in CH_2Cl_2 (10 mL) was added over 20 h to a solution of 7,7-dimethyl-6,8-dioxa-2-thiaspiro[3.5]nonane (**22**) (0.522g, 3.00 mmol) and $Rh_2(OAc)_4$ (26.5 mg, 60.0 μmol) in CH_2Cl_2 (10 mL) at reflux. The resultant mixture was stirred for a further 27 h. After cooling, the solvent was removed and the residue was purified by column chromatography on silica gel (eluent: 8% ethyl acetate in hexanes) to afford product **24** (0.611 g, 1.94 mmol, 65% yield) together with thietane **22** (23.0 mg, 0.132 mmol). The pure product **24** could be obtained from recrystallization using hexanes. ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 6.03 (dd, *J* = 17.1, 10.5 Hz, 1H), 5.29 (d, *J* = 17.1 Hz, 1H), 5.10 (d, *J* = 10.5 Hz, 1H), 3.82 (d, *J* = 11.7 Hz, 1H), 3.81 (d, *J* = 11.6 Hz, 1H), 3.74 (dd, *J* = 11.7, 2.1 Hz, 1H), 3.65 (dd, *J* = 11.6, 2.1 Hz, 1H), 3.10 (d, *J* = 11.4 Hz, 1H), 2.97 (d, *J* = 11.4 Hz, 1H), 2.44 (d, *J* = 13.7 Hz, 1H), 1.68 (d, *J* = 13.7 Hz, 1H), 1.45 (s, 9H), 1.44 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm): 171.8, 139.5, 114.1, 98.1, 81.9, 67.6, 67.2, 63.7, 47.8, 43.2, 39.4, 27.7, 27.3, 20.1. HRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{16}H_{26}O_4SNa$ 337.1450, found 337.1451.

*tert-Butyl 4,4-Bis(hydroxymethyl)-2-vinyltetrahydrothiophene-2-carboxylate (**25**).* Dowex 50WX8 (2.00 g) was added to a solution of thiolane **24** (0.272 g, 0.866 mmol) in a mixture of MeOH–H_2O (9/1, 10 mL). The reaction mixture was stirred at 23 °C for 20 h, and filtered through a pad of Celite. The filtrate was concentrated, and the residue was diluted with water and extracted with CH_2Cl_2. The combined organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (eluent: 10% ethyl acetate in hexanes) to afford product **25** (0.219 g, 0.799 mmol, 92% yield). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.04 (dd, *J* = 17.2, 10.5 Hz, 1H), 5.27 (d, *J* = 17.2 Hz, 1H), 5.11 (d, *J* = 10.5 Hz, 1H), 3.75–3.61 (m, 4H), 3.24 (dd, *J* = 8.5, 5.1 Hz, 1H), 2.86 (d, *J* = 11.1 Hz, 1H), 2.75 (dd, *J* = 13.9, 1.1 Hz, 1H), 2.71 (brs, 1 H), 2.58 (dd, *J* = 11.1, 1.1 Hz, 1H), 1.74 (d, *J* = 13.9 Hz, 1H), 1.47 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 173.7, 139.7, 114.1, 82.5, 68.8, 65.6, 63.8, 54.6, 41.3, 37.6, 27.7. HRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{13}H_{22}O_4SNa$ 297.1137, found 297.1126.

Lipase Resolution Reaction of Diol 25. Amano Lipase AK (27.4 mg) was added to a solution of diol **25** (27.4 mg, 0.100 mmol) and vinyl butyrate (0.25 mL, 1.97 mmol) in methyl *tert*-butyl ether (2 mL). The reaction mixture was heated at 40 °C for 48 h. After cooling, the reaction mixture was then filtered through a pad of Celite, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (eluent: 15–20% ethyl acetate in hexanes) to afford product **26** (31.2 mg, 90.6 μmol, dr 49:51, 91% yield). The two diastereomers could be separated partially on column chromatography.

*(2R,4R)-tert-Butyl 4-(Butyryloxymethyl)4-(hydroxymethyl)2-vinyltetrahydrothiophene-2-carboxylate (**ent-26a**).* ee: 72% (Chiralcel OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 210 nm; t_1 = 22.9 min; t_2 = 25.3 min). $[\alpha]^{23}_D$ +8.0 (*c* 1.48, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.04 (dd, *J* = 17.1, 10.5 Hz, 1H), 5.28 (d, *J* = 17.1 Hz, 1H), 5.12 (d, *J* = 10.5 Hz, 1H), 4.17 (d, *J* = 11.5 Hz, 1H), 4.14 (d, *J* = 11.5 Hz, 1H), 3.55 (d, *J* = 12.1 Hz, 1H), 3.52 (d, *J* = 12.1 Hz, 1H), 2.86 (d, *J* = 11.3 Hz, 1H), 2.68 (d, *J* = 13.9 Hz, 1H), 2.64 (d, *J* = 11.3 Hz, 1H), 2.31 (t, *J* = 7.4 Hz, 2H), 1.76 (d, *J* = 13.9 Hz, 1H), 1.71–1.60 (m, 2H), 1.47 (s, 9H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 173.8, 173.2, 139.6, 114.2, 82.5, 66.1, 63.7, 63.0, 53.9, 41.2, 37.6, 36.1, 27.7, 18.4, 13.7. HRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{17}H_{28}O_5SNa$ 367.1555, found 367.1549.

*(2S,4R)-tert-Butyl 4-(Butyryloxymethyl)4-(hydroxymethyl)2-vinyltetrahydrothiophene-2-carboxylate (**ent-26b**).* ee: 74% (Chiralcel OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1 = 27.8 min; t_2 = 32.6 min). $[\alpha]^{23}_D$ −19.5 (*c* 1.46, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.06 (dd, *J* = 17.1, 10.5 Hz, 1H), 5.35 (d, *J* = 17.1 Hz, 1H), 5.14 (d, *J* = 10.5 Hz, 1H), 4.25 (d, *J* = 11.3 Hz, 1H), 4.19 (d, *J* = 11.3 Hz, 1H), 3.50 (d, *J* = 11.5 Hz, 1H), 3.44 (d, *J* = 11.5 Hz, 1H), 2.81 (d, *J* = 11.7 Hz, 1H), 2.78 (d, *J* = 11.7 Hz, 1H), 2.58 (d, *J* = 13.9 Hz, 1H), 2.34 (t, *J* = 7.4 Hz, 2H), 1.89 (d, *J* = 13.9 Hz, 1H), 1.72–1.61 (m, 2H), 1.46 (s, 9H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 174.5, 171.7, 139.2, 114.5, 82.0, 65.6, 64.8, 64.5, 54.2, 42.5, 37.3, 36.1, 27.8, 18.5, 13.7. HRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{17}H_{28}O_5SNa$ 367.1555, found 367.1558.

Synthesis of Diene 27. Oxalyl chloride (1.6 mL, 19.1 mmol) was added to a solution of DMSO (2.7 mL, 38.2 mmol) in CH_2Cl_2 (80 mL) at −78 °C. A solution of alcohol ***ent*-26** (3.29 g, 9.55 mmol) in CH_2Cl_2 (80 mL) was added after 0.5 h. After the solution was stirred for a further 0.5 h, *i*-Pr_2NEt (13.3 mL, 76.4 mmol) was added. The resultant mixture was stirred at −78 °C for 0.5 h and then allowed to warm to 0 °C for additional 0.5 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The combined organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (eluent: 8% ethyl acetate in hexanes) to afford aldehyde (3.08 g, 9.00 mmol, 94% yield).

To a suspension of CH_3PPh_3Br (4.82 g, 13.5 mmol) in THF (40 mL) was added $NaN(SiMe_3)_2$ (0.6 M in toluene, 19.5 mL, 11.7 mmol) dropwise at 0 °C. The resultant mixture was stirred for 0.5 h before being transferred to a solution of the above aldehyde (3.08 g, 9.00 mmol) in THF (20 mL) at 0 °C. After being stirred at the same temperature for 0.5 h, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2. The combined organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (eluent: 8% ethyl acetate in hexanes) to afford alkene (2.67 g, 7.84 mmol, 87% yield).

Potassium carbonate (1.08 g, 7.83 mmol) was added to a solution of above alkene (2.67 g, 7.84 mmol) in MeOH (100 mL). After being stirred at 23 °C for 3.5 h, the reaction mixture was brought to pH of about 6 with addition of dry ice, diluted with H_2O, and extracted with CH_2Cl_2. The combined organic phase was washed with water, brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (eluent: 15–20% ethyl acetate in hexanes) to afford **27b** (0.848 g, 3.14 mmol, 40% yield) and **27a** (1.02 g, 3.77 mmol, 48% yield).

*(2R,4S)-tert-Butyl 4-(Hydroxymethyl)-2,4-divinyltetrahydrothiophene-2-carboxylate (**27a**).* $[\alpha]^{23}_D$ 0.12 (*c* 1.4, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.05 (dd, *J* = 17.1, 10.4 Hz, 1H), 5.84 (dd, *J* = 17.8, 10.8 Hz, 1H), 5.31 (d, *J* = 17.1 Hz, 1H), 5.30–5.22 (m, 2H), 5.11 (d, *J* = 10.4 Hz, 1H), 3.60 (d, *J* = 6.4 Hz, 2H), 2.99 (d, *J* = 11.2 Hz, 1H), 2.95 (d, *J* = 11.2 Hz, 1H), 2.72 (d, *J* = 13.4 Hz, 1H), 1.99 (d, *J* = 13.4 Hz, 1H), 1.52 (t, *J* = 6.4 Hz, 1H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 171.7, 140.4, 140.1, 115.9, 113.9, 81.7, 66.7, 64.3, 56.4, 44.6, 38.4, 27.7. HRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{14}H_{22}O_3SNa$ 293.1187, found 293.1180.

*(2S,4S)-tert-Butyl 4-(Hydroxymethyl)-2,4-divinyltetrahydrothiophene-2-carboxylate (**27b**).* $[\alpha]^{23}_D$ −1.2 (*c* 1.7, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.04 (dd, *J* = 17.2, 10.5 Hz, 1H), 5.98–5.82 (m, 1H), 5.23 (d, *J* = 17.2 Hz, 1H), 5.20–5.12 (m, 2H), 5.09 (d, *J* = 10.5 Hz, 1H), 3.67 (dd, *J* = 11.8, 4.9 Hz, 1H), 3.54 (dd, *J* = 11.8, 9.6

Hz, 1H), 2.97 (d, *J* = 11.0 Hz, 1H), 2.86 (dd, *J* = 13.8, 1.4 Hz, 1H), 2.81 (dd, *J* = 9.9, 4.9 Hz, 1H), 2.66 (dd, *J* = 10.9, 1.4 Hz, 1H), 1.81 (dd, *J* = 13.8, 0.9 Hz, 1H), 1.48 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 173.6, 141.4, 140.2, 114.6, 113.8, 82.5, 65.4, 63.6, 55.9, 43.3, 39.3, 27.7. HRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{14}H_{22}O_3SNa$ 293.1187, found 293.1193.

((2R*,4R*)-2,4-Divinyltetrahydrothiophene-2,4-diyl)dimethanol (S7). Lithium aluminum hydride (0.100 g, 2.63 mmol) was added to a solution of ester **27a** (80.0 mg, 0.296 mmol) in THF (2 mL) at 0 °C. After the solution was stirred at 23 °C for 1 h, the reaction was carefully quenched by addition of 0.1 mL of water. After the solution was stirred for 5 min, 0.1 mL of aqueous NaOH (15% w/w) solution was added, and the mixture was stirred for 5 min. Water (0.3 mL) was added, and the mixture was stirred for an additional 5 min. The white solid was filtered off, the filtrate was concentrated, and the residue was purified by column chromatography on silica gel (eluent: 50% ethyl acetate in hexanes) to afford product **S7** (45.5 mg, 0.227 mmol, 77% yield). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.95 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.86 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.35 (d, *J* = 17.2 Hz, 1H), 5.21 (d, *J* = 10.9 Hz, 1H), 5.15 (d, *J* = 17.6 Hz, 1H), 5.15 (d, *J* = 10.6 Hz, 1H), 3.68 (d, *J* = 10.9 Hz, 1H), 3.59 (d, *J* = 10.9 Hz, 1H), 3.50 (d, *J* = 11.3 Hz, 1H), 3.46 (d, *J* = 11.3 Hz, 1H), 2.92 (d, *J* = 11.3 Hz, 1H), 2.88 (d, *J* = 11.3 Hz, 1H), 2.11 (d, *J* = 13.4 Hz, 1H), 2.05 (d, *J* = 13.4 Hz, 1H), 2.02 (brs, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 141.9, 141.2, 115.4, 114.8, 68.4, 65.7, 64.0, 56.6, 43.0, 38.3. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{10}H_{16}O_2S$ 200.0871, found 200.0862.

(2R*,4R*)-2,4-Bis(allyloxymethyl)-2,4-divinyltetrahydrothiophene (28). Lithium aluminum hydride (46.7 mg, 1.23 mmol) was added to a solution of *trans*-**12** (63.0 mg, 0.246 mmol) in THF (5 mL) at 0 °C. After the solution was stirred at 23 °C for 1 h, the reaction was carefully quenched by addition of 50 μL of water. After the solution was stirred for 5 min, 50 μL of aqueous NaOH (15% w/w) solution was added, and the mixture was stirred for 5 min. Water (0.15 mL) was added, and the mixture was stirred for an additional 5 min. The white solid was filtered off, the filtrate was concentrated, and the diol was directly used for the next step. The ^1H NMR data for this diol matched the data of **S7**.

Sodium hydride (60% dispersion in mineral oil, 29.5 mg, 0.738 mmol) was added to a solution of the above diol in DMF (4 mL). After the solution was stirred for 0.5 h, allyl bromide (70 μL, 0.812 mmol) was added. The reaction mixture was stirred overnight, quenched with a saturated aqueous solution of NH_4Cl, and extracted with diethyl ether. The combined organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (eluent: 8% ethyl acetate in hexanes) to afford product **28** (50.4 mg, 0.180 mmol, 73% yield over two steps). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.02 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.96 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.93−5.83 (m, 2H), 5.30 (dd, *J* = 17.2, 1.1 Hz, 1H), 5.30−5.20 (m, 2H), 5.20−5.12 (m, 3H), 5.11 (dd, *J* = 10.9, 0.9 Hz, 1H), 5.06 (dd, *J* = 10.6, 1.0 Hz, 1H), 4.01 (dt, *J* = 5.6, 1.4 Hz, 2H), 3.96 (dt, *J* = 5.2, 1.3 Hz, 2H), 3.56 (d, *J* = 9.2 Hz, 1H), 3.50 (d, *J* = 9.0 Hz, 1H), 3.48 (d, *J* = 9.2 Hz, 1H), 3.38 (d, *J* = 9.0 Hz, 1H), 2.97 (d, *J* = 11.3 Hz, 1H), 2.90 (d, *J* = 11.3 Hz, 1H), 2.10 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 142.59, 142.57, 134.8, 134.7, 116.9, 116.7, 113.6, 113.0, 77.7, 74.3, 72.3, 72.2, 60.8, 55.2, 44.5, 38.8. HRMS-FI (*m*/*z*): $[M]^+$ calcd for $C_{16}H_{24}O_2S$ 280.1497, found 280.1481.

Tricyclic Compound 29. A solution of thiolane **28** (15.0 mg, 53.3 μmol) and Grubbs II catalyst (2.3 mg, 2.67 μmol) in benzene (5 mL) was heated at 80 °C for 17 h. After cooling, the solvent was removed, and the residue was purified by column chromatography on silica gel (eluent: 8% ethyl acetate in hexanes) to afford product **29** (10.4 mg, 46.4 μmol, 87% yield). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.84 (dt, *J* = 10.1, 2.3 Hz, 1H), 5.74 (dt, *J* = 10.2, 2.4 Hz, 1H), 5.69 (dt, *J* = 10.2, 2.2 Hz, 1H), 5.64 (dt, *J* = 10.1, 2.6 Hz, 1H), 4.16−4.10 (m, 3H), 4.07 (dt, *J* = 16.6, 2.3 Hz, 1H), 3.99 (dd, *J* = 10.9, 0.9 Hz, 1H), 3.82 (d, *J* = 11.1 Hz, 1H), 3.76 (d, *J* = 11.1 Hz, 1H), 3.55 (dd, *J* = 10.9, 1.2 Hz, 1H), 2.94 (dd, *J* = 11.6, 0.9 Hz, 1H), 2.80 (dd, *J* = 11.6, 1.1 Hz, 1H), 1.88 (d, *J* = 13.9 Hz, 1H), 1.83 (d, *J* = 13.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 132.2, 130.9, 126.7, 125.2, 75.5, 72.3, 65.6, 65.0, 54.3, 49.5, 48.9, 40.9. HRMS-FI (*m*/*z*): $[M]^+$ calcd for $C_{12}H_{16}O_2S$ 224.0871, found 224.0860.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray crystallographic data and copies of ^1H and ^{13}C NMR spectra and HPLC traces. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01177.

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Notes

The authors declare no competing financial interest.

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