Tetrahedron 66 (2010) 5852–5862

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis and chemical diversity analysis of bicyclo[3.3.1]non-3-en-2-ones

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ARTICLE INFO

Article history:
Received 7 April 2010
Accepted 25 April 2010
Available online 22 May 2010

Keywords:
Bicyclo[3.3.1]nonenones
Chemical diversity analysis
Ring-opening
Epoxyketone rearrangement

ABSTRACT

Functionalized bicyclo[3.3.1]non-3-en-2-ones are obtained from commercially available phenols by a hypervalent iodine oxidation, enone epoxidation, epoxide thiolysis, and intramolecular aldol reaction sequence. Reaction optimization studies identified room temperature as well as microwave-mediated procedures, providing moderate to good yields (57–88%) in the thiophenol-mediated epoxide opening and intramolecular aldol reaction. In addition, the isolation of a key intermediate and in situ NMR studies supported the mechanistic hypothesis. The bicyclic ring products occupy novel chemical space according to ChemGPS and Chemaxon chemical diversity and cheminformatics analyses.

1. Introduction

Inspired by the steady advancements in genomics, proteomics, and other omics,[1] as well as the vast strides that have been made in our understanding of signaling pathways,[2] the National Institutes of Health (NIH) have launched an ambitious Molecular Libraries Program (MLP; an NIH Roadmap Initiative),[3] aiming to enhance chemical biology efforts through High Throughput Screening (HTS). HTS followed by focused chemical library syntheses are expected to yield small molecule probes effective at modulating a given biological process or disease state. The MLP is supported by five Centers for Chemical Methodologies and Library Development (CMLD),[4] who are charged with the validation of efficient, general, state-of-the-art methodologies for the design, synthesis, analysis, and handling of chemical diversity libraries. We are particularly interested in developing new synthetic approaches toward chemotypes that are currently underrepresented in the NIH Libraries (MLSMR),[5] a collection of ca. 340,000 small organic molecules whose structures and biological annotation are conveniently accessible through the PubChem web interface.[6]

The discussion of what constitutes diversity-oriented synthesis (DOS) and probe-relevant chemical space has led to a growing number of cheminformatics and structural analysis tools, supporting chemists in their assessment of chemical diversity.[7,8] Estimates of the expanse of the chemical universe vary greatly, from 10^{23} to $>10^{60}$ possible compounds,[9] but only ca. 10^{9} molecules have been structurally defined to date.[10] A more practical question that must be addressed before the total number can be computed is how to design new small-molecules with novel structures and properties while populating mainly the biologically relevant regions of chemical space.[11] As it is often the case in organic chemistry, natural products, specifically the development of natural product-like libraries, might offer one opportunity to expand current chemical diversity in meaningful directions.[12] Our strategy focused on diversifying the highly functionalized bicyclo[3.3.1]non-3-en-2-one core of the natural products gymnastatins F and Q (Fig. 1).[13]

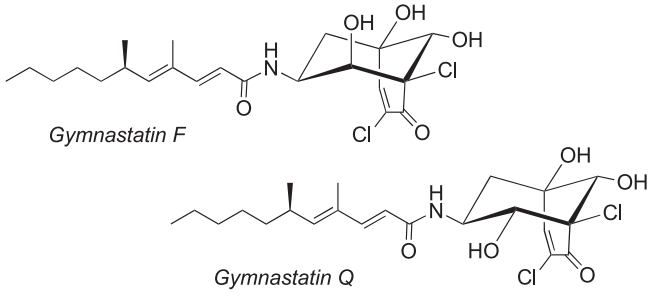

Figure 1. Structures of the bicyclo[3.3.1]non-3-en-2-ones gymnastatin F and Q.

Gymnastatins F and Q were isolated from the extract of the *Halichondria* sponge-derived fungus *Gymnascella dankaliensis*, and found to exhibit potent growth inhibition against murine P388 lymphocytic leukemia and other human cancer cell lines.

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doi:10.1016/j.tet.2010.04.112

Furthermore, gymnastatin Q showed appreciable growth inhibition in BSY-1 (breast) and MKN7 (stomach) human cancer cell lines.[13]

During the course of our total synthesis of aranorosin,[14] we discovered that the treatment of spirodiepoxyketone intermediate **1** with thiophenol in the presence of base initiated a novel ring-opening/rearrangement cascade, resulting in the formation of the bicyclic core present in the gymnastatins (Fig. 2).[15]

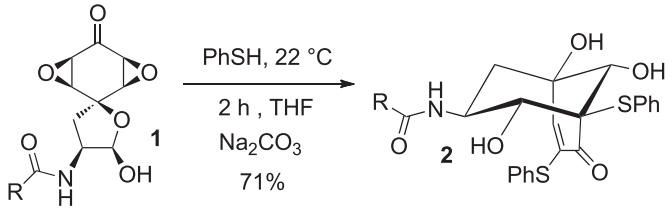
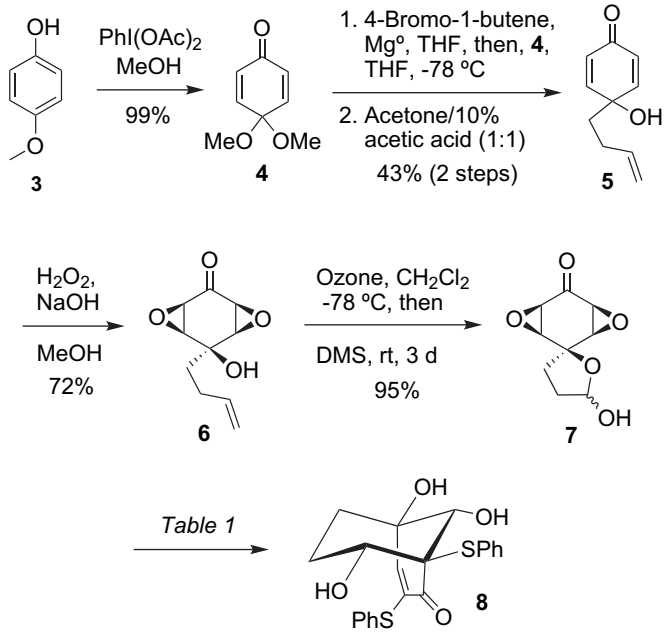


Figure 2. Rearrangement of spirolactol **1** to bicyclic enone **2**.

Inspired by this process, we sought to access new regions of biologically relevant space with this methodology and prepare bicyclo[3.3.1]non-3-en-2-one derivatives from commercially available thiophenols through hypervalent iodine oxidation.[16]

2. Results and discussion

The utility of hypervalent iodine reagents in organic synthesis has been well documented.[17] In particular, phenyl iodosobenzene diacetate (PIDA) has been shown to facilitate the oxidative addition of nucleophiles to phenols to give the corresponding substituted dienones.[18] The large scale production of the spirolactol **1**, however, was hampered by the low (20–30%) yield in the PIDA oxidation of tyrosine, most likely due to the presence of the amide functionality in this precursor.[14,19] During their investigation of the total synthesis of aranorosin, the McKillop group synthesized the deaminated spirolactol **7**, which we used as a more synthetically tractable starting point for our core diversifications (Scheme 1).[20] Oxidative addition of MeOH to *p*-methoxy phenol (3) in the presence of PIDA provided quinone monoketal **4** in quantitative yield. In situ generation of butenylmagnesium bromide followed by addition to **4** and ketal hydrolysis led to the desired bis-α,β-unsaturated ketone **5**. Diepoxidation of **5** with basic hydrogen peroxide proceeded smoothly in methanol to afford the all *syn*-oxygenated diepoxyketone **6** in 72% yield. Finally, ozonolysis in CH_2Cl_2 at −78 °C followed by treatment with an excess of DMS for several days to ensure decomposition of the unusually stable ozonide intermediate[20] provided the diepoxyketone lactol **7** in 95% yield on 1 g scale as a 1:1 mixture of lactols, as determined by ^1H NMR.



Scheme 1. Synthesis of diepoxyketone lactol **7** and conversion to bicycle **8** after reaction optimization.

2.1. Reaction optimization for bicycle formation

When spirolactol **7** was treated with 5 equiv of thiophenol and 10 equiv of sodium hydride in THF, according to our previously described procedure,[21] a disappointing 28% yield of the desired bicyclo[3.3.1]non-3-en-2-one **8** was isolated (Table 1, entry 1). Screening bases of various strengths (not shown) revealed that treatment of **7** with 10 equiv of potassium carbonate and 5 equiv of thiophenol in THF provided the desired product **8** in 72% yield (Table 1, entry 2). A solvent screen further increased the yield of the desired product to 84% in diethyl ether (Table 1, entry 3); however a significant increase in reaction time was required for complete conversion. Ultimately, methylene chloride was found to be the optimal solvent, providing **8** in 84% yield over 5 h reaction time.

Table 1
Optimization of ring-opening/rearrangement reaction of spirolactol **7**, forming bicycle **8**

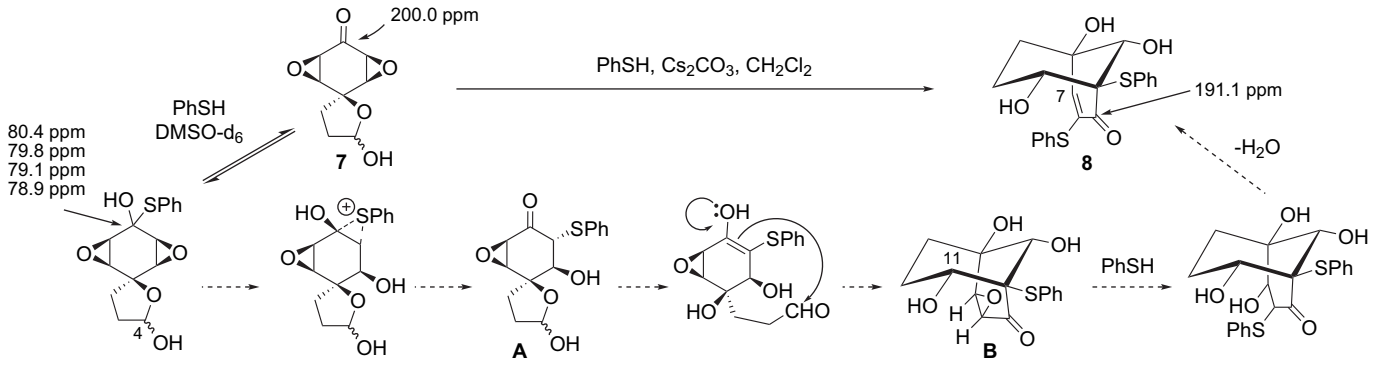
Entry	PhSH (equiv)	Base (equiv)	Temperature	Solvent	Time	Yield[a] (%)
1	5	NaH (10)	rt	THF	6 h	28
2	5	K_2CO_3 (10)	rt	THF	8 h	72
3	5	K_2CO_3 (10)	rt	Et_2O	23 h	84
4	5	K_2CO_3 (10)	rt	CH_2Cl_2	5 h	84
5	3	Cs_2CO_3 (5)	rt	CH_2Cl_2	1.5 h	83
6	2	Cs_2CO_3 (2)	rt	CH_2Cl_2	3 h	70
7	3	Cs_2CO_3 (5)	66 °C	THF	15 min	70
8	3	Cs_2CO_3 (5)	60 °C (MW)	CH_2Cl_2	2 min	88

[a] Isolated yields.

Next, the effect of the counter cation on the carbonate base was probed. Cesium carbonate proved the most advantageous, affording both decreased reaction times and a reduction in necessary equivalents of both the base and nucleophile. A slight excess of thiophenol (3 equiv) and cesium carbonate (5 equiv) for 1.5 h at rt provided **8** in 83% yield (Table 1, entry 5). The use of stoichiometric amounts of both base and nucleophile led to a slight decrease in yield to 70% (Table 1, entry 6). In order to further reduce reaction times, the reaction was also performed at elevated temperatures (THF, 66 °C) to afford the desired product in only 15 min, albeit in slightly reduced 70% yield (Table 1, entry 7). Finally, to decrease the reaction time while minimizing decomposition during thermal exposure, microwave conditions were investigated. Gratifyingly, stirring **7** with 3 equiv of thiophenol and 5 equiv of cesium carbonate in the microwave at 60 °C for 2 min afforded **8** in 88% yield (Table 1, entry 8).

2.2. Mechanistic investigation

^{13}C NMR studies allowed for a further refinement of our previous mechanistic hypothesis (Scheme 2).[15] An initial reversible nucleophilic attack of thiophenol at the carbonyl group generates the observed mixed *O*,*S*-acetals, which under basic conditions, undergo a 1,2-migration to open the epoxide, giving ketone **A**. Next, prior to



Scheme 2. Proposed mechanism for the ring-opening and intramolecular aldol reaction of diepoxyketone **7** with thiophenol.

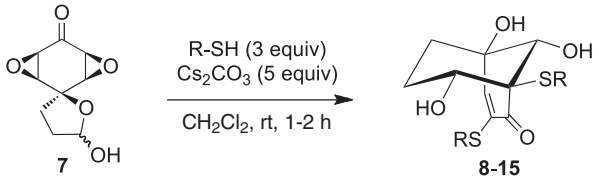
the addition of a second equivalent of thiophenol, a base catalyzed, intermolecular aldol reaction with the hemiacetal occurs to give the isolated intermediate **B**. Finally, opening of the epoxide α to the carbonyl group with a second equivalent of thiophenol, followed by dehydration, provides product **8**. Specifically, incubation of spirolactol **7** with 3 equiv of thiophenol in DMSO-d_6 leads to a complete conversion of the carbonyl carbon (200.0 ppm) to all four possible diastereomeric acetals (new ^{13}C peaks at 80.4, 79.8, 79.1, and 78.9 ppm). Upon addition of 5 equiv of Cs_2CO_3, these acetal peaks converge to a single α,β-unsaturated carbonyl resonance at 191.1 ppm, characteristic of bicyclo[3.3.1]non-3-en-2-one **8**. Monitoring of the reaction mixture by ^1H NMR revealed the complete disappearance of the lactol hydrogen at C4 (5.76 ppm) and two of the epoxide hydrogens (3.40–3.36 ppm) in **7**, as well as the appearance of a doublet of doublets corresponding to the hydrogen at C11 of **B** (3.34 ppm), prior to the formation of product **8** (as indicated by the alkene hydrogen at C7 of **8**, 5.96 ppm). When spirolactol **7** was subjected to the optimized room temperature conditions and the mixture was quenched after only 5 min reaction time, epoxyketone **B** was isolated in 18% yield along with a 53% yield of **8**. As expected, upon resubmission of **B** to the reaction conditions, bicyclo[3.3.1]non-3-en-2-one **8** was formed in 77% yield.

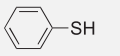
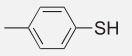
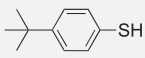
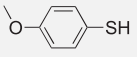
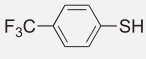
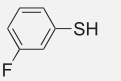
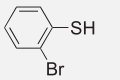
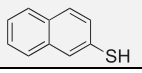
2.3. Scope and limitations of the ring-opening rearrangement reaction

2.3.1. Survey of aryl thiol nucleophiles. Since 2 equiv of aryl thiol are introduced in the product bicyclo[3.3.1]non-3-en-2-one, these reagents are important for structural diversification. Therefore, we probed the electronic and steric limitations of the aryl thiol nucleophiles. Alkyl substitution at the *p*-position (Table 2, entries 2 and 3) was well tolerated and provided the desired bicycles in good yields. The presence of an electron-donating *p*-methoxy group had little effect and provided similar yields (Table 2, entry 4). Electron-withdrawing substituents on the arene, including the *m*-fluoro and *p*-trifluoromethyl groups, also proceeded smoothly and provided the corresponding products in good yields (Table 2, entries 5 and 6). The *o*-bromo derivative was the highest yielding reagent under rt conditions and provided a handle for subsequent cross-coupling reactions (entry 7). The more sterically demanding 2-naphthyl derivative exhibited a slightly lower yield (57%), possibly due to the reduced solubility of both thiol reagent and product bicycle in methylene chloride (entry 8). Furthermore, after 2 min at 60 °C in the microwave, the desired products were obtained in all cases in comparable yields to the rt conditions, and the naphthyl derivative provided the desired product **15** in improved 74% yield.

The structure assignments of the bicyclic products were supported by 1D and 2D NMR analyses. A single diastereomer was observed, representing the thermodynamically favored product

Table 2
Scope of the rearrangement reaction of epoxyketone **7**



Entry	R-SH	Product	Yield[a,c] (%)
1		**8**	83 (88)
2		**9**	73 (74)
3		**10**	72 (84)
4		**11**	74 (80)
5[b]		**12**	74 (71)
6		**13**	74 (77)
7		**14**	87 (83)
8		**15**	57 (74)

[a] Yields in parentheses correspond to microwave heating of R-SH (3 equiv) and Cs_2CO_3 (5 equiv) in CH_2Cl_2 for 2 min at 60 °C.
[b] Product contained a minor intractable aromatic impurity (<4% by ^1H NMR).
[c] Isolated yields.

with the hydroxyl substituents in the equatorial orientation. Furthermore, the structure of analogue **14** was unambiguously established via X-ray crystallography (Fig. 3).

2.3.2. Investigation of diepoxyketone substitution. In order to access more highly substituted bicyclo[3.3.1]non-3-en-2-ones, the effect of substituents on the diepoxyketone was also probed. The required precursors were obtained by the addition of MeOH to commercially available phenols in the presence of PIDA.

The known quinone monoketals **16** and **21** were synthesized in good yields on multi-gram scale (Schemes 3 and 4).[20a,22] Addition of

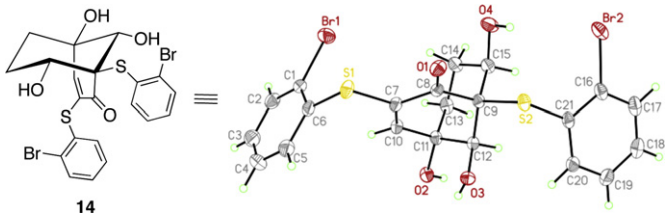
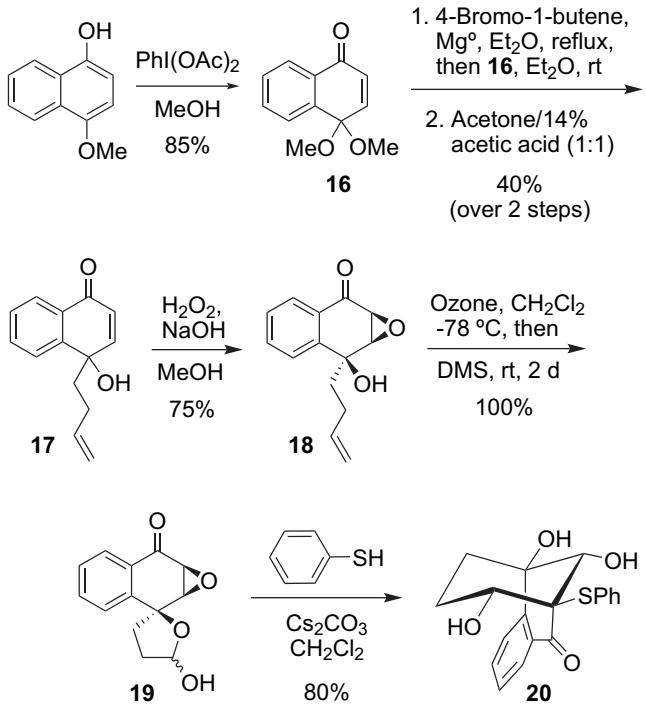


Figure 3. ORTEP drawing of *o*-bromo-bicyclo[3.3.1]non-3-en-2-one **14** (with 50% probability atomic displacement parameters).



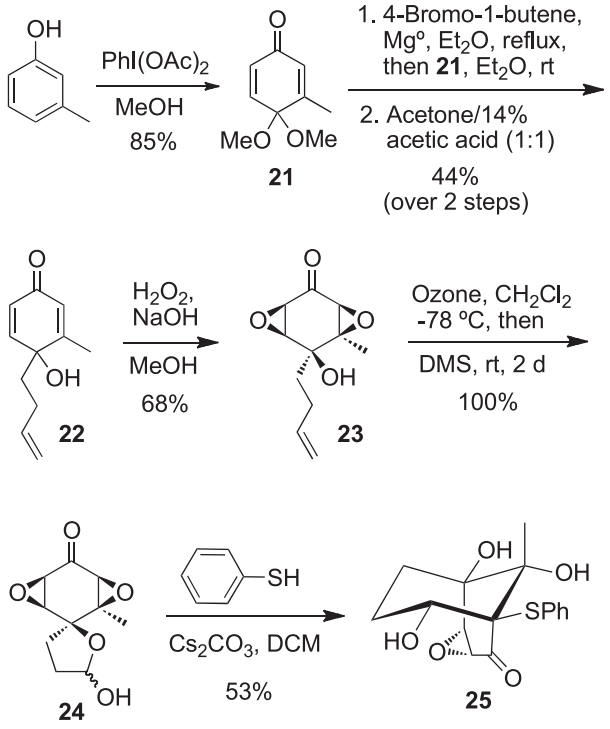
Scheme 3. Synthesis of naphthoquinone monoacetal **16** by hypervalent iodine oxidation and rearrangement to bicycle **20**.

in situ generated butenylmagnesium bromide to the monoketal **16** followed by ketal hydrolysis provided **17** in 40% yield over two steps. Diepoxidation and ozonolysis proceeded in 75% and 100% yield, respectively, to give **19** as a 2:1 mixture of lactol epimers by ^{1}H NMR.

In the presence of thiophenol and cesium carbonate base, **19** rearranged to provide **20** in 80% yield. The structure of **20** was also confirmed by X-ray analysis; all hydroxyl groups again assumed the equatorial orientation on the cyclohexane chair (see Supplementary data).

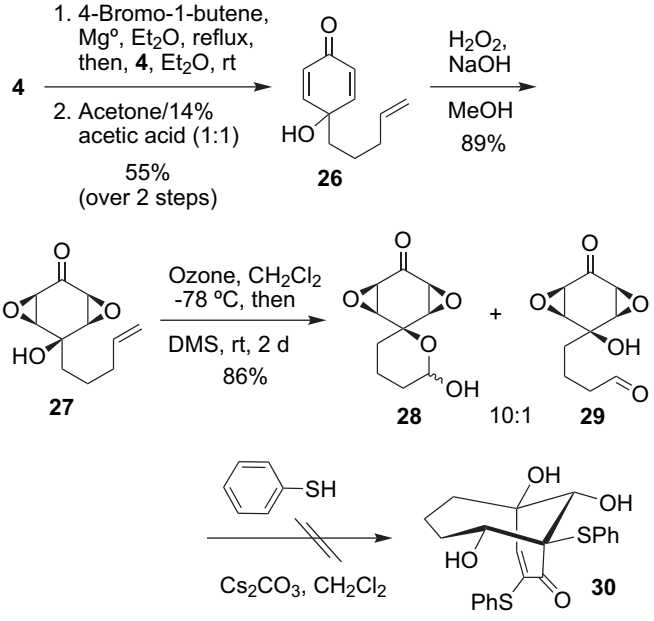
In an analogous fashion to the naphthyl derivatives, the quinone monoacetal **21** and the methylated spirolactol **24** were prepared (Scheme 4). Upon treatment of **24** with thiophenol under the previously optimized conditions, 53% of the epoxy ketone **25** was isolated as the major product. Even under forcing microwave conditions (10 equiv of thiophenol and 10 equiv of Cs_2CO_3, CH_2Cl_2, 80 °C, for 3 h), none of the expected bicyclo[3.3.1]non-3-en-2-one was formed. Apparently, the presence of the axial methyl group in **25** decreases the flexibility of the bicyclic system sufficiently to prevent an *endo*-addition of the second equivalent of thiophenol to the remaining epoxide moiety in **25**. However, this apparent resistance of the epoxide moiety toward nucleophilic attack bodes well for the use of more rigid epoxyketones in biological assays.

An attempt to extend the methodology towards the formation of bicyclo[3.4.1]dec-3-en-2-ones was unsuccessful (Scheme 5). In situ



Scheme 4. Synthesis of *m*-cresol quinone monoacetal **21** by hypervalent iodine oxidation and rearrangement to bicycle **25**.

generation of pentenylmagnesium bromide followed by addition to quinone monoketal **4** and ketal hydrolysis provided the desired bis-α,β-unsaturated ketone **26** in 55% yield. Diepoxidation proceeded smoothly to give **27** in 89% yield, and subsequent ozonolysis gave a 10:1 ratio of lactol **28** and aldehyde **29**. However, in the presence of thiophenol and base, a complex mixture formed, and none of the desired bicyclo[3.4.1]dec-3-en-2-one **30** was isolated. It is likely that intermolecular aldol processes leading to undesired side products are more favored in this series than the intramolecular seven-membered ring formation.



Scheme 5. Attempted preparation of bicyclo[3.4.1]dec-3-en-2-one **30**.

2.4. Contribution to chemical diversity

The molecular diversity of the newly synthesized structures was analyzed using the ChemGPS-NP map of chemical space (Fig. 4).[23] ChemGPS-NP provides a coordinate system tuned for exploration of biologically relevant compounds, derived from principal component analysis of the physiochemical properties of known bioactive and natural product molecules. The first three principle components (PC1, PC2, and PC3) roughly correspond to the molecular size, number of π electrons (aromaticity) and lipophilicity of a compound.

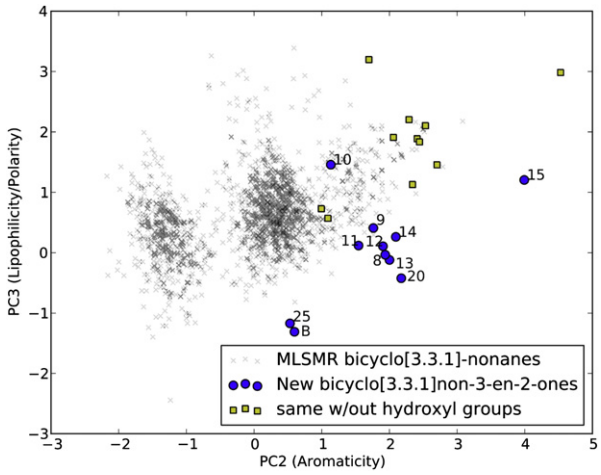


Figure 4. ChemGPS-NP coordinates of the newly synthesized bicyclic products (blue circles) and the bicyclo[3.3.1]-nonanes in the MLSMR library[3] (crosses). Also shown are the coordinates of bicyclo[3.3.1]non-3-en-2-ones with all hydroxyl groups removed (yellow boxes).

The newly synthesized bicyclic products were compared to the space spanned by the bicyclo[3.3.1]-nonanes already contained in the MLSMR library (1907 compounds). The new compounds occupy a simultaneously more aromatic and less lipophilic region of chemical space than this reference collection (Fig. 4). The greater degree of aromaticity is due to the benzene rings introduced through the aryl thiol moieties. In particular, the two naphthyl groups of structure **15** move this compound far outside the space of known bicyclo[3.3.1.]nonanes (see number of aromatic rings in Table 3). The dense hydroxylation pattern is responsible for the compounds' lower lipophilicity and increased polarity; as shown in Figure 4, without the hydroxyl groups, the compounds' lipophilicity is greatly increased.

Table 3
Selected physiochemical properties of new bicyclic products **8**–**15**.[24]

Product	MW	XLogP	Lipinski HBD	Lipinski HBA	Lipinski violations	Aryl rings
B	308.35	−0.27	3	5	0	1
8	400.51	3.06	3	4	0	2
9	428.56	3.65	3	4	0	2
10	512.72	6.20	3	4	2	2
11	460.56	2.77	3	6	0	2
12	536.51	4.87	3	4	1	2
13	436.49	3.33	3	4	0	2
14	558.30	4.66	3	4	1	2
15	500.63	5.16	3	4	2	4
20	342.41	1.92	3	4	0	2
25	322.38	0.12	3	5	0	1

In terms of size and shape, the new derivatives do not appear to occupy significantly new space, as shown by projection into the first and fourth ChemGPS-NP principle components (Fig. 5a). However, these compounds occupy lead-like portions of the chemical space. They are generally less flexible than the MLSMR reference compounds, decreasing the likelihood of non-specific binding in ligand-receptor interactions. PC5 and PC6 (Fig. 5b) are greatly influenced by the electronegative atom content and the aliphatic electropositive ratio, respectively. As might be expected, the new compounds occupy open space on the negative PC5 axis clustered around the origin of the PC6 axis, respectively.

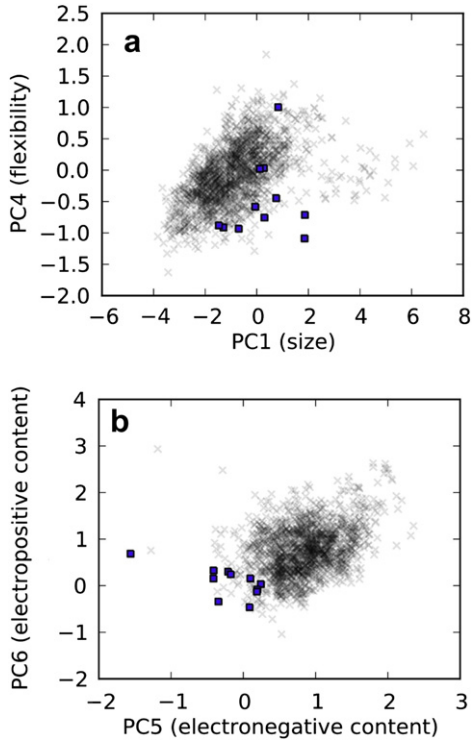


Figure 5. ChemGPS-NP coordinates of the newly synthesized bicyclic products (blue) and the bicyclo[3.3.1]-nonanes in the MLSMR library (crosses). (a) PC1 and PC4 highlight size and flexibility, respectively. (b) PC5 and PC6, showing electronegative and electropositive atomic content, respectively.

Physiochemical descriptors for each compound were computed using the OpenEye toolkit (Table 3) as well as ChemAxon (not shown).[24] All but two of the compounds obey Lipinski's rule of 5;[25] in each case the number of hydrogen bond acceptors is well below 10, and the number of hydrogen bond donors is <5. These properties provide a measure of the efficiency of drug transport across biological membranes. All but two of the compounds also have an XLogP value of <5.0, indicating low lipophilicity and promising bioavailability. The two compounds with high LogP (**10** and **15**) contain large hydrocarbon R-groups, which increase their solubility in non-polar solvents. Drugs are often significantly more potent and selective than lead compounds, which can be accomplished by increasing molecular weight and modulating lipophilicity, while preserving the parent scaffold.[26]

The present analysis demonstrates that the highly hydroxylated substitution pattern of **8**–**25** allows these compounds to expand into new regions of the bicyclononane chemical space. With comparatively little variation in shape and volume and easy synthetic access and modification, **8**–**25** are more hydrophilic than existing bicyclononanes, while meeting Lipinski rules and exhibiting reduced potential for non-specific binding.

3. Conclusions

The aromatic thiol-mediated ring-opening, intramolecular rearrangement reaction of epoxyketones can be used for the

preparation of densely functionalized bicyclo[3.3.1]non-3-en-ones. The key synthetic intermediates are readily available from commercially available phenols by hypervalent iodine oxidations. Specifically, after scaleup of diepoxyketone **7**, two optimized procedures were developed for the diversity-generating transformations. The mild room temperature conditions provided the desired products in 1.5 h and 57–87% yield, while microwave conditions were found to shorten the reaction time to 2 min at 60 °C, providing the bicyclic products **8**–**15** in comparable yields (71–88%). Both sets of conditions were shown to tolerate electron-donating as well as electron-withdrawing substituents on the aromatic thiol. Although the reaction conditions proved not to be amenable to the formation of bicycl[3.4.1]decenones, the process was tolerant of fused bicyclic systems. Methyl substitution on the diepoxyketone was found to significantly decrease the rate of addition of the second equivalent of thiophenol; however, this reaction provided access to an interesting epoxyketone derivative with a relatively inert epoxy functionality. Finally, a brief mechanistic investigation led to a refinement of our mechanistic hypothesis as well as the isolation of an intermediate in the pathway, which might be useful for the selective addition of two different thiol nucleophiles. A ChemGPS-NP based chemical diversity analysis revealed substantial structural difference between the new set of bicyclo[3.3.1]non-3-en-2-ones and the related bicyclic scaffolds currently available in the MLSMR collection. Studies to further extend the scope of the reaction to include a greater variety of thiol nucleophiles, more highly substituted diepoxyketones, and selective thiol additions are in progress.

4. Experimental part

4.1. General

All moisture sensitive reactions were performed using syringe-septum techniques under an atmosphere of either dry N_2 or dry argon unless otherwise noted. All glassware were dried in an oven at 140 °C for a minimum of 6 h or flame-dried under an atmosphere of dry nitrogen prior to use. Reactions carried out at −78 °C employed a $CO_{2(s)}$/acetone bath. Diethyl ether and tetrahydrofuran were dried by distillation over sodium/benzophenone under an argon atmosphere. Dry methylene chloride was purified by filtration through an activated alumina column. Methylene chloride was degassed using the freeze/pump/thaw method (3×). Methanol was stored over molecular sieves (3 Å). Deuterated chloroform was stored over anhydrous potassium carbonate. Reactions were monitored by TLC analysis (pre-coated silica gel 60 F_{254} plates, 250 μm layer thickness) and visualized by using UV lamp (254 nm) or by staining with either Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ and 0.2 g of $Ce(SO_4)_2$ in 100 mL of a 3.5 N H_2SO_4) or a potassium permanganate solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% NaOH solution). Flash column chromatography was performed with 40–63 μm silica gel (Silicycle). Microwave reactions were performed on a Biotage Initiator microwave reactor. Infrared spectra were measured on a Smiths Detection IdentifyIR FT-IR spectrometer (ATR). Unless otherwise indicated, all NMR data were collected at room temperature in $CDCl_3$ on a 300, 500, 600, or 700 MHz Bruker instrument. Chemical shifts (δ) are reported in parts per million (ppm) with internal $CHCl_3$ (δ 7.26 ppm for ^1H and 77.00 ppm for ^{13}C), internal acetone (δ 2.05 ppm for ^1H and 29.85 ppm for ^{13}C), or internal DMSO (δ 2.50 ppm for ^1H and 39.52 for ^{13}C) as the reference. ^1H NMR data are reported as follows: chemical shift, multiplicity (s=singlet, br s=broad singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets, dt=doublet of triplets, td=triplet of doublets, qd=quartet of doublets, sep=septet), integration, and coupling constant(s) (J) in hertz (Hz).

4.2. General procedure A

Addition/Rearrangement to bicyclo[3.3.1]nonane Scaffold. To a stirred solution of **7** (0.0500 g, 0.252 mmol, 1 equiv) in dry, degassed CH_2Cl_2 (12 mL) was added Cs_2CO_3 (0.411 g, 1.26 mmol, 5 equiv) and the thiol nucleophile (0.757 mmol, 3 equiv). The reaction mixture was allowed to stir at rt for 1–2 h, diluted with EtOAc (40 mL), and washed with brine. The organic layer was separated and the aqueous layer was extracted with EtOAc (2×10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude mixture was dissolved in CH_2Cl_2 and purified by chromatography on SiO_2.

4.3. General procedure B

Microwave Assisted Addition/Rearrangement to Bicyclo[3.3.1]nonane Scaffold. To a stirred solution of **7** (0.0100 g, 0.0505 mmol, 1 equiv) in dry, degassed CH_2Cl_2 (2 mL) was added Cs_2CO_3 (0.0822 g, 0.252 mmol, 5 equiv) and the thiol nucleophile (0.151 mmol, 3 equiv). The reaction mixture was heated in the microwave reactor for 2 min at 60 °C, diluted with CH_2Cl_2 (10 mL), and washed with brine. The organic layer was separated and the aqueous layer was extracted with EtOAc (2×10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude mixture was dissolved in CH_2Cl_2 and purified by chromatography on SiO_2.

*4.3.1. 4,4-Dimethoxycyclohexa-2,5-dienone (**4**)*[12]. To a stirred solution of 4-methoxyphenol (10.0 g, 80.6 mmol, 1 equiv) in dry MeOH (200 mL) at 0 °C under a nitrogen atmosphere was added phenyliodonium diacetate (PIDA; 25.9 g, 80.6 mmol, 1 equiv), and the resulting solution was stirred for 45 min. After 45 min, the mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (300 mL) and extracted with Et_2O (3×). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The reaction mixture was purified by chromatography on SiO_2 (deactivated with 0.1% Et_3N; EtOAc/hexanes 1:5 to 1:1) to give **4** (12.3 g, 99% yield) as a colorless oil: R_f 0.41 (EtOAc/hexanes, 1:3); IR (neat) 2991, 2941, 2830, 1685, 1671, 1636, 1178, 1105, 1083, 1059, 1034, 1034, 958, 853 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.84–6.79 (m, 2H), 6.29–6.24 (m, 2H), 3.37 (s, 6H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 185.1, 143.2, 130.0, 92.4, 50.4; HRMS (EI^+) m/z calcd for $C_8H_{10}O_3$ 154.0630, found 154.0628.

*4.3.2. 4-(But-3-enyl)-4-hydroxycyclohexa-2,5-dienone (**5**)*[12]. To a dry, 100 mL, three-necked, round-bottom flask equipped with an addition funnel and reflux condenser was added magnesium turnings (2.27 g, 93.4 mmol, 1.2 equiv) and a crystal of iodine. Heat (Bunsen burner flame) was applied to the stirred turnings until a purple gas coated the interior of the flask. The sample was allowed to cool under argon and suspended in dry THF (30 mL). To the stirred solution was added via an addition funnel a solution of 4-bromo-1-butene (9.48 mL, 93.4 mmol, 1.2 equiv) in dry THF (10 mL) at a rate so that the solution maintained a gentle reflux. After the addition was completed, the reaction mixture was allowed to stir at reflux for 45 min, cooled to rt and cannulated over 30 min into a pre-cooled (−78 °C) solution of **4** (12.0 g, 77.8 mmol, 1 equiv) in dry THF (150 mL). The reaction mixture was allowed to stir at −78 °C for 3 h and quenched with a saturated aqueous solution of NH_4Cl, warmed to rt, and extracted with EtOAc (3×150 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting oil was diluted with H_2O/acetone (1:1, 500 mL) and glacial acetic acid (50 mL) was added. The reaction mixture was allowed to stir at rt for 3 h, and extracted with EtOAc (3×150 mL). The

combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil, which was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:3) to give **5** (7.05 g, 43% yield) as a volatile pale yellow oil: R_f 0.24 (EtOAc/hexanes, 1:3); IR (neat) 3339, 3276, 2937, 1662, 1606, 1396, 1052, 1018, 991, 859, 716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.86–6.81 (m, 2H), 6.21–6.16 (m, 2H), 5.77 (dddd, 1H, J=6.3, 6.3, 10.2, 16.5 Hz), 5.06–4.96 (m, 2H), 2.52 (s, 1H), 2.09–2.01 (m, 2H), 1.88–1.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.5, 150.9, 137.1, 128.4, 115.4, 69.8, 38.8, 27.8; HRMS (EI^+) m/z calcd for $C_{10}H_{12}O_2$ 164.0837, found 164.0829.

*4.3.3. 4-(But-3-enyl)-4-hydroxycyclohexa-2,5-dioxirane (**6**)*[12]. To a stirred solution of enone **5** (4.25 g, 25.9 mmol, 1 equiv) in methanol (100 mL) and 30% aqueous hydrogen peroxide (7.93 mL, 77.6 mmol, 3 equiv) at 0 °C was added 6 M NaOH (2.16 mL, 7.00 mmol, 0.5 equiv) dropwise. The reaction mixture was allowed to stir at 0 °C for 2 h, poured onto DI water and thoroughly extracted with EtOAc (7×100 mL). The combined organic layers were washed with brine, poured onto activated 4 Å molecular sieves, and allowed to stir at rt for 3 h. The mixture was filtered and concentrated under reduced pressure to give **6** (3.68 g, 72% yield) as an off-white solid: R_f 0.62 (EtOAc/CH_2Cl_2, 1:1); IR (neat) 3459, 3028, 2976, 2940, 1702, 1366, 1328, 1239, 1090, 1060, 1025, 926, 917 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (dddd, 1H, J=6.6, 10.2, 16.8 Hz), 5.09–5.01 (m, 2H), 3.50 (s, 4H), 3.03 (s, 1H), 2.27–2.15 (m, 2H), 1.96–1.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 136.7, 115.9, 68.9, 63.9, 57.0, 35.6, 26.9; HRMS (ESI^+) m/z calcd for $C_{10}H_{12}O_4$ 196.0736, found 196.0726.

*4.3.4. 1-Oxaspiro[4.5.]deca-6,9-diepoxy-2,8-lactol (**7**)*[12]. A solution of **6** (1.00 g, 5.10 mmol, 1 equiv) in CH_2Cl_2 (30 mL) was cooled to −78 °C. Ozone was passed through the stirred solution for 3.5 h followed by O_2 for 1 min.[27] Dimethylsulfide (7.54 mL, 102 mmol, 20 equiv) was then added dropwise at −78 °C. The reaction mixture was allowed to stir at −78 °C for 1 h and then allowed to warm to rt and stirred at rt for 3 days. The solvent was removed under reduced pressure. The crude product was purified by chromatography on SiO_2 (EtOAc) to give **7** (0.962 g, 95% yield) as an off-white solid: R_f 0.45 (EtOAc); mp 164–166 °C; IR (neat) 3369, 3440, 2965, 1722, 1459, 1431, 1349, 1243, 1202, 1038, 976, 919 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 5.69 (d, 1H, J=1.8 Hz), 5.53 (br s, 1H), 3.62 (t, 1H, J=2.4 Hz), 3.49 (t, 1H, J=2.1 Hz), 3.35 (t, 1H, J=2.4 Hz), 3.31 (t, 1H, J=2.4 Hz), 2.35–2.27 (m, 1H), 2.19–2.11 (m, 2H), 2.05–2.00 (m, 1H); ^{13}C NMR (125 Hz, acetone-d_6) δ 200.5, 100.6, 80.3, 65.2, 63.6, 56.1, 55.9, 33.9, 31.1; HRMS (EI^+) m/z calcd for $C_9H_{10}O_5$ 198.0528, found 198.0523.

*4.3.5. (1S,8R,9S)-5,8,9-Trihydroxy-1,3-bis(phenylthio)bicyclo[3.3.1]non-3-en-2-one (**8**).* Prepared according to general procedure A utilizing **7** (0.025 g, 0.126 mmol, 1 equiv), Cs_2CO_3 (0.205 g, 0.631 mmol, 5 equiv), and thiophenol (0.039 mL, 0.38 mmol, 3 equiv). The crude mixture was purified by chromatography on SiO_2 (EtOAc/hexanes 1:2 to 1:1) to give **8** (0.0416 g, 83% yield) as a white solid: R_f 0.33 (EtOAc/hexanes, 1:1); mp 185–188 °C; IR (neat) 3502, 3335, 3051, 2945, 2879, 1666, 1590, 1472, 1439, 1310, 1228, 1100, 1032, 954, 738, 689 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52–7.51 (m, 2H), 7.46–7.41 (m, 5H), 7.33–7.32 (m, 3H), 5.96 (d, 1H, J=0.9 Hz), 3.85–3.83 (m, 1H), 3.48 (s, 1H), 3.32 (s, 1H), 3.24 (s, 1H) 2.27 (s, 1H), 2.06–2.03 (m, 1H), 1.89 (dd, 1H, J=1.5, 6.6 Hz), 1.76 (dt, 1H, J=2.1, 8.1 Hz), 1.67 (s, 1H), 1.38 (dq, 1H, J=3.0, 8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.0, 143.3, 141.9, 134.9, 133.4, 133.1, 130.1, 129.9, 129.5, 129.2, 128.4, 73.0, 69.9, 63.4, 58.4, 33.3, 29.1; HRMS (EI^+) m/z calcd for $C_{21}H_{20}O_4S_2$ 400.0803, found 400.0822.

*4.3.6. (1R,2R,4S,6S,7R,10S)-1,7,10-trihydroxy-6-(phenylthio)-3-oxatricyclo[4.3.1.0^{2,4}]decan-5-one (**B**).* To a stirred solution of **7** (0.250 g, 1.27 mmol, 1 equiv) in CH_2Cl_2 (25 mL) were added thiophenol (0.391 mL, 3.82 mmol, 3 equiv) and Cs_2CO_3 (3.46 g, 6.37 mmol, 5 equiv). The reaction mixture was allowed to stir at rt for 5 min then quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (3×). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude mixture was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:1) to give **B** (0.070 g, 18% yield) as a colorless film: R_f 0.45 (EtOAc); IR ($CDCl_3$) 3465, 2943, 2877, 1709, 1274, 1437, 1326, 1111, 1085, 1025, 904, 729, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, 2H, J=7.5 Hz), 7.50–7.36 (m, 3H), 3.69 (d, 1H, J=3.3 Hz), 3.62 (d, 1H, J=2.1 Hz), 3.47 (d, 2H, J=4.2 Hz), 3.36 (s, 1H), 3.32 (s, 1H), 2.92 (d, 1H, J=12.3 Hz), 2.14–2.07 (m, 2H), 1.50–1.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.3, 138.2, 130.4, 129.3, 126.0, 73.6, 71.7, 70.7, 70.6, 60.8, 56.6, 29.9, 27.7; HRMS (EI^+) m/z calcd for $C_{15}H_{16}O_5S$ 308.0718, found 308.0713.

*4.3.7. (1S,8R,9S)-5,8,9-Trihydroxy-1,3-bis(p-tolylthio)bicyclo[3.3.1]non-3-en-2-one (**9**).* Prepared according to general procedure A utilizing **7** (0.0500, 0.252 mmol, 1 equiv), Cs_2CO_3 (0.411 g, 1.26 mmol, 5 equiv), and *p*-thiocresol (0.0940 mL, 0.757 mmol, 3 equiv). The crude reaction mixture was purified by chromatography on SiO_2 (EtoAc/hexanes, 1:1) to give **9** (78.6 mg, 73% yield) as a white solid: R_f 0.29 (EtOAc/hexanes, 1:1); mp 191–193 °C; IR (neat) 3496, 3345, 3060, 2942, 1664, 1578, 1472, 1420, 1314, 1217, 1100, 1031, 868, 731 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 7.64–7.62 (m, 2H), 7.40–7.38 (m, 2H), 7.28 (d, 2H, J=8.1 Hz), 7.23 (d, 2H, J=8.1 Hz), 5.84 (d, 1H, J=2.4 Hz), 4.44 (br s, 1H), 3.99 (s, 1H), 3.37 (dd, 1H, J=6.0, 10.8 Hz), 3.17 (d, 1H, J=2.4 Hz), 2.36 (s, 3H), 2.35 (s, 3H), 1.99–1.92 (m, 1H), 1.58–1.51 (m, 1H), 1.48–1.32 (m, 2H); ^{13}C NMR (75 MHz, acetone-d_6) δ 190.9, 143.1, 140.8, 140.0, 139.9, 139.1, 135.6, 131.4, 130.6, 128.1, 126.1, 77.5, 75.8, 74.2, 69.2, 31.4, 28.4, 21.2, 21.2; HRMS (EI^+) m/z calcd for $C_{23}H_{24}O_4S_2$ 428.1116, found 428.1101.

*4.3.8. (1S,8R,9S)-1,3-Bis(4-tert-butylphenylthio)-5,8,9-trihydroxybicyclo[3.3.1]non-3-en-2-one (**10**).* Prepared according to general procedure A utilizing **7** (0.0500, 0.252 mmol, 1 equiv), Cs_2CO_3 (0.411 g, 1.26 mmol, 5 equiv), and 4-*tert*-butylthiophenol, (0.13 mL, 0.76 mmol, 3 equiv). The crude reaction mixture was purified by chromatography on SiO_2 (EtOAc/hexanes, 5:1 to 3:1) to give **10** (0.0935 g, 72% yield) as a white solid: R_f 0.86 (EtOAc/hexanes, 1:1); mp 203–207 °C; IR (neat): 3475, 2956, 2902, 2866, 1674, 1591, 1489, 1265, 1099, 1034, 1012, 831, 729 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 7.71–7.69 (m, 1H), 7.68–7.67 (m, 1H), 7.52–7.41 (m, 6H), 5.94 (d, 1H, J=2.4 Hz), 4.62 (br s, 1H), 4.48 (br s, 1H), 4.04 (d, 1H, J=1.8 Hz), 3.40 (dd, 1H, J=6.0, 11. 1 Hz), 3.19 (d, 1H, J=2.1 Hz), 2.01–1.93 (m, 1H), 1.61–1.54 (m, 1H), 1.49–1.35 (m, 2H), 1.33 (s, 9H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, acetone-d_6) δ 190.9, 153.7, 152.8, 143.8, 139.5, 138.9, 134.9, 128.4, 127.6, 126.9, 126.1, 77.7, 75.8, 74.2, 69.3, 35.3, 35.2, 31.5, 31.4, 28.3; HRMS (EI^+) m/z calcd for $C_{29}H_{36}O_4S_2$ 512.2055, found 512.2076.

*4.3.9. (1S,8R,9S)-5,8,9-Trihydroxy-1,3-bis(4-methoxyphenylthio)bicyclo[3.3.1]non-3-en-2-one (**11**).* Prepared according to general procedure A utilizing **7** (0.0500, 0.252 mmol, 1 equiv), Cs_2CO_3 (0.411 g, 1.26 mmol, 5 equiv), and 4-methoxythiophenol (0.093 mL, 0.76 mmol, 3 equiv). The crude reaction mixture was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:1) to give **11** (0.0857 g, 74% yield) as a white solid. R_f 0.29 (EtOAc/hexanes, 1:1); mp 105–107 °C; IR (neat) 3487, 2937, 2911, 2903, 1670, 1588, 1491, 1285, 1243, 1172, 1101, 1025, 950, 829 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 7.69–7.65 (m, 2H), 7.45–7.42 (m, 2H), 7.06–7.02 (m, 2H), 6.99–6.95 (m, 2H), 5.70 (d, 1H, J=2.4 Hz), 4.55 (br s, 1H), 4.37 (s, 1H), 3.97 (d, 1H J=2.1 Hz), 3.85 (s, 3H), 3.83 (s, 3H), 3.36 (dd, 1H, J=6.0, 10.8 Hz), 3.15 (s, 1H), 1.98–1.91 (m, 1H), 1.56–1.50 (m, 1H), 1.46–1.32 (m, 2H); ^{13}C NMR (75 MHz, acetone-d_6) δ 191.1, 162.0,

161.7, 141.7, 140.9, 140.5, 137.9, 121.4, 119.9, 116.3, 115.4, 77.4, 75.8, 74.1, 69.1, 55.8, 55.7, 31.5, 28.3; HRMS (EI^+) m/z calcd for $C_{23}H_{24}O_6S_2$ 460.1014, found 460.1009.

*4.3.10. (1S,8R,9S)-5,8,9-Trihydroxy-1,3-bis(4-(trifluoromethyl)phenylthio)bicyclo[3.3.1]non-3-en-2-one (**12**).* Prepared according to general procedure A utilizing **7** (0.0500, 0.252 mmol, 1 equiv), Cs_2CO_3 (0.411 g, 1.26 mmol, 5 equiv), and 4-trifluoromethylthiophenol (0.135 g, 0.757 mmol, 3 equiv). The crude reaction mixture was purified by chromatography on SiO_2 (EtOAc/hexane, 1:1) to give **12** (0.100 g, 74% yield) as a foam: R_f 0.21 (EtOAc/hexanes, 1:1); mp 145–148 °C; IR (neat) 3498, 1685, 1604, 1319, 1163, 1120, 1103, 1062, 1013, 839 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 8.00 (d, 2H, J=8.1 Hz), 7.74 (d, 2H, J=8.1 Hz), 7.69 (d, 2H, J=8.4 Hz), 7.60 (d, 2H, J=8.4 Hz), 6.69 (d, 1H, J=2.7 Hz), 4.84 (br s, 1H), 4.28 (s, 1H), 3.54 (dd, 1H, J=5.7, 10.5 Hz), 3.32 (d, 1H, J=2.4 Hz), 2.03–1.96 (m, 1H), 1.80–1.47 (m, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 190.0, 152.8, 139.6, 135.8, 135.4, 131.9, 126.8 (q, J=3.75 Hz), 126.4 (q, J=3.75 Hz), 78.0, 76.0, 75.0, 69.6, 31.0, 28.8. HRMS (ESI^+) m/z calcd for $C_{23}H_{18}O_4F_6NaS_2$ 559.0448, found 559.0490.

*4.3.11. (1S,8R,9S)-1,3-Bis(3-fluorophenylthio)-5,8,9-trihydroxybicyclo[3.3.1]non-3-en-2-one (**13**).* Prepared according to general procedure A utilizing **7** (0.0500, 0.252 mmol, 1 equiv), Cs_2CO_3 (0.411 g, 1.26 mmol, 5 equiv), and 3-fluorothiophenol (0.064 mL, 0.76 mmol, 3 equiv). The crude reaction mixture was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:1) to give **13** (0.110 g, 74% yield) as a white solid: R_f 0.46 (EtOAc/hexanes, 1:1); mp 190–192 °C; IR (neat) 3349, 3345, 3060, 2942, 2918, 1664, 1578, 1472, 1420, 1472, 1314, 1217, 1155, 1099, 868, 731 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 7.63–7.56 (m, 2H), 7.51–7.41 (m, 2H), 7.30–7.21 (m, 3H), 7.16–7.09 (m, 1H), 6.39 (d, 1H, J=2.4 Hz), 4.76 (br s, 1H), 4.19 (s, 1H), 3.48 (dd, 1H, J=6.0, 11.1 Hz), 3.29 (d, 1H, 2.4 Hz), 2.06–1.98 (m, 1H), 1.72–1.63 (m, 1H), 1.58–1.42 (m, 2H); ^{13}C NMR (75 MHz, acetone-d_6) δ 190.3, 165.1 (d, J=48.8 Hz), 161.8 (d, J=48.8 Hz), 149.3, 137.0, 135.9 (d, J=8.3 Hz), 135.2 (d, J=3.0 Hz), 132.3 (d, J=7.5 Hz), 132.0 (d, J=9.0 Hz), 131.3 (d, J=8.3 Hz), 129.1 (d, J=3.0 Hz), 125.5 (d, J=21.0 Hz), 119.7 (d, J=22.5 Hz), 117.6 (d, J=21.0 Hz), 115.7 (d, J=21.0 Hz), 77.8, 76.0, 74.7, 69.4, 31.2, 28.6; HRMS (EI^+) m/z calcd for $C_{21}H_{19}F_2O_4S_2$ 436.0615, found 436.0633.

*4.3.12. (1S,8R,9S)-1,3-Bis(2-bromophenylthio)-5,8,9-trihydroxybicyclo[3.3.1]non-3-en-2-one (**14**).* Prepared according to general procedure A utilizing **7** (0.0500, 0.252 mmol, 1 equiv), Cs_2CO_3 (0.411 g, 1.26 mmol, 5 equiv), and 2-bromobenzenethiol (0.091 mL, 0.76 mmol, 3 equiv). The crude reaction mixture was purified by chromatography on SiO_2 (EtOAc/hexanes 1:3 to 1:1) to give **14** (0.121 g, 87% yield) as a white solid. A small portion was recrystallized (acetone/Et_2O) to give colorless crystals for X-ray analysis: R_f 0.28 (EtOAc/hexanes, 1:1); mp 171–173 °C; IR (neat) 3427, 3468, 2937, 2883, 2868, 1659, 1599, 1446, 1420, 1331, 1272, 1248, 1110, 1019, 954, 760, 732 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 8.06 (dd, 1H, J=2.4, 7.2 Hz), 7.79 (dd, 1H, 2.1, 7.2 Hz), 7.75 (dd, 1H, J=0.9, 8.1 Hz), 7.56 (dd, 1H, J=1.5, 7.8 Hz), 7.45–7.29 (m, 4H), 6.19 (d, 1H, J=2.7 Hz), 4.86 (br s, 1H), 4.63 (s, 1H), 3.79 (d, 1H, J=2.1 Hz), 3.47 (dd, 1H, J=5.7, 10.2 Hz), 3.43 (d, 1H, J=2.1 Hz), 1.74–1.55 (m, 4H); ^{13}C NMR (75 MHz, acetone-d_6) δ 190.0, 148.5, 141.6, 135.8, 135.6, 134.5, 134.4, 134.3, 133.2, 132.4, 131.5, 130.8, 129.6, 129.1, 127.6, 78.1, 76.2, 70.0, 69.9, 31.3, 28.4; HRMS (ESI^+) m/z calcd for $C_{21}H_{18}O_4NaS_2Br_2$ 578.8911, found 578.8945.

*4.3.13. (1S,8R,9S)-5,8,9-Trihydroxy-1,3-bis(naphthalen-2-ylthio)bicyclo[3.3.1]non-3-en-2-one (**15**).* Prepared according to general procedure A utilizing **7** (0.0250, 0.126 mmol, 1 equiv), Cs_2CO_3 (0.206 g, 0.631 mmol, 5 equiv), and napthalene-2-thiol (0.0606 g, 0.378 mmol, 3 equiv). The crude reaction mixture was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:1) to give **15** (0.0357 g, 57% yield) as a white solid: R_f 0.44 (EtOAc/hexanes, 1:1); mp 230–233 °C; IR (neat) 2509, 3351, 3047, 2984, 2871, 1662, 1584, 1129, 1099, 1032, 954, 857, 820, 745 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.39 (s, 1H), 8.09 (s, 1H), 8.00–7.88 (m, 6H), 7.83 (d, 1H, J=8.4 Hz), 7.59–7.57 (m, 4H), 7.49 (d, 1H, J=8.1 Hz), 6.05 (d, 1H, J=1.8 Hz), 5.62 (d, 1H, J=3.6 Hz), 5.51 (s, 1H), 5.22 (d, 1H, J=3.9 Hz), 3.03 (s, 1H), 1.83–1.81 (m, 1H), 1.46–1.38 (m, 2H), 1.22–1.14 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 190.7, 146.7, 138.5, 136.0, 134.6, 133.5, 132.9, 132.4, 132.3, 129.8, 129.3, 128.7, 128.0, 127.9, 127.7, 127.6, 127.2, 127.0, 126.9, 126.5, 76.6, 74.7, 74.0, 68.1, 30.6, 28.4; HRMS (ESI^+) m/z calcd for $C_{29}H_{24}O_4NaS_2$ 523.1014, found 523.1017.

*4.3.14. 4,4-Dimethoxynaphthalen-1(4H)-one (**16**)[15].* To a stirred solution of 4-methoxynapthol (5.00 g, 28.7 mmol, 1 equiv) in MeOH (150 mL) was added PIDA (11.1 g, 34.4 mmol, 1.2 equiv), and the resulting solution was stirred at rt for 1 h. The mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude mixture was purified by chromatography on SiO_2 (deactivated with 0.1% Et_3N; EtOAc/hexanes, 1:3) to give **16** (5.00 g, 85% yield) as a blue semi-solid: R_f 0.52 (EtOAc/hexanes, 1:3); IR ($CDCl_3$) 2935, 2827, 1668, 1629, 1597, 1455, 1297, 1056, 974, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 8.01 (d, 1H, J=7.5 Hz), 7.67 (d, 1H, J=7.2 Hz), 7.59 (t, 1H, J=8.1 Hz), 7.43 (t, 1H, J=8.1 Hz), 6.88 (d, 1H, J=10.5 Hz), 6.53 (d, 1H, J=10.5 Hz), 3.13 (s, 6H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 183.6, 144.0, 139.5, 133.3, 132.4, 131.4, 129.1, 126.5, 126.1, 94.8, 51.0; HRMS (ESI^+) m/z calcd for $C_{12}H_{13}O_3$ [M+H] 205.0865, found 205.0870.

*4.3.15. 4-(But-3-enyl)-4-hydroxynaphthalen-1(4H)-one (**17**).* To a dry, 250 mL round-bottom flask equipped with an addition funnel was added magnesium turnings (0.714 g, 29.4 mmol, 1.2 equiv) and a crystal of iodine. Heat (Bunsen burner flame) was applied to the stirred turnings until a purple gas coated the interior of the flask. The sample was allowed to cool under argon and suspended in dry ether (20 mL). To the stirred solution was added via an addition funnel a solution of 4-bromo-1-butene (2.98 mL, 29.4 mmol, 1.2 equiv) in dry ether (20 mL). The reaction mixture was allowed to stir at reflux for 1 h, allowed to cool to rt, and a solution of **16** (5.00 g, 24.5 mmol, 1 equiv) in dry ether (40 mL) was added and quantitatively transferred with dry ether (20 mL). The heterogeneous reaction mixture was allowed to stir at rt for 15 min, cooled to 0 °C, quenched with a saturated aqueous solution of NH_4Cl and extracted with ether (×3). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude oil was suspended in acetone/water (1:1, 200 mL) and glacial acetic acid (14 mL) was added. The reaction mixture was allowed to stir at 0 °C for 2 h and extracted with Et_2O (×2). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude mixture was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:10 to 5:1 to 1:1) to give **17** (2.09 g, 40% yield) as a yellow oil: R_f 0.68 (EtOAc/hexanes, 1:1); IR ($CDCl_3$) 3407, 3066, 2937, 1657, 1597, 1456, 1297, 1150, 1051, 1014, 911, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, 1H, J=7.8 Hz), 7.70 (d, 1H, J=7.5 Hz), 7.60 (t, 1H, 6.6 Hz), 7.40 (t, 1H, 8.1 Hz), 6.92 (d, 1H, J=10.2 Hz), 6.31 (d, 1H, J=10.2 Hz), 5.62 (dddd, 1H, J=6.3, 6.3, 10.5, 12.6 Hz), 4.91–4.85 (m, 2H), 2.81 (s, 1H), 2.12–1.96 (m, 2H), 1.96–1.82 (m, 1H), 1.58–1.45 (m, 1H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 184.6, 151.9, 146.0, 137.0, 133.4, 130.2, 128.4, 128.1, 126.3, 126.1, 115.0, 71.0, 42.0, 28.1; HRMS (ESI^+) m/z calcd for $C_{14}H_{14}O_2Na$ 237.0891, found 237.0900.

*4.3.16. (1aS,7S,7aR)-7-(But-3-enyl)-7-hydroxy-7,7a-dihydronaphtho[2,3-b]oxiren-2(1aH)-one (**18**).* To a stirred solution of **17** (1.90 g,

8.87 mmol, 1 equiv) and 30% aqueous hydrogen peroxide (2.72 mL, 26.6 mmol, 3 equiv) in methanol (80 mL) at 0 °C was added 6 M NaOH (0.74 mL, 4.4 mmol, 0.5 equiv) dropwise. The reaction mixture was allowed to stir at 0 °C for 2 h, poured onto a saturated aqueous NH_4Cl solution and extracted with EtOAc (×2). The combined organic layers were checked for peroxides, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give **18** (1.53 g, 75% yield) as a light green powder: R_f 0.73 (EtOAc/hexanes, 1:1); mp 76–78 °C; IR (neat) 3437, 3004, 2953, 1675, 1597, 1452, 1334, 1293, 1062, 1010, 868, 773, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86–7.83 (m, 1H), 7.69–7.62 (m, 2H), 7.42 (td, 1H, J=2.7, 6.0 Hz), 5.71–5.58 (m, 1H), 4.94–4.87 (m, 2H), 3.79 (d, 1H, J=4.2 Hz), 3.75 (d, 1H, J=4.2 Hz), 2.75 (s, 1H), 1.98–1.81 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.5, 143.3, 136.9, 134.4, 128.5, 128.3, 126.7, 126.6, 115.2, 72.4, 58.8, 55.5, 40.6, 27.4; HRMS (EI^+) m/z calcd for $C_{14}H_{14}O_3Na$ 253.0841, found 253.0862.

*4.3.17. (1a′R,2S,7a′S)-5-Hydroxy-4,5-dihydro-1a′H,3H-spiro[furan-2,2′-naphtho[2,3-b]oxiren]-7′(7a′H)-one (**19**).* A solution of **18** (1.10 g, 4.99 mmol, 1 equiv) in CH_2Cl_2 (40 mL) was cooled to −78 °C. Ozone was passed through the stirred solution for 1.5 h, which was then purged with O_2 for 1 min.[27] Dimethylsulfide (7.39 mL, 99.9 mmol, 20 equiv) was then added dropwise at −78 °C. The reaction mixture was allowed to stir at −78 °C for 1 h and then allowed to warm to rt and stirred at rt for 3 days. The solvent was removed under reduced pressure and the crude mixture was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:2 to 1:1) to give **19** (1.18 g, 100% yield) as a 2:1 mixture of diastereomers as an off-white solid: R_f 0.43 (EtOAc/hexanes, 1:1); IR ($CDCl_3$) 3446, 2984, 1685, 1599, 1456, 1338, 1297, 1047, 1027, 986, 755, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, 1H, J=7.5 Hz), 7.63 (d, 1H, J=9.0 Hz), 7.44–7.38 (m, 2H), 6.02 (d, 1H, J=3.5 Hz), 4.04 (d, 1H, J=4.2 Hz), 3.79 (br s, 1H), 3.74 (d, 1H, J=4.5 Hz), 2.55–2.45 (m, 1H), 2.22–2.08 (m, 2H), 1.77 (ddd, 1H, J=3.0, 8.1, 11.4 Hz); ^{13}C NMR (75 Hz, $CDCl_3$) δ 194.2, 142.8, 134.4, 128.3, 127.2, 126.5, 125.2, 100.3, 82.8, 58.4, 54.1, 35.8, 32.0; HRMS (EI^+) m/z calcd for $C_{13}H_{12}O_4$ 232.0736, found 232.0735. NMR data are for the major diastereomer only.

*4.3.18. (5R,8S,9R,11R)-5,8,11-Trihydroxy-9-(phenylthio)-6,7,8,9-tetrahydro-5,9-methanobenzo[8]annulen-10(5H)-one (**20**).* To a stirred solution of **19** (0.0500 g, 0.215 mmol, 1 equiv) in dry CH_2Cl_2 (5 mL) were added Cs_2CO_3 (0.351 g, 1.08 mmol, 5 equiv) and thiophenol (0.066 mL, 0.646 mmol, 3 equiv). The reaction was allowed to stir at rt for 1 h. The crude mixture was diluted with CH_2Cl_2 (4 mL), washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 10:1 to 1:1) to give **20** (59.0 mg, 80% yield) as a white solid. A small portion was recrystallized (acetone/Et_2O) to give colorless crystals for X-ray analysis: R_f 0.32 (EtOAc/hexanes, 1:1); mp 180–182 °C; IR ($CDCl_3$) 3489, 1675, 1597, 1286, 1271, 1228, 1055, 1027, 760, 767 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 7.92 (d, 1H, J=7.8 Hz), 7.80 (d, 2H, J=7.8 Hz), 7.75 (s, 1H), 7.71 (t, 1H, J=6.9 Hz), 7.54–7.42 (m, 4H), 4.62 (br s, 1H), 4.49 (s, 1H), 4.04 (s, 1H), 3.52 (dd, 1H, J=5.7, 11.7 Hz), 3.42 (s, 1H), 1.89–1.83 (m, 1H), 1.72–1.57 (m, 2H), 0.99 (dq, 1H, J=5.7, 12.3 Hz); ^{13}C NMR (75 MHz, acetone-d_6) δ 193.9, 146.8, 139.2, 135.4, 133.5, 130.6, 129.9, 129.9, 128.2, 127.3, 125.8, 77.5, 75.2, 74.6, 69.8, 35.1, 28.6; HRMS (EI^+) m/z calcd for $C_{19}H_{18}O_4S$ 342.0926, found 342.0925.

*4.3.19. 4,4-Dimethoxy-3-methylcyclohexa-2,5-dienone (**21**)[14].* To a stirred solution of *m*-cresol (9.67 mL, 92.5 mmol, 1 equiv) in MeOH (300 mL) at 0 °C was added PIDA (44.7 g, 139 mmol, 1.5 equiv). The reaction mixture was allowed to warm to rt and stirred for 1 h. At this point, an additional batch of PIDA (20.0 g, 62.1 mmol, 0.7 equiv) was added. The mixture was allowed to stir at rt for an additional 1 h, and quenched with a saturated aqueous solution of Na_2CO_3, and extracted with Et_2O (×2). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (deactivated with 0.1% Et_3N; EtOAc/hexanes, 1:4) to give **21** (13.1 g, 85% yield) as a yellow oil: R_f 0.38 (EtOAc/hexanes, 1:3); IR ($CDCl_3$) 2937, 1674, 1640, 1616, 1439, 1385, 1107, 1057, 965 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.62 (d, 1H, J=10.2 Hz), 6.23 (dd, 1H, J=1.8, 10.5 Hz), 6.06 (s, 1H), 3.08 (s, 6H), 1.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.5, 155.6, 143.5, 131.9, 129.4, 95.0, 50.6, 16.3; HRMS (EI^+) m/z calcd for $C_9H_{12}O_3$ 168.0786, found 168.0785.

*4.3.20. 4-(But-3-en-1-yl)-4-hydroxy-3-methylcyclohexa-2,5-dienone (**22**).* To a dry, 25 mL round-bottom flask equipped with an addition funnel was added magnesium turnings (0.0305 g, 1.26 mmol, 1.2 equiv) and a crystal of iodine. Heat (Bunsen burner flame) was applied to the stirred turnings until a purple gas coated the interior of the flask. The sample was allowed to cool under argon and suspended in dry ether (6 mL). To the stirred solution was added via an addition funnel a solution of 4-bromo-1-butene (0.13 mL, 1.26 mmol, 1.2 equiv) in dry ether (2 mL). The reaction mixture was allowed to stir at reflux for 40 min, allowed to cool to rt, and a solution of **21** (0.176 g, 1.05 mmol, 1 equiv) in dry ether (3 mL) was added. The heterogeneous mixture was allowed to stir at rt for 15 min, cooled to 0 °C and quenched with a saturated aqueous solution of NH_4Cl and extracted with Et_2O (×3). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude amber oil was suspended in acetone/water (1:1, 20 mL) and glacial acetic acid (1.4 mL) was added. The reaction mixture was allowed to stir at 0 °C for 4 h and extracted with Et_2O (×2). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude mixture was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:5 to 1:3) to give **22** (0.0813 g, 44%) as a yellow oil: R_f 0.35 (EtOAc/hexanes, 1:2); IR ($CDCl_3$) 3420, 2920, 1666, 1633, 1446, 1431, 1394, 1375, 1243, 1049, 1001, 893 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.76 (dd, 1H, J=3.0, 10.2 Hz), 6.57 (s, 1H), 6.07 (d, 1H, J=9.9 Hz), 5.71 (dddd, 1H, J=6.0, 6.0, 10.2, 16.5 Hz), 4.98–4.90 (m, 2H), 3.34 (s, 1H) 2.00–1.92 (m, 2H), 1.80 (s, 3H), 1.80–1.74 (m, 2H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 186.6, 151.4, 147.0, 137.3, 134.5, 127.8, 115.0, 69.8, 38.8, 27.8, 15.5; HRMS (EI^+) m/z calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.0994

*4.3.21. (1R,3S,5R,6S,7S)-6-(But-3-en-1-yl)-6-hydroxy-5-methyl-4,8-dioxatricyclo[5.1.0.0^{3,5}]octan-2-one (**23**).* To a stirred solution of **22** (1.00 g, 5.61 mmol, 1 equiv) and 30% aqueous hydrogen peroxide (5.73 mL, 56.1 mmol, 10 equiv) in methanol 50 mL at rt was added 6 M NaOH (0.935 mL, 5.61 mmol, 1 equiv) dropwise. After 5 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution and extracted with EtOAc (×2). The combined organic layers were checked for peroxides, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:2) to give **23** (0.800 g, 68% yield) as a pale yellow oil: R_f 0.66 (EtOAc/hexanes, 1:1); IR ($CDCl_3$) 3483, 2976, 2933, 2859, 1705, 1640, 1437, 1159, 1085, 1023, 919, 841 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 5.78 (dddd, 1H, J=6.3, 6.3, 10.5, 12.6 Hz), 5.06–5.01 (m, 2H), 3.51 (d, 1H, J=4.2 Hz), 3.49 (t, 1H, J=4.2 Hz), 3.29 (d, 1H, J=3.5 Hz), 2.94 (br s, 1H), 2.17–2.08 (m, 2H), 1.96–1.89 (m, 2H), 1.43 (s, 3H); ^{13}C NMR (176 Hz, $CDCl_3$) δ 199.9, 136.6, 116.0, 70.3, 69.0, 63.8, 62.3, 57.2, 35.6, 27.1, 15.7; HRMS (ESI^+) m/z calcd for $C_{11}H_{14}O_4Na$ 233.0790, found 233.0797.

*4.3.22. (1′R,2S,3′S,5′R,7′S)-5-Hydroxy-1′-methyldihydro-3H-4′,8′-dioxaspiro[furan-2,2′-tricyclo[5.1.0.0^{3,5}]octan]-6′-one (**24**).* A solution

of **23** (0.0700 g, 0.333 mmol, 1 equiv) in CH_2Cl_2 (3 mL) was cooled to −78 °C. Ozone was passed through the stirred solution for 1.5 h, which was then purged with O_2 for 1 min.[27] Dimethylsulfide (0.49 mL, 6.7 mmol, 20 equiv) was then added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 1 h and then allowed to warm to rt and stirred for 3 days. The solvent was removed under reduced pressure and the crude mixture was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:1) to give **24** (0.0710 g, 100% yield) as a colorless oil and as a 1:1 mixture of lactols: R_f 0.22 (EtOAc/hexanes, 1:1); IR ($CDCl_3$) 3496, 2976, 1705, 1442, 1457, 1204, 1159, 1094, 1034, 982, 915, 868, 795 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.82 (s, 1H), 4.44 (br s, 1H), 3.69 (t, 0.5H, J=3.6 Hz), 3.55 (d, 0.5H, J=3.3 Hz), 3.44–3.38 (m, 1.5H), 3.21 (d, 0.5H, J=3.3 Hz), 2.37–1.95 (m, 4H), 1.37 (s, 3H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 200.1 (200.1), 99.8 (99.8), 79.6, (79.6), 70.6, (69.0), 64.3, (62.7), 61.1, (60.7), 55.9, (55.5), 33.0, (33.0), 30.5, (30.4), 15.5, (15.5); HRMS (EI^+) m/z calcd for $C_{10}H_{12}O_5$ 212.0685, found 212.0680. ^{13}C NMR data for a diastereomer are listed in parenthesis.

*4.3.23. (1S,2R,4S,6S,7R,10S)-1,7,10-Trihydroxy-10-methyl-6-(phenylthio)-3-oxatricyclo[4.3.1.0^{2,4}]decan-5-one (**25**).* To a stirred solution of **24** (0.0500 g, 0.236 mmol, 1 equiv) in dry CH_2Cl_2 (2 mL) were added Cs_2CO_3 (0.384 g, 1.18 mmol, 5 equiv) and thiophenol (0.072 mL, 0.707 mmol, 3 equiv). The reaction was allowed to stir at rt for 2 h. The crude reaction mixture was diluted with EtOAc, and washed with brine. The aqueous layer was extracted with EtOAc (×2), the organic layers were combined, washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude mixture was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:3 to 1:1) to give **25** (40.0 mg, 53% yield) as a colorless film: R_f 0.29 (EtOAc/hexanes, 1:1); IR ($CDCl_3$) 3476, 2933, 2877, 1720, 1437, 1426, 1360, 1113, 1081, 1032, 752, 729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (t, 1H, J=1.8 Hz), 7.63 (d, 1H, J=1.5 Hz), 7.48–7.35 (m, 3H), 3.48–3.47 (m, 1H), 3.42 (app t, 2H, J=2.4 Hz), 3.33 (dd, 1H, J=5.4, 11.7 Hz), 2.92 (dd, 1H, J=2.4 Hz, 12.3 Hz), 2.18–2.02 (m, 2H), 1.54 (s, 3H), 1.51–1.25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 138.2, 130.2, 129.2, 126.4, 73.9, 72.1, 70.6, 70.6, 67.2, 62.3, 29.6, 27.6, 14.8; HRMS (EI^+) m/z calcd for $C_{16}H_{18}O_5S$ 322.0875, found 322.0880.

*4.3.24. 4-Hydroxy-4-(pent-4-enyl)cyclohexa-2,5-dienone (**26**).* To a dry, 25 mL, two-necked, round-bottom flask equipped with an addition funnel was added magnesium turnings (0.341 g, 14.0 mmol, 1.2 equiv) and a crystal of iodine. Heat (Bunsen burner flame) was applied to the stirred turnings until a purple gas coated the interior of the flask. The sample was allowed to cool under argon and suspended in THF (4 mL). To the stirred solution was added via an addition funnel a solution of 5-bromo-1-pentene (1.7 mL, 14 mmol, 1.2 equiv) in THF (8 mL). The reaction mixture was allowed to stir at ca. 40 °C for 1 h, allowed to cool to rt, and added via dropwise addition to a solution of **4** (1.80 g, 11.7 mmol, 1 equiv) in THF (20 mL) at −78 °C. The reaction mixture was allowed to stir at −78 °C for 1 h and quenched with a saturated aqueous solution of NH_4Cl, warmed to rt, and extracted with EtOAc (×3). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was suspended in acetone/water (1:1, 100 mL), glacial acetic acid (10 mL) was added, and the reaction mixture was allowed to stir at rt for 2 h. The reaction mixture was concentrated under reduced pressure. The remaining aqueous layer was extracted with EtOAc (×3) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:5 to 1:3) to give **26** (1.14 g, 55% yield) as a yellow oil: R_f 0.2 (EtOAc/hexanes, 1:3); IR (neat) 3403, 2935, 2860, 1664, 1619, 1392, 1267, 1169, 1004, 859, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.84–6.79 (m, 2H), 6.19–6.14 (m, 2H), 5.73 (dddd, 1H, J=6.6, 6.6, 10.2, 16.8 Hz), 5.02–4.94 (m, 2H), 2.43 (s, 1H), 2.04 (q, 2H, J=7.2 Hz), 1.78–1.73 (m, 2H), 1.40–1.29 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.7, 151.3, 137.7, 128.2, 115.3, 69.9, 39.1, 33.6, 22.8; HRMS (ESI^+) m/z calcd for $C_{11}H_{14}O_2K$ 217.0631, found 217.0639.

*4.3.25. 5-(Pent-4-enyl)-4-hydroxycyclohexa-2,5-dioxirane (**27**).* To a stirred solution of **26** (1.00 g, 5.61 mmol, 1 equiv) and 30% aqueous hydrogen peroxide (1.72 mL, 16.8 mmol, 3 equiv) in methanol (50 mL) at 0 °C was added 6 M NaOH (0.467 mL, 2.81 mmol, 0.5 equiv) dropwise. The reaction mixture was allowed to stir at 0 °C for 2 h, poured onto a saturated aqueous NH_4Cl solution and extracted with EtOAc (×3). The combined organic layers were washed with brine, poured onto activated 4 Å molecular sieves, and allowed to stir at rt for 3 h. The mixture was filtered and concentrated under reduced pressure to give **27** (1.05 g, 89% yield) as a yellow oil: R_f 0.43 (EtOAc/hexanes, 1:1); IR (neat) 3481, 2935, 1702, 1638, 1435, 1435, 1239, 1084, 995, 926, 887, 788 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.75 (dddd, 1H, J=6.6, 6.6, 10.2, 13.5 Hz), 5.05–4.99 (m, 2H), 3.50 (s, 4H), 3.09 (s, 1H), 2.11 (q, 2H, J=6.9 Hz), 1.84–1.78 (m, 2H), 1.53–1.42 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 137.2, 115.8, 69.0, 64.0, 57.0, 35.8, 33.7, 21.9; HRMS (ESI^+) m/z calcd for $C_{11}H_{14}O_4Na$ 233.0790, found 233.0785.

*4.3.26. (1′R,2S,3′S,5′R,7′S)-6-Hydroxytetrahydro-4′,8′-dioxaspiro[pyran-2,2′-tricyclo[5.1.0.0^{3,5}]octan]-6′-one (**28**).* A solution of **27** (0.92 g, 4.38 mmol, 1 equiv) in CH_2Cl_2 (22 mL) was cooled to −78 °C. Ozone was passed through the stirred solution for 2 h, which was then purged with O_2 for 1 min.[27] Dimethylsulfide (6.47 mL, 87.5 mmol, 20 equiv) was then added dropwise at −78 °C. The reaction mixture was allowed to stir at −78 °C for 1 h and then allowed to warm to rt and stirred at rt for 3 days. The solvent was removed under reduced pressure. The crude product was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:2 to 1:1) to give **28** (0.803 g, 86% yield) as a 10:1 mixture of the open and closed forms of the lactol, as an off-white solid: R_f 0.25 (EtOAc/hexanes, 1:1); mp 112–115 °C; IR ($CDCl_3$) 3424, 2961, 2913, 1698, 1442, 1251, 1101, 1010, 988, 956, 902, 868, 788 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.60 (s, 1H), 4.32 (br s, 1H), 4.17 (t, 1H, J=4.2 Hz), 3.50 (t, 1H, J=3.6 Hz), 3.42–3.40 (m, 2H), 2.14–2.06 (m, 1H), 1.85–1.81 (m, 2H), 1.79–1.71 (m, 3H); ^{13}C NMR (151 Hz, acetone-d_6) δ 199.1, 91.9, 69.7, 64.0, 62.9, 56.2, 55.5, 29.5, 29.3, 13.8; HRMS (EI^+) m/z calcd for $C_{10}H_{12}O_5$ 212.0685, found 212.0691. Only the major lactol diastereomer is listed.

Acknowledgements

The authors thank Dr. Steven Geib (University of Pittsburgh) for the X-ray structure analyses of **14** and **20**, and NIH/NIGMS (P41GM081275; P50GM067082) for financial support.

Supplementary data

^1H NMR and ^{13}C NMR spectra of all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.04.110. These data include MOL files and InChIKeys of the most important compounds described in this article.

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