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A CYCLOADDITION APPROACH TO BREYNOLIDE

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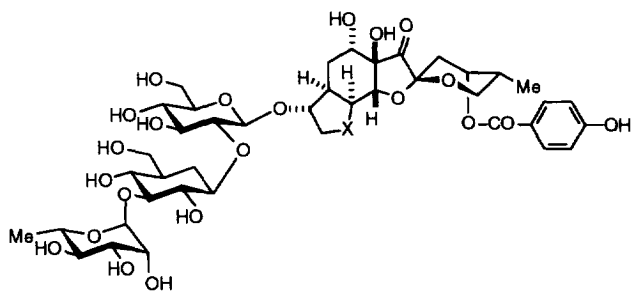
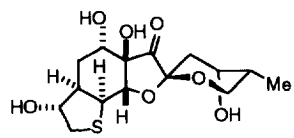
Abstract. A novel approach to the functionalized hydrobenzothiophene subunit of the sesquiterpene breynolide (**3**) has been developed. The sequence features the Diels-Alder reaction of the vinyl sulfones **12** and **13** with the Danishefsky diene **9** to give the cycloadducts **14** and **16** as the major products. Reduction of the sulfone moieties of **14** and **16** gave the sulfides **20** and **21**, respectively. Subsequent dipolar cycloaddition of **20** and **21** with a functionalized nitrile oxide gave the corresponding adducts **24** and **25**, which possess functionality suitable for elaboration into breynolide (**3**). © 1997 Elsevier Science Ltd.

The breynins A and B (**1** and **2**, respectively) are two novel sulfur containing glycosides that were isolated from the Taiwanese plant *Breynia officinalis hems 1*.[1] In subsequent biological screening experiments, these compounds were found to exhibit significant hypocholesterolemic activity.[2,3] In initial degradation studies, exhaustive hydrolysis of **1** yielded the aglycone breynolide (**3**), the structure of which was established by X-ray crystallography, together with D-glucose, L-rhamnose, and *p*-hydroxybenzoic acid.[4] The structures of breynins A and B were then resolved by the groups of Smith and Ohkuma.[5] The novelty of the structure of breynolide has stimulated a number of independent synthetic investigations,[6-10] and the total synthesis of **3** has been reported by Williams[7] and Smith.[8]



1: X = S
2: X = SO

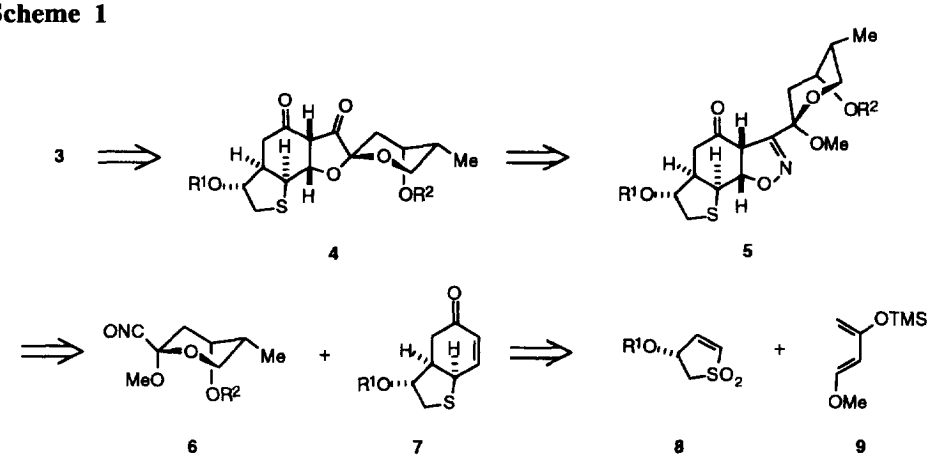


3

Our own interest in breynolide (**3**) emerged from our synthesis of the structurally related sesquiterpene phyllanthocin, and the strategy that evolved for our approach to **3** (Scheme 1) was derived from that effort.[11] We reasoned that breynolide (**3**) should be accessible by refunctionalization of **4**, which should in turn be available by reduction of the oxazoline moiety in **5** followed by acid-catalyzed transketalization of the intermediate hydroxy ketone in close analogy with our previous work.[10,12] The most convergent approach to **5** was envisaged to involve dipolar cycloaddition of the nitrile oxide **6** with the unsaturated bicyclic ketone **7**,[13] which would be

derived from the product of the Diels-Alder reaction of the dienophile **8** with the Danishefsky diene **9**.[14] We now wish to disclose the full details of our initial experiments in this area and the preparation of **24** and **25**, which are potential intermediates in the synthesis of breynolide (**3**).

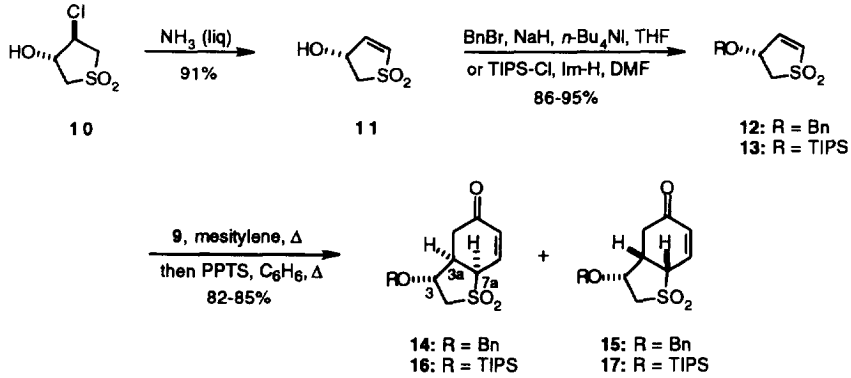
Scheme 1



4 **5** **6** **7** **8** **9**

The first phase of the investigation required constructing a suitable derivative of a hydrobenzothiophene of the general type **7**. Although a number of Diels-Alder reactions involving different dienes and dienophiles were examined, those outlined in Scheme 2 represent the more useful sequences. The allylic alcohol **11** was readily prepared by dehydrochlorination of the commercially available chlorohydrin **10**. The secondary hydroxyl group was protected as its benzyl and triisopropylsilyl ether to give **12** and **13**, respectively, thereby setting the stage for the Diels-Alder reactions. In the event, the dienophile **12** was first heated with the Danishefsky diene **9** at 170–180 °C for 48 h. The intermediate crude cycloadduct underwent desilylation with concomitant loss of methanol when heated in refluxing benzene containing pyridinium *p*-toluenesulfonate (PPTS) to give a mixture (1.2:1) of the cycloadducts **14** and **15** in 82% yield. We reasoned that a more bulky protecting group on the hydroxyl function might lead to higher diastereofacial selectivity in the cycloaddition, so the dienophile **13** was subjected to the same sequence of reactions. Although this process was indeed more stereoselective, the

Scheme 2



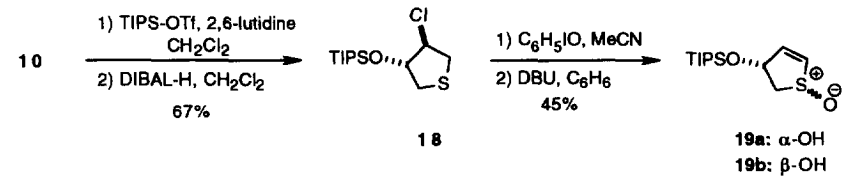
10 **11** **12**: R = Bn; **13**: R = TIPS

14: R = Bn; **16**: R = TIPS **15**: R = Bn; **17**: R = TIPS

improvement was not dramatic, and a mixture (2.5:1) of **16** and **17** was obtained in 85% yield. The regiochemical outcome of these cycloadditions was ascertained upon analysis of the ^{1}H NMR spectra, including COSY, of the cycloadducts, but it was not possible to establish unequivocally the facial selectivity by NMR owing to the complexity of the multiplets arising from the bridgehead protons at C(3), C(3a) and C(7a). To resolve this critical issue, the structures of **14**[15] and **17**[16] were unambiguously secured by X-ray analyses.

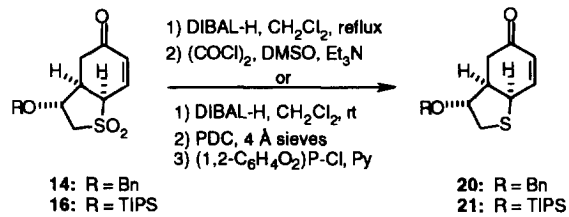
A number of experimental variables were examined to ascertain whether higher diastereoselectivities in cycloadditions to **13** might be achieved. For example, reactions of **13** with **9** and the corresponding TBDMS derivative of **9** were conducted in the presence of a variety of Lewis acids and at lower temperatures, but no improvement in diastereoselectivity was observed. In preliminary experiments, we then explored the feasibility of using a sulfoxide as the dienophile, because sulfoxides are known to undergo Diels-Alder reactions with high diastereoselectivities.[17] However, heating a mixture (ca. 1.2:1) of the sulfoxides **19a,b**, which were prepared by the unoptimized sequence summarized in Scheme 3, with **9** at temperatures up to 200-210 °C did not give any isolable cycloadduct. Only starting **19a,b** was recovered, even in the presence of Lewis acids such as Eu(hfc)$_3$ and $MgBr_2$. Although more vigorous conditions were not examined, the low stereoselectivities associated with producing the sulfoxides in diastereomerically pure form, even under conditions developed by Kagan,[18] conspired against further experimentation.

Scheme 3



With useful quantities of the Diels-Alder adducts **14** and **16** in hand, we were ready to examine the key dipolar cycloaddition reaction. In view of the harshness of the conditions typically required to reduce sulfones to sulfides, we elected to reduce the sulfone moiety prior to the nitrile oxide dipolar cycloaddition. Thus, reaction of **14** with a large excess of DIBAL-H in refluxing dichloromethane[19] gave a mixture (ca. 6:1) of intermediate allylic alcohols that was oxidized by Swern oxidation[20] to give **20** in 43% unoptimized overall yield (Scheme 4). Unfortunately, the triisopropylsilyl protecting group on **16** was not stable to the vigorous conditions that were required to reduce the sulfone completely to a sulfide, so a modified sequence was developed for converting **16** to **21**. Thus, sequential reaction of **16** with DIBAL-H (4 equiv) and PDC in the presence of 4 Å molecular sieves[21]

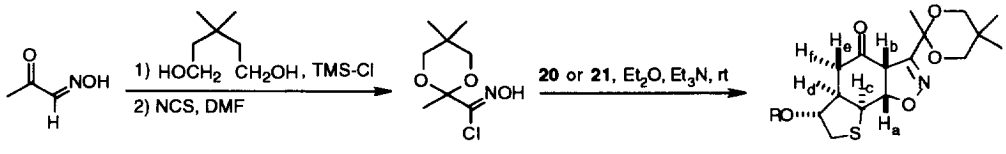
Scheme 4



gave a mixture of sulfoxide and sulfide enones, which was treated with 1,2-phenylene phosphorochloridite[22] to reduce the residual sulfoxide groups and furnish **21** in 55% overall yield from **16**. The transformation of **16** to **21** was typically executed without isolating intermediates, but all intermediates were purified and characterized.

With the hydrobenzothiophenes **20** and **21** in hand, the stage was set for the dipolar cycloaddition. Although use of the nitrile oxide **6** would offer a more convergent entry to intermediates that could be elaborated into **3**, we elected to examine first the regio- and stereochemical course of the pivotal dipolar cycloaddition of **20** and **21** with simple nitrile oxides in several model studies. Toward this end, the oxime **22** was converted into the hydroxamoyl chloride **23** by sequential ketalization and chlorination (Scheme 5). The nitrile oxide derived from **23** was slowly generated *in situ* in the presence of the enone **20** to furnish the cycloadduct **24** in 37% yield. Owing to the apparent low reactivity of **20** toward dipolar cycloaddition, it was necessary to use a large excess of the nitrile oxide precursor **23** to obtain a modest yield of **24**, and significant quantities of furoxan that was produced by dimerization of the nitrile oxide were also obtained.

Scheme 5



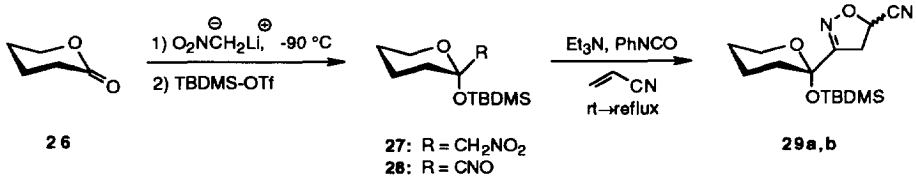
22 **23** **24**: R = Bn; **25**: R = TIPS

The regio- and stereochemical outcomes of this key cycloaddition reaction were assigned based upon careful examination of the ^{1}H NMR spectra of **24** using COSY and C-H correlation experiments. Diagnostic signals were those for the protons H_a (δ 5.26; dd, J = 3.4, 10.0 Hz), H_b (δ 4.08; dd, J = 1.9, 10.0 Hz), H_c (δ 4.18; dd, J = 3.4, 5.6 Hz), H_e (δ 1.76; ddd, J = 1.9, 2.8, 15.1 Hz), and H_f (δ 2.73; dd, J = 11.1, 15.1 Hz). The chemical shift of H_a, which is furthest downfield and coupled with two protons H_b and H_c, is indicative of its attachment to the carbon adjacent to the oxygen of the isoxazoline ring. This regiochemistry is consistent with other examples of the dipolar cycloadditions of nitrile oxides with enones.[13] The appearance of a long range W-type coupling between H_b and H_e (J = 1.9 Hz) indicates that both of these protons are approximately equatorial on the six-membered ring, which would then appear to reside in a distorted chair conformation. Based upon this assumption and examination of molecular models, the observed coupling constant between H_a and H_c of 3.4 Hz suggests a trans relationship between H_a and H_c with a dihedral angle of about 110-115° rather than a cis relationship wherein the dihedral angle would be approximately 0-15° and the expected coupling constant would be much larger. Similarly, the cycloaddition of the nitrile oxide generated *in situ* from **23** with the enone **21** gave the adduct **25**, whose spectral properties were similar to those of **24**.

We also evaluated the feasibility of inducing dipolar cycloadditions between **20** and the nitrile oxide **28**, which was generated *in situ* from the nitro compound **27** under conditions developed by Mukaiyama;[23] **27** was prepared by addition of the anion of nitromethane to δ-valerolactone (**26**) followed by protection (Scheme 6). Although the nitrile oxide **28** added efficiently to acrylonitrile to give a mixture (1:1) of the isoxazolines **29a,b**, no cycloadduct was isolated when either of the less reactive dipolarophiles **16** or **21** was used as the reaction

partner. This result augurs poorly for the reaction of the more highly functionalized nitrile oxide **6** with the dipolarophiles **20** and **21**.

Scheme 6



26 **27:** R = CH_2NO_2 **28:** R = CNO **29a,b**

In summary, the successful syntheses of **24** and **25** in this study establish the underlying viability of the novel approach to breynolide (**3**) that is outlined in Scheme 1. Although the stereoselectivity of the key Diels-Alder reaction was modest, the present route allows rapid and relatively efficient access to the hydrobenzothiophene subunit present in breynolide (**3**). Unmasking the methyl ketone group in **24** or **25** should lead to intermediates that may be transformed into breynolide (**3**).

Acknowledgment. We wish to thank the National Institutes of Health and the Robert A. Welch Foundation for support of this research. Dr. A. Gaucher is grateful to the Ministère de la Recherche et de la Technologie of France for partial support.

EXPERIMENTAL SECTION

2,3-Dihydrothiophene-3-ol-1,1-dioxide (11). The chlorohydrin **10** (16.0 g, 93.8 mmol) was added to liquid ammonia (250 mL) in 2 g portions over a 10 min period. The mixture was stirred for 1 h at -78 °C and then heated at reflux for 30 min. The ammonia was allowed to evaporate, and the residue was extracted with EtOAc (3 x 50 mL). The excess solvent was removed under reduced pressure, and the residual oil was purified by Kügelrohr distillation (0.1 mm Hg, 210 °C) to give 11.4 g (91%) of **11** as a clear oil. ^{1}H NMR (acetone-d_6) δ 6.84 (m, 2 H), 5.14 (m, 1 H), 3.63 (dd, J = 13.8, 7.3 Hz, 1 H), 3.50 (br s, 1 H), 3.01 (dd, J =13.8, 3.2 Hz, 1 H); ^{13}C NMR (acetone-d_6) δ 141.4, 132.3, 67.3, 56.2; IR (neat) υ 3450, 3060, 1410, 1300, 1150, 900 cm^{-1}; mass spectrum (CI, methane), *m/z* 135.0115 (M^+ + H) ($C_4H_7O_3S$ requires 135.0116), 135 (base), 117, 89, 70.

3-Benzyloxy-2,3-dihydrothiophene-1,1-dioxide (12). To a suspension of NaH (500 mg of a 60% dispersion in mineral oil, 13.8 mmol) in dry THF (7 mL) under N_2 was added a solution of **11** (1.20 g, 8.94 mmol) in dry THF (15 mL). After stirring for 20 min, tetrabutylammonium iodide (369 mg, 1.00 mmol) was added, and the resultant mixture was stirred for 15 min at rt. Benzyl bromide (1.71 g, 10.0 mmol) was added to the reaction mixture and stirring continued for an additional 2 h. Water (20 mL) was added slowly, and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with saturated NaCl (30 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to afford 1.12 g (56%) of **12** as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 5 H), 6.73 (dd, J = 6.9, 2.2 Hz, 1 H), 6.69 (d, J = 6.9 Hz, 1 H), 4.89 (m, 1 H), 4.63 (d, J = 11.8 Hz, 1 H), 4.58 (d, J = 11.8 Hz, 1 H), 3.53 (dd, J = 13.7, 7.2 Hz, 1 H), 3.18 (dd, J = 13.7, 4.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 139.1, 136.8, 128.7, 128.4, 128.0, 74.5, 72.1, 54.7; mass spectrum (CI, methane), *m/z* 225.0583 (M^+ + H) ($C_{11}H_{13}O_3S$ requires 225.0585).

3-(Triisopropylsiloxy)-2,3-dihydrothiophene-1,1-dioxide (13). Triisopropylsilyl chloride (0.860 g, 4.46 mmol) was added to a solution of **11** (0.56 g, 3.73 mmol) and imidazole (0.64 g, 9.32 mmol) in dry DMF (1.2 mL) under N_2, and the mixture was stirred at rt for 24 h. The reaction mixture was diluted with Et_2O (50 mL) and washed with 1% HCl (30 mL). The organic layer was washed successively with H_2O (30 mL) and saturated NaCl (30 mL), and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residual oil was purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 1.02 g (95%) of **13** as a colorless oil. ^1H NMR ($CDCl_3$) δ 6.66 (m, 2 H), 5.21 (m, 1 H), 3.64 (dd, J = 13.3, 7.0 Hz, 1 H), 3.14 (dd, J = 13.3, 4.6 Hz, 1 H), 1.07 (m, 21 H); ^{13}C NMR ($CDCl_3$) δ 142.0, 132.4, 68.9, 57.6, 17.7, 12.0; mass spectrum (CI, methane), *m/z* 291.1454 (M^+ + H) ($C_{13}H_{27}O_3SSi$ requires 291.1450).

(3α,3aα,7aα)- and (3α,3aβ,7aβ)-3-Benzyloxy-2,3,3a,7a-tetrahydrobenzo[*b*]thiophen-5(4*H*)-one-1,1-dioxide (14) and (15). A solution of **12** (260 mg, 1.16 mmol) and **9** (990 mg, 5.76 mmol) in dry mesitylene (4 mL) in a base-washed, dry tube was degassed by three freeze-thaw cycles under vacuum and then sealed. The sealed tube was heated at 170-180 °C (oil bath) for 48 h and then cooled to rt. The solvent was removed in vacuo, whereupon benzene (10 mL) and pyridinium *p*-toluenesulfonate (500 mg, 1.99 mmol) were added. The reaction mixture was heated at reflux for 24 h. The mixture was cooled and washed with 5% aqueous $NaHCO_3$ (20 mL), and the aqueous phase was extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with H_2O (20 mL), saturated aqueous NaCl (20 mL) and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was purified by HPLC using hexanes/EtOAc to give a mixture (1.2:1) of **14** and **15** in 82% combined yield. For **14** (less polar): white solid, mp 126-127 °C; ^1H NMR ($CDCl_3$) δ 7.34 (m, 5 H), 6.88 (dd, J = 10.2, 4.1 Hz, 1 H), 6.28 (dd J = 10.2, 1.6 Hz, 1 H), 4.59 (d, J = 11.8 Hz, 1 H), 4.52 (d, J = 11.8 Hz, 1 H), 4.24 (m, 1 H), 4.04 (app. q, J = 5.7 Hz, 1 H), 3.46 (dd, J = 13.8, 6.6 Hz, 1 H), 3.34 (dd, J = 13.8, 4.5 Hz, 1 H), 3.24 (app. p, J = 6.6 Hz, 1 H), 2.76 (dd, J = 16.8, 8.3 Hz, 1 H), 2.61 (dd, J = 16.8, 5.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 194.6, 137.2, 136.3, 133.4, 128.7, 128.4, 127.8, 75.4, 72.2, 59.8, 56.8, 41.8, 36.3; IR ($CHCl_3$) υ 1680, 1320, 1100 cm^{-1}; mass spectrum, (CI, methane), *m/z* 293.0839 (M^+ + H) ($C_{15}H_{17}O_4S$ requires 293.0847), 293 (base), 185, 122, 117; Anal. Calcd. for $C_{15}H_{17}O_4S$: C, 61.62; H, 5.51; S, 10.96. Found: C, 61.60; H, 5.61; S, 10.81. For **15** (more polar): white solid, mp 105-106 °C; ^1H NMR ($CDCl_3$) δ 7.31 (m, 2 H), 7.26 (m, 1 H), 7.19 (m, 2 H), 6.81 (dd, J = 10.3, 2.9 Hz, 1 H), 6.20 (dd, J = 10.3, 2.4 Hz, 1 H), 4.52 (d, J = 12.2 Hz, 1 H), 4.32 (d, J = 12.2 Hz, 1 H), 4.25 (app. q, J = 4.5 Hz, 1 H), 4.00 (overlapping dt, J = 2.9, 5.8 Hz, 1 H), 3.29 (m, 2 H), 3.23 (m, 1 H), 2.67 (dd, J = 17.0, 6.6 Hz, 1 H), 2.57 (dd, J = 17.0, 4.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 194.4, 136.6, 136.0, 132.9, 128.5, 128.2, 127.8, 75.4, 72.0, 59.9, 55.3, 39.6, 35.9; IR ($CHCl_3$) υ 1680, 1330, 1075 cm^{-1}; mass spectrum, (CI, methane), *m/z* 293.0853 (M^+ + H) ($C_{15}H_{17}O_4S$ requires 293.0847).

(3α,3aα,7aα)- and (3α,3aβ,7aβ)-3-(Triisopropylsiloxy)-2,3,3a,7a-tetrahydrobenzo[*b*]-thiophen-5(4*H*)-one-1,1-dioxide (16) and (17). A mixture (2.5:1) of **16** and **17** was isolated in 85% combined yield from the reaction of **13** and **9** according to the preceeding procedure. For **16** (less polar): off-white foam; ^1H NMR ($CDCl_3$) δ 6.89 (dd, J = 10.2, 4.9 Hz, 1 H), 6.30 (dd, J = 10.2, 1.3 Hz, 1 H), 4.42 (m, 1 H), 4.31 (app. t, J = 5.8 Hz, 1 H), 3.52 (dd, J = 13.8, 5.7 Hz, 1 H), 3.30 (dd, J=13.8, 2.8 Hz, 1 H), 3.10 (m, 1 H), 2.61 (d, J = 5.6 Hz, 1 H), 2.58 (d, J = 2.4 Hz, 1 H), 1.04 (m, 21 H); ^{13}C NMR ($CDCl_3$) δ 194.6, 136.9, 133.7, 70.0, 60.4, 59.2, 45.6, 36.3, 17.8, 11.8; IR (neat) υ 1690, 1330, 1260, 1210, 1140, 1075 cm^{-1}; mass spectrum, (CI, methane) *m/z* 359.1715 (M^+ + H) ($C_{17}H_{31}O_4SSi$ requires 359.1712), 201 (base), 175, 157, 121.

For **17** (more polar): white solid: mp 120-122 °C; IR ($CHCl_3$) υ 1685, 1325, 1210, 1120, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.86 (dd, *J* = 10.2, 4.5 Hz, 1 H), 6.31 (dd, *J* = 10.2, 1.5 Hz, 1 H), 4.81 (app. q, *J* = 6.6 Hz, 1 H), 4.02 (m, 1 H), 3.54 (dd, *J* = 13.4, 7.2 Hz, 1 H), 3.27 (overlapping dd and m, *J* = 13.4 , 7.2 Hz, 2 H), 2.73 (d, *J* = 1.0 Hz, 1 H), 2.70 (d, *J* = 3.4 Hz, 1 H), 1.04 (m, 21 H); ^{13}C NMR ($CDCl_3$) δ 195.3, 135.9, 134.0, 68.8, 61.5, 58.1, 42.1, 34.4, 17.8, 12.0; mass spectrum, (CI, methane) *m/z* 359.1681 (M^+ + H) ($C_{17}H_{31}O_4SSi$ requires 359.1712), 359 (base), 315, 201, 137, 121.

(3α,3aα, 7aα)-3-(Benzyloxy)-2,3,3a,7a-tetrahydrobenzo[b]thiophen-5(*4H*)-one (20). A solution of DIBAL-H (12.8 mL of 1.0 *M* solution in CH_2Cl_2, 12.8 mmol) was added dropwise to a solution of **14** (250 mg, 0.855 mmol) in dry CH_2Cl_2 under N_2 at 0 °C. The resulting mixture was stirred at 0 °C for 2 h and another portion of DIBAL-H (12.8 mL of 1.0 *M* solution in CH_2Cl_2, 12.8 mmol) was added slowly. The mixture was allowed to warm to rt and then heated at reflux for 20 h. The mixture was cooled to -78 °C, and a solution of glacial acetic acid (1.06 g, 17.6 mmol) in THF (1 mL) was added very slowly. The mixture was allowed to warm to rt, stirred for 15 min and then cooled to 0 °C. Saturated NH_4Cl (7 mL) and then 1 N HCl (2 mL) were slowly added. The resulting mixture was extracted with Et_2O (3 x 15 mL), and the combined organic layers were washed with H_2O (15 mL), saturated aqueous NaCl (15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give about 150 mg of a mixture (6:1) of allylic alcohol sulfides that were used in the next step without further purification.

A solution of DMSO (80 μL, 1.13 mmol) in dry CH_2Cl_2 (150 μL) was added dropwise to a solution of oxalyl chloride (50 μL, 0.58 mmol) in dry CH_2Cl_2 (1.5 mL) at -60 °C and the solution maintained at -60 °C for 5 min, whereupon a solution of the crude allylic alcohol sulfides (150 mg, 0.57 mmol) in dry CH_2Cl_2 (0.8 mL) was added dropwise. Stirring was continued at -60 °C for 20 min, the mixture cooled to -78 °C, and Et_3N (400 μL, 2.88 mmol) was added slowly. The resulting white slurry was warmed to rt and H_2O (1.2 mL) added. The mixture was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were washed with saturated NaCl (5 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to afford 110 mg (49%) of **20** as a light yellow oil. ^1H NMR ($CDCl_3$) δ 7.32 (m, 5 H), 6.75 (dd, *J* = 10.0, 3.7 Hz, 1 H), 5.92 (d, *J* = 10.0 Hz, 1 H), 4.58 (d, *J* = 11.7 Hz, 1 H), 4.51 (d, *J* = 11.7 Hz, 1 H), 4.20 (m, 1 H), 3.97 (q, *J* = 5.8 Hz, 1 H), 3.25 (dd, *J* = 10.9, 5.6 Hz, 1 H), 2.97 (dd, *J* = 10.9, 5.6 Hz, 1 H), 2.87 (p, *J* = 6.3 Hz, 1 H), 2.66 (dd, *J* = 16.4, 6.9 Hz, 1 H), 2.52 (dd, *J* =16.4, 5.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 196.8, 148.8, 137.5, 128.5, 128.0, 127.7, 127.3, 83.3, 72.1, 46.6, 41.8, 37.4, 35.8; IR (neat) υ 1680 cm^{-1}; mass spectrum *m/z* 260.0866 ($C_{15}H_{16}O_2S$ requires 260.0871) 260, 123, 107, 91 (base).

(3α,3aα,7aα)-3-(Triisopropylsiloxy)-2,3,3a,7a-tetrahydrobenzo[b]thiophen-5(*4H*)-one (21). A solution of DIBAL-H (13.5 mL of 1.0 *M* solution in CH_2Cl_2, 13.5 mmol) was added with stirring to a solution of **16** (483 mg, 1.35 mmol) in dry CH_2Cl_2 (10 mL) at rt. After 24 h, saturated potassium sodium tartrate (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 75 mL). The combined organic layers were washed with saturated NaCl (50 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give about 350 mg of a crude mixture (ca. 1:2) containing allylic alcohol sulfides and sulfoxides. This mixture was dissolved in dry CH_2Cl_2 (25 mL) containing PDC (776 mg, 2.07 mmol) and 4 Å molecular sieves (1.1 g), and the resulting mixture was stirred at rt for 2 h. Et_2O (15 mL) was added, and the mixture was stirred for 1 h. The solids were removed by filtration through a plug of silica gel, and the solvent was removed under reduced

pressure to give about 280 mg of a mixture of **21** and the corresponding sulfoxides. This mixture was not separated but rather dissolved in dry benzene (1 mL) at rt. Dry pyridine (65 mg, 0.78 mmol) and 1,2-phenylene phosphorochloridite (140 mg, 0.78 mmol) were added sequentially with stirring, and after 3 h at rt, the mixture was washed with 2 N NaOH (4 x 1 mL) followed by H_2O (1 x 1 mL). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by flash chromatography eluting with hexane/EtOAc (4:1) to give 242 mg (55%) of **21** as a white solid, mp 66-67 °C (recry from hexane). ^1H NMR ($CDCl_3$) δ 6.83 (dd, J = 10.0, 4.3 Hz, 1 H), 5.97 (dd, J = 10.0, 1.1 Hz, 1 H), 4.36 (app q, J = 4.7 Hz, 1 H), 4.29 (app. t, J = 4.8 Hz, 1 H), 3.33 (dd, J = 10.8, 4.7 Hz, 1 H), 2.94 (dd, J = 10.8, 4.0 Hz, 1 H), 2.73 (m, 1 H), 2.53 (dd, J = 16.3, 9.3 Hz, 1 H), 2.43 (dd, J = 16.3, 5.4 Hz, 1 H), 1.06 (comp, 21 H); ^{13}C NMR ($CDCl_3$) δ 196.9, 148.4, 1279, 78.1, 50.1, 42.3, 40.1, 37.4, 18.0, 12.5; IR (CCl_4) υ 1686 cm^{-1}; mass spectrum (CI, methane) *m/z* 327.1819 (M^+ + H) ($C_{17}H_{31}O_2SSi$ requires 327.1814), 283, 233, 201 (base), 189.

2-(Methylenehydroximmo)-2,5,5-trimethyl-1,3-dioxacyclohexane. A solution of 2,2-dimethyl-1,3-propanediol (900 mg, 864 mmol), pyruvic aldehyde 1-oxime (**22**) (300 mg, 3.45 mmol) and trimethylsilylchloride (2.25 g, 20.7 mmol) in dry CH_2Cl_2 (10 mL) was heated at reflux for 36 h. After cooling, the mixture was added to cold 5% $NaHCO_3$ (15 mL), and the aqueous mixture was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with saturated NaCl (20 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The viscous oil thus obtained was purified by flash chromatography eluting with hexanes/EtOAc (1:5) to afford 404 mg (68%) of the ketal oxime as a white crystalline solid, mp 68-69 °C; ^1H NMR ($CDCl_3$) δ 9.07 (br s, 1 H), 7.38 (s, 1 H), 3.63 (d, J = 11.1 Hz, 2 H), 3.42 (d, J = 11.1 Hz, 2 H), 1.49 (s, 3 H), 1.17 (s, 3 H), 0.73 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 151.0, 96.8, 72.2, 30.0, 26.7, 22.7, 21.9; (IR ($CHCl_3$) υ 3280, 2880, 1610, 1445 cm^{-1}; mass spectrum *m/z* 173.1049 ($C_8H_{15}NO_3$ requires 173.1052), 173, 158, 129 (base), 88, 56, 43; Anal. Calcd. for $C_8H_{15}NO_3$: C, 55.47; H, 8.72; N, 8.09. Found: C, 55.67; H, 8.87; N, 8.04.

2-[(Chloromethylene)hydroxyimino]-2,5,5-trimethyl-1,3-dioxacyclohexane (23). *N*-chlorosuccinimide (1.50 g, 11.2 mmol) was added in three equal portions to a solution of the above ketal oxime (1.75 g, 10.0 mmol) in dry DMF (10 mL) while maintaining an internal temperature of less than 40 °C. The resulting clear solution was stirred at rt for 2 h, and cold water (60 mL) was added. The mixture was extracted with Et_2O (3 x 40 mL), and the combined organic layers were washed with cold water (4 x 40 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure to provide 1.75 g (85%) of **23** as a white crystalline solid, mp 112-114 °C; ^1H NMR ($CDCl_3$) δ 8.18 (br s, 1 H), 3.58 (d, J = 11.2 Hz, 2 H), 3.44 (d, J = 11.2 Hz, 2 H), 1.64 (s, 3 H), 1.22 (s, 3 H), 0.74 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 140.4, 98.8, 72.4, 29.3, 26.9, 22.8, 21.9; IR ($CHCl_3$) υ 3300, 1720 cm^{-1}; mass spectrum, (CI, methane) *m/z* 208.0748 (M^+ + H) ($C_8H_{15}ClNO_3$ requires 208.0740), 129 (base), 87, 69, 57, 41.

(3β,5aα,6α,8aα,8bβ)-6-Benzyloxy-3-(2'5'5'-trimethyl-1',3'-dioxacyclohexyl)-3a,5a,6,7,8a,8b-hexahydrothieno[2,3-g]-1,2-benzisoxazol-4(5*H*)-one (24). To a solution of enone **20** (50 mg, 0.19 mmol) in Et_2O (0.5 mL) under N_2 at rt was added simultaneously over 32 h via a syringe pump a solution of **23** (355 mg, 1.71 mmol) in Et_2O (1.4 mL) and a solution of Et_3N (173 mg, 1.71 mmol) in Et_2O (1.0 mL). After the addition was complete, the resulting suspension was stirred at rt for 24 h. The reaction mixture was filtered through a plug of Celite, and the solvent was removed under reduced pressure to give an orange oil that was purified by flash chromatography eluting with hexane/EtOAc (10:1) to provide 30 mg (37%)

of **24** as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.31 (m, 5 H), 5.26 (dd, *J* = 10.0, 3.4 Hz, 1 H), 4.53 (d, *J* = 12.0 Hz, 1 H), 4.51 (d, *J* = 12.0 Hz, 1 H), 4.18 (dd, *J* = 5.6, 3.4 Hz, 1 H), 4.08 (dd, *J* = 10.0, 1.9 Hz, 1 H), 3.95 (m, 1 H), 3.49 (m, 4 H), 3.32 (m, 1 H), 3.02 (d, *J* = 12.0 Hz, 1 H), 2.94 (dd, *J* = 12.0, 3.7 Hz, 1 H), 2.73 (dd, *J* = 15.1, 11.1 Hz), 1.76 (ddd, *J* = 15.1, 2.8, 1.9 Hz, 1 H), 1.57 (s, 3 H), 0.99 (s, 3 H), 0.90 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 203.3, 157.6, 137.5, 128.5, 127.9, 127.5, 96.2, 87.4 , 86.9, 71.7, 71.4, 70.8, 59.0, 45.3, 44.3, 37.1, 35.3, 29.7, 22.7, 22.6, 22.5; IR ($CHCl_3$) υ 1724, 1601 cm^{-1}; mass spectrum, *m/z* 431.1835 ($C_{23}H_{29}NO_5S$ requires 431.1766), 431, 416, 288, 129, (base) 91, 69, 43.

(3β,5aα,6α,8aα,8bβ)-6-Triisopropylsiloxy-3-(2'5'5'-trimethyl-1',3'-dioxacyclohexyl)-3a,5a,6,7,8a,8b-hexahydrothieno[2,3-g]-1,2-benzisoxazol-4(5*H*)-one (25). Prepared as a colorless oil in 27% yield from **21** and **23** using the same procedure described above for the preparation of **24**. ^{1}H NMR ($CDCl_3$) δ 5.30 (dd, *J* = 10.1, 3.5 Hz, 1 H), 4.34 (br s, 1 H), 4.22 (dd, *J* = 5.3, 3.5 Hz, 1 H), 4.12 (dd, *J* = 10.1, 1.6 Hz, 1 H), 3.53 (comp, 4 H), 3.13 (m, 1 H), 3.02 (dd, *J* = 11.6, 3.4 Hz, 1 H), 2.85 (d, *J* = 11.6 Hz, 1 H), 2.71 (dd, *J* = 15.4, 11.3 Hz, 1 H), 1.74 (dt, *J* = 15.4, 2.3 Hz, 1 H), 1.60 (s, 3 H), 1.06 (comp, 21 H), 1.02 (s, 3 H) 0.93 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 203.3, 157.6, 96.2, 86.8, 81.8, 71.7, 71.4, 59.1, 48.9, 44.5, 39.2, 37.1, 29.7, 22.8, 22.6, 22.5,18.0, 12.1; IR (film) υ 1727, 1589 cm^{-1}; mass spectrum (CI, methane) *m/z* 498.2700 ($M^+ + H$) ($C_{25}H_{44}NO_5SSi$ requires 498.2709), 454, 412, 238, 157, 129 (base).

2-(*tert*-Butyldimethylsiloxy)-2-nitromethyltetrahydropyran (27). A solution of 3.62 M *n*-BuLi in hexane (483 μL, 1.75 mmol) was added to a solution of dry THF (4 mL) and dry HMPA (800 μL) at -90 °C. Nitromethane (61 mg, 1.00 mmol) was added, and the mixture was stirred for 10 min at -90 °C and then at -60 °C for 2 h. This resultant yellow solution was then cooled to -78 °C, and valerolactone (50 mg, 0.50 mmol) was added. The mixture was allowed to warm to -40 °C and stirred for 3.5 h. The solution was again cooled to -90 °C, and *i*-Pr_2NEt (371 mg, 2.87 mmol) and TBDMS triflate (528 mg, 2.0 mmol) were added sequentially. The reaction mixture was stirred at -90 °C for 30 min and then at -40 °C for 2 h. A mixture of acetic acid (250 μL) and THF(200 μL) was added and the mixture allowed to warm to rt. Water (10 mL) was added, and the mixture was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with H_2O (15 mL), saturated NaCl and dried (Na_2SO_4), and the solvents were removed under reduced pressure. The crude product was purified by HPLC eluting with hexanes/EtOAc (1:20) to give 68 mg (42%) of **27** as a light yellow oil; the open chain derivative was also isolated in 42% yield. For **27**: ^{1}H NMR ($CDCl_3$) δ 4.54 (d, *J* = 10.3 Hz, 1 H), 4.47 (d, *J* = 10.3 Hz, 1 H), 3.90 (m, 1 H), 3.69 (m, 1 H), 1.98-1.51 (comp, 6 H), 0.90 (s, 9 H), 0.18 (s, 3 H), 0.16 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 96.1, 82.2, 63.1, 33.8, 25.7, 24.5, 19.2, 18.2, -2.6, -2.9.

3-[2'-(*tert*-Butyldimethylsiloxy)oxacyclohexyl]-5-cyano-4,5-dihydroisoxazole (29a,b). A solution of nitroketal **27** (40 mg, 0.14 mmol) and Et_3N (20 μL, 15 mg, 0.15 mmol) in C_6H_6 (40 μL) was added dropwise to a solution of acrylonitrile (10 μL, 8.1 mg, 0.15 mmol) and phenylisocyanate (30 μL, 33 mg, 0.28 mmol) in C_6H_6 (62 μL). The resulting mixture was stirred at rt for 1 h and then heated at reflux for 1 h. The diphenyl urea was removed by vacuum filtration, and the filtrate was concentrated to give a crude mixture of two products. This crude oily mixture was purified by flash chromatography (20% EtOAc hexanes) to afford 30 mg (65%) of a mixture (1:1) of **29a,b**. For **29a** (less polar): mp 59-61 °C; ^{1}H NMR ($CDCl_3$) δ 5.18 (dd, *J* = 10.6, 6.0 Hz, 1 H), 3.97 (dt, *J* = 11.5, 4.9 Hz, 1 H), 3.55 (dd, *J* = 11.5, 5.7 Hz, 1 H), 3.44 (m, 2 H), 2.16 (m, 1 H), 1.80 (m, 3 H), 1.56 (m, 2 H), 0.88 (s, 9 H), 0.14 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 160.3, 117.1, 95.4, 66.0, 63.9, 40.4, 35.1, 25.7, 24.7, 20.1, 18.1, -2.7, -3.0; mass spectrum (CI, methane), *m/z* 310.1714

($C_{15}H_{26}N_2O_3Si$ requires 310.1713), 295, 215 (base) 179, 152. For **29b** (more polar): mp 63-65 °C; ^1H NMR ($CDCl_3$) δ 5.15 (dd, J = 9.0, 8.6 Hz, 1 H), 3.93 (m, 1 H), 3.48 (m, 1 H), 3.42 (d, J = 8.6 Hz, 2 H), 2.06 (ddd, J = 12.8, 8.0, 4.6 Hz, 1 H), 1.85 (ddd, J = 12.8, 8.0, 4.3 Hz, 1 H), 1.77 (m, 2 H), 1.53 (m, 2 H), 0.90 (s, 9 H), 0.16 (s, 3 H), 0.14 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 160.4, 117.0, 94.9, 65.8, 63.3, 40.3, 34.9, 25.7, 24.7, 19.6, 18.2, -2.8, -3.1; mass spectrum, (CI, methane), *m/z* 310.1737 ($C_{15}H_{26}N_2O_3Si$ requires 310.1713).

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