TOTAL SYNTHESIS OF VALLARTANONE A

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by

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For my parents

and

my future

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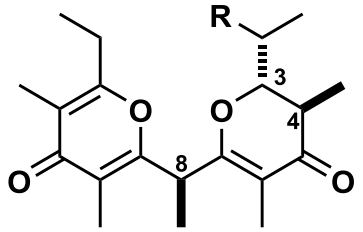
Abstract

Vallartanones A (**1**) and B (**2**) are polypropionates isolated from *Siphonaria maura*. Their structures were reported by Faulkner and Manker in 1989.[1] The only structural difference between **1** and **2** is an extra methyl group in the peripheral region of the molecule and thus both natural products share similar ^{1}H NMR and ^{13}C NMR properties. Vallartanone A (**1**) was assigned the (3*R*,4*R*,8*R*) relative configuration through ^{1}H NMR and conformational analyses of **1** and 8-*epi*-**1** along with their respective 6,7-dihydro derivatives; the absolute configuration was assigned on the basis of circular dichroism. The same (3*R*,4*R*,8*R*) absolute configuration was assigned for vallartanone B based on the close similarity of its spectroscopic properties with those reported for **1**.

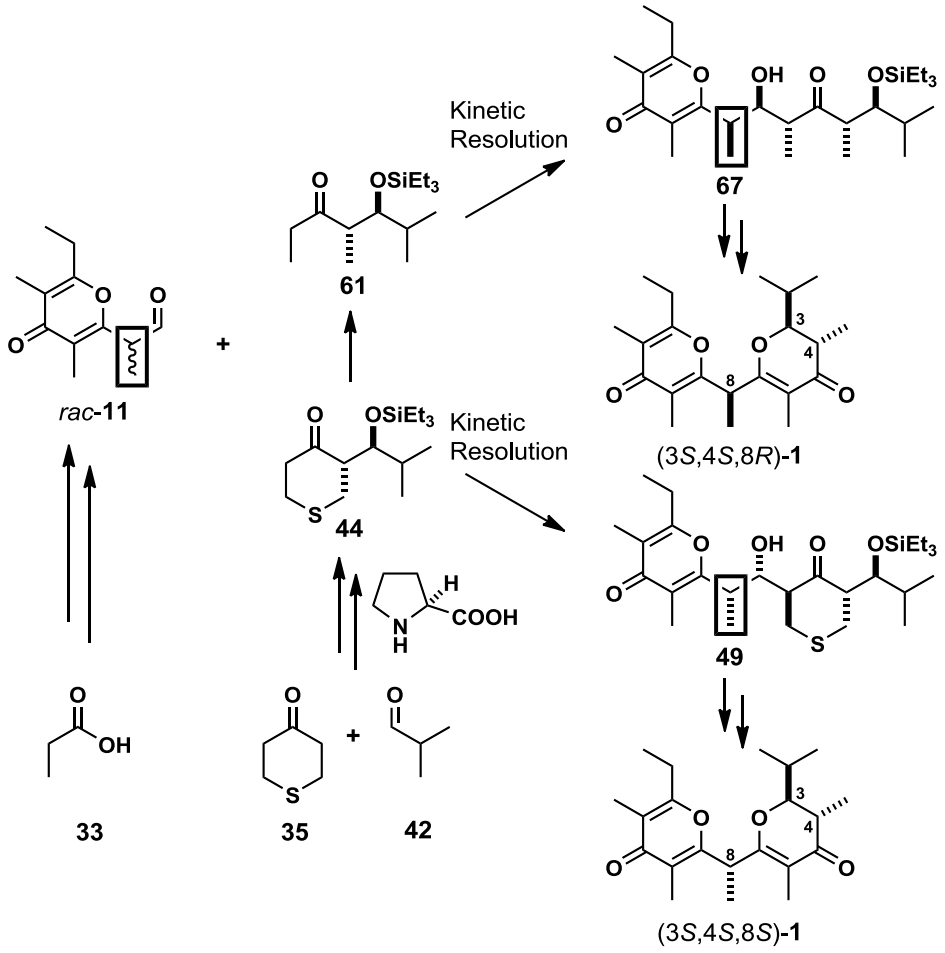


vallartanone A, **1**, R = Me
vallartanone B, **2**, R = H
Proposed Absolute Configuration: (3*R*,4*R*,8*R*)

Arimoto and co-workers reported the syntheses of (3*S*,4*S*,8*R*)-vallartanone B and its C-8 epimer in 1996 and concluded that the structure of vallartanone B should be revised to the (3*S*,4*S*,8*S*) absolute configuration.[2] Consequently, it is likely that **1** also possesses the (3*S*,4*S*,8*S*) configuration; however, this has not been proven and there have been no previous synthetic studies reported.

The research presented herein describes the first enantioselective total syntheses of vallartanone A and its (8*R*) epimer both starting with propanoic acid and isobutyraldehyde. The key steps involved a proline-catalyzed intermolecular aldol reaction and a second aldol reaction that

proceeded with kinetic resolution. It is concluded that the absolute configuration of vallartanone A should be revised to (3*S*,4*S*,8*S*).



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$[\alpha]_D$	specific rotation at the sodium D line (expressed without units; implied actual units are: (deg·mL)/(g·dm)) and/or $((10^{-1}\cdot deg\cdot cm^2)/g)$
$[M]^+$	molecular ion (in mass spectrometry)
[O]	oxidation
$(c\text{-Hex})_2BCl$	chlorodicyclohexyl borane
°C	degrees Celsius
β	beta
γ	gamma
δ	NMR chemical shift in parts per million downfield from tetramethylsilane
ε	molar absorptivity
µ	micro
µm	micrometer(s); micron(s)
ν	frequency
Å	angstrom(s)
^{1}H NMR	proton nuclear magnetic resonance
^{13}C NMR	carbon 13 nuclear magnetic resonance
AcMe	acetone
anti	antiperiplanar
ap	apparent (spectral)
aq	aqueous
Bn	benzyl
br	broad (spectral)
c	concentration of the reported specific rotation (g/100 mL)
c-Hex	cyclohexyl
calcd	calculated

CD	circular dichroism
CI	chemical ionization (ionization method in mass spectrometry)
cm	centimeter
cm^{-1}	wavenumber(s)
COSY	correlation spectroscopy
d	day(s); doublet (spectral); deci
d	density
D and L	absolute stereochemical configuration descriptors for carbohydrates and α-amino acids
deg	degrees Celsius
DEPT	distortionless enhancement by polarization transfer
dil.	dilute
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyltetrahydropyrimidin-2(1*H*)-one
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
DRIFT	diffuse reflectance Fourier transform infrared
E and *Z*	configurational descriptors for alkenes. *E* denotes that the substituents of highest CIP (Cahn-Ingold-Prelog) priority at each end of the double bond are on opposite sides. If the pertinent substituents are on the same side, the descriptor is *Z*.
ee	enantiomeric excess
EI	electron impact (ionization method in mass spectrometry)
ent	enantiomer of
epi	epimer of
equiv	equivalent(s)
er	enantiomeric ratio
ESI	electrospray ionization (ionization method in mass spectrometry)

Et	ethyl
Et_2BOMe	diethylmethoxy borane
Et_2O	diethyl ether
Et_3N	triethylamine
EtCHO	propanal
$EtNMe_2$	*N*,*N*-dimethylethylamine
EtOAc	ethyl acetate
eV	electronvolt
$F_3B{\cdot}OEt_2$	boron trifluoride diethyl etherate
FCC	flash column chromatography
FID	free induction decay
FTIR	Fourier transform infrared spectroscopy
g	gram(s); prefix to NMR abbreviation denoting gradient-selected (e.g., gCOSY, gHSQC)
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	Hertz
i.e.	*id est*
IBX	2-iodoxybenzoic acid
Imd_2CO	1,1'-carbonyldiimidazole
i-Pr	isopropyl
i-Pr_2NEt	*N*,*N*-diisopropylethylamine
IR	infrared
J	coupling constant (spectral)

KHMDS	potassium hexamethyldisilazide
KR	kinetic resolution
L	liter(s)
LC-MS	liquid chromatography–mass spectroscopy
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
LRMS	low resolution mass spectroscopy
LTMP	lithium tetramethylpiperidide
m	multiplet (spectral); milli; meter(s)
M	molar
m/*z*	mass-to-charge ratio
max	maximum
Me	methyl
MeCN	acetonitrile
MeLi	methyl lithium
MeOH	methanol
$Mg(OMe)_2$	magnesium methoxide
MHz	megahertz
min	minute(s); minimum
mL	milliliter(s)
mm	millimeter(s)
mmol	millimole(s)
mol	mole(s)
MOPAC	molecular orbital package
mp	melting point
MS	mass spectroscopy

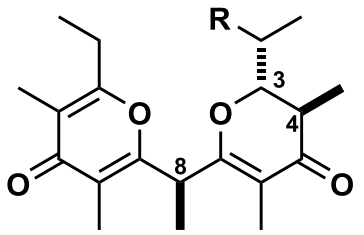
n	normal (e.g., *n*-butane)
NaHMDS	sodium hexamethyldisilazide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
p-TsOH	*para*-toluenesulfonic acid
Pd/C	palladium on carbon
Pg	protecting group
Ph	phenyl
Ph_3P	triphenylphosphine
PM3	parametric method 3
PPA	polyphosphoric acid
ppm	part(s) per million
pt	point
PTLC	preparative thin layer chromatography
Py	2-ethyl-3,5-dimethy-4-pyrone-6-yl
q	quartet (spectral)
R	alkyl
R and *S*	absolute stereochemical configuration descriptors in the CIP (Cahn-Ingold-Prelog) system
rac	racemic
RBF	round-bottom flask
ref.	reference
rel	relative
R_f	retention factor
rt	room temperature
s	singlet (spectral)

sat.	saturated
$SiEt_3$	triethylsilyl
$Sn(OTf)_2$	tin (II) trifluoromethanesulfonate
syn	synperiplanar
t	triplet (spectral)
TBAF	tetra-*n*-butylammonium fluoride
TBDMSCl	chloro-*tert*-butyldimethylsilane
TBDPS	*tert*-butyldiphenylsilyl
TBDPSCl	chloro-*tert*-butyldiphenylsilane
TBS	*tert*-butyldimethylsilyl
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
tert	tertiary
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
$TfOSiEt_3$	triethylsilyl trifluoromethanesulfonate
THF	tetrahydrofuran
$Ti(OiPr)_4$	titanium (IV) isopropoxide
TLC	thin layer chromatography
TMS	trimethylsilyl
v/v	volume-to-volume ratio
wt.	weight

1. INTRODUCTION

1.1 Isolation of vallartanones A and B

Vallartanones A (**1**) and B (**2**) are metabolites isolated from the marine mollusc, *Siphonaria maura*, collected near Puerto Vallarta, Mexico. Their structures were reported by Faulkner and Manker in 1989 (Figure 1.1).[1] Neither of these compounds was crystalline and the assignment of relative and absolute configurations of vallartanone A was based on spectral and conformational analyses.



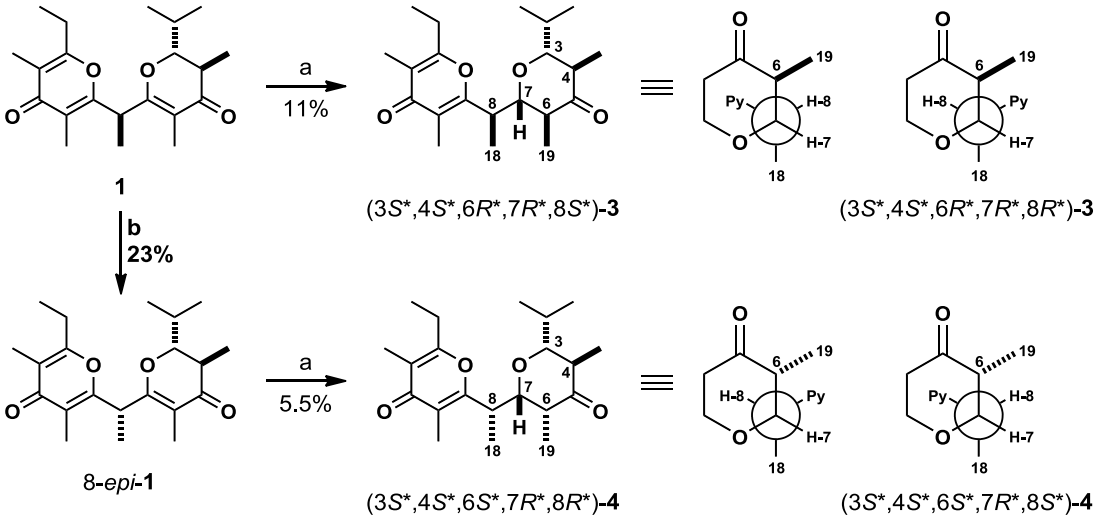
vallartanone A, **1**, R = Me
vallartanone B, **2**, R = H
Proposed Absolute Configuration: (3*R*,4*R*,8*R*)

Figure 1.1 Metabolites isolated from *Siphonaria maura*.

1.2 Elucidation of relative and absolute configurations of vallartanone A

Because HC-3 and HC-4 in **1** are adjacent to each other in a six-membered ring, their *trans* relationship could be confidently assigned on the basis of their large vicinal coupling constant ($J_{3,4}$ = 13 Hz). Determination of the relative configuration of C-8 was not straightforward. Thus, **1** was subjected to Pd-catalyzed hydrogenation and the corresponding derivative, 6,7-dihydrovallartanone A (**3**), was investigated (Scheme 1.1). The observed large coupling constant between HC-3 and HC-4 ($J_{3,4}$ = 10.5 Hz) in **3** suggested the *trans* relationship in **1** was retained in the dihydrohydro derivative **3**. The newly added HC-6 and HC-7 were also in a *trans* relationship as evidenced by their large vicinal coupling constant ($J_{6,7}$ = 10 Hz) implying that isomerization at C-6 had occurred under the reaction conditions, presumably giving the thermodynamically more stable epimer via keto-enol tautomerism. These large *J* values together with the observation of a positive nOe between HC-3 and HC-7, led to the assignment of the relative configuration of **3** as (3*S**,4*S**,6*R**,7*R**). Because all the substituents on the six-membered tetrahydropyran ring in **3** were in equatorial orientations, a single chair conformer would dominate. Faulkner hypothesized that the preferred torsion of the C-7–C-8 single bond would be strongly biased by steric repulsion between H_3C-18 and H_3C-19. Consequently, the H-C7–C8-H torsion angles for the (7*R**,8*S**) and (7*R**,8*R**) isomers were predicted to be 60° and 180°, respectively. The observed small coupling constant ($J_{7,8}$ = 4 Hz) supported the 7*R**,8*S** relative configuration and **3** was assigned (3*S**,4*S**,6*R**,7*R**,8*S**).

Scheme 1.1 Faulkner's analysis of the relative configuration at C-8 for vallartanone A.



(a) Pd/C, H_2; (b) NaOH

To further validate the above assignment, **1** was epimerized by treatment with sodium hydroxide to give a mixture of **1** and 8-*epi*-**1**. Hydrogenation of the latter produced **4** that was analyzed by ^{1}H NMR (Scheme 1.1). Unlike **3**, HC-6 and HC-7 in **4** were in a *cis* relationship as indicated by the small coupling constant between HC-6 and HC-7 ($J_{6,7}$ = 2 Hz), while the *trans* relationship between HC-3 and HC-4 ($J_{3,4}$ = 11 Hz) was maintained. Nuclear Overhauser enhancement was observed between HC-3 and HC-7 in **4** and a (3*S**,4*S**,6*S**,7*R**) relative configuration was assigned. Similar to the analysis of **3** described above, the authors concluded that having three large groups in equatorial orientations would result in a predominant chair conformer where the C-7–C-8 torsion would be governed by minimization of the steric interaction between H_3C-18 and H_3C-19. Thus the predicted H-C7–C8-H torsion angles for the (7*R**,8*S**) and (7*R**,8*R**) isomers were 60° and 180°, respectively. The large HC-7 and HC-8 coupling constant ($J_{7,8}$ = 10 Hz) observed in **4** supported the assignment of the (3*S**,4*S**,6*S**,7*R**,8*R**) relative configuration.

The absolute configuration of C-8 was assigned through circular dichroism (CD) spectroscopy where a negative split Cotton effect – a sharp negative absorption followed by a rapid change in the

opposite direction – was observed (Figure 1.2). This observation was in accordance with the two pyrone rings oriented with a left-handed helicity. In order to minimize steric interaction between H_3C-18 and H_3C-19, **1** was presumed to adopt a conformation where C-18 and C-19 were opposite of each other. The resulting torsion between C-7 and C-8 was expected to produce a left-handed helicity between the pyrone rings if the absolute configuration at C-8 was (*R*). Consequently, vallartanone A was assigned the (8*R*) absolute configuration.

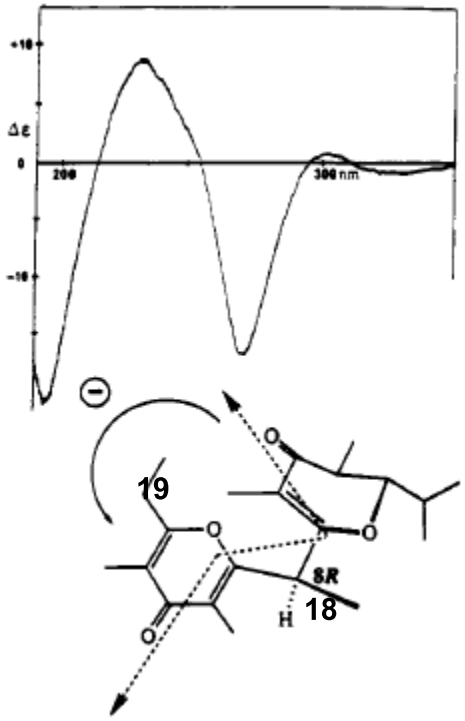


Figure 1.2 Negative split Cotton effect exhibited by **1**. Adapted with permission from Manker, D. C.; Faulkner, D. J. Vallartanone A and B, polypropionate metabolites of *Siphonaria maura* from Mexico. *J. Org. Chem.* **1989**, *54*, 5374-5377. Copyright 1989 American Chemical Society.

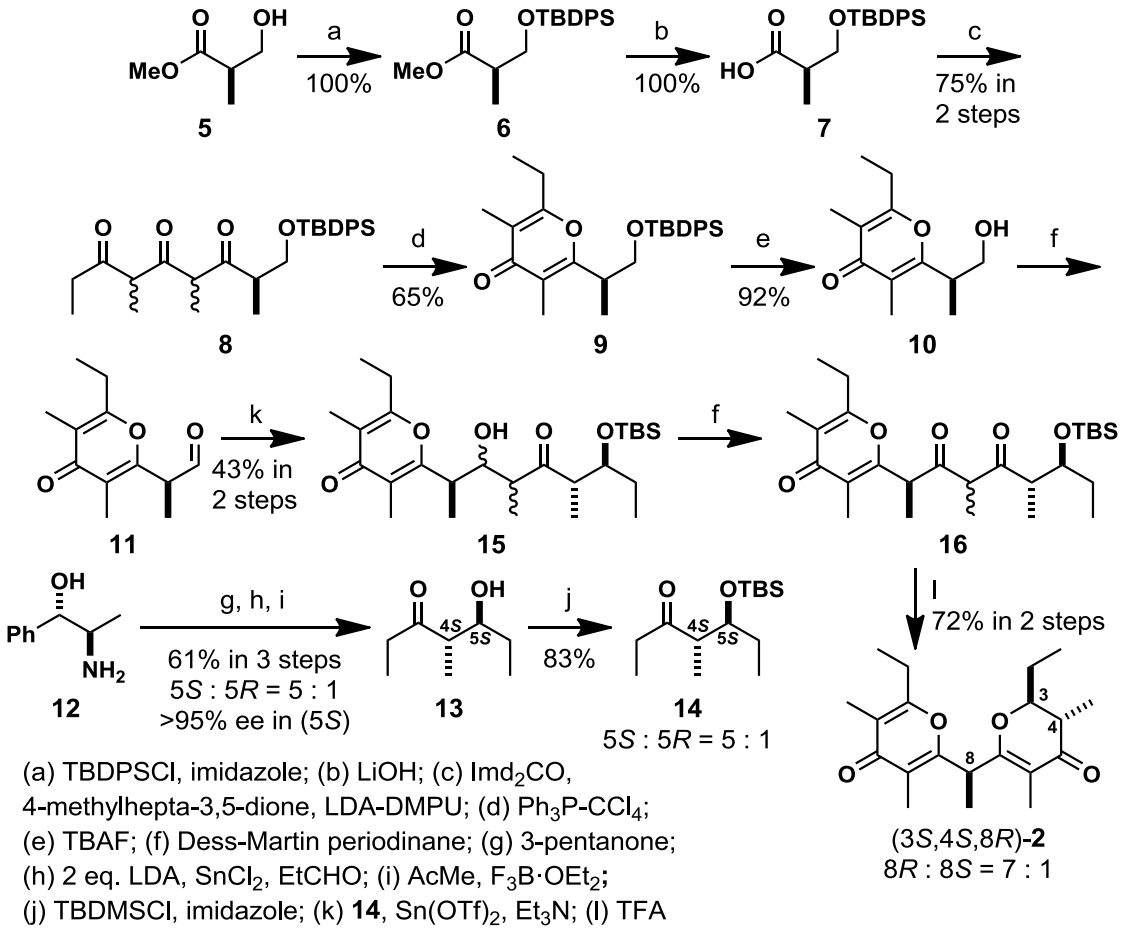
In conclusion, the relative configuration of **1** was assigned from spectral and conformational analyses of **1**, **3** and **4**. The absolute configuration of **1** was assigned (3*R*,4*R*,8*R*) through CD spectroscopy. Because the ^{1}H NMR, ^{13}C NMR data and the specific rotation of **2** closely resembled those of **1**, the absolute configuration of **2** was presumed to also be (3*R*,4*R*,8*R*).

Unfortunately, all of the structural drawings in Faulkner's paper illustrated **1** and **2** with (3*S*,4*S*,8*R*) absolute configurations. This anomaly raised some uncertainty about the proposed absolute configurations of the natural products **1** and **2** because the text (3*R*,4*R*,8*R*) did not match the structure drawings (3*S*,4*S*,8*R*).

1.3 Arimoto synthesis of (3*S*,4*S*,8*R*)-vallartanone B

In 1996, Arimoto and coworkers reported syntheses of **2** and its C-8 epimer and concluded that the absolute configuration of vallartanone B should be revised to (3*S*,4*S*,8*S*) (Scheme 1.2).[2] Apparently Arimoto et al. presumed that the structure of vallartanone B proposed by Faulkner was (3*S*,4*S*,8*R*). Thus, the Arimoto group initially focused their efforts on the preparation of (3*S*,4*S*,8*R*)-vallartanone B.

Scheme 1.2 Arimoto synthesis of (3*S*,4*S*,8*R*)-vallartanone B.



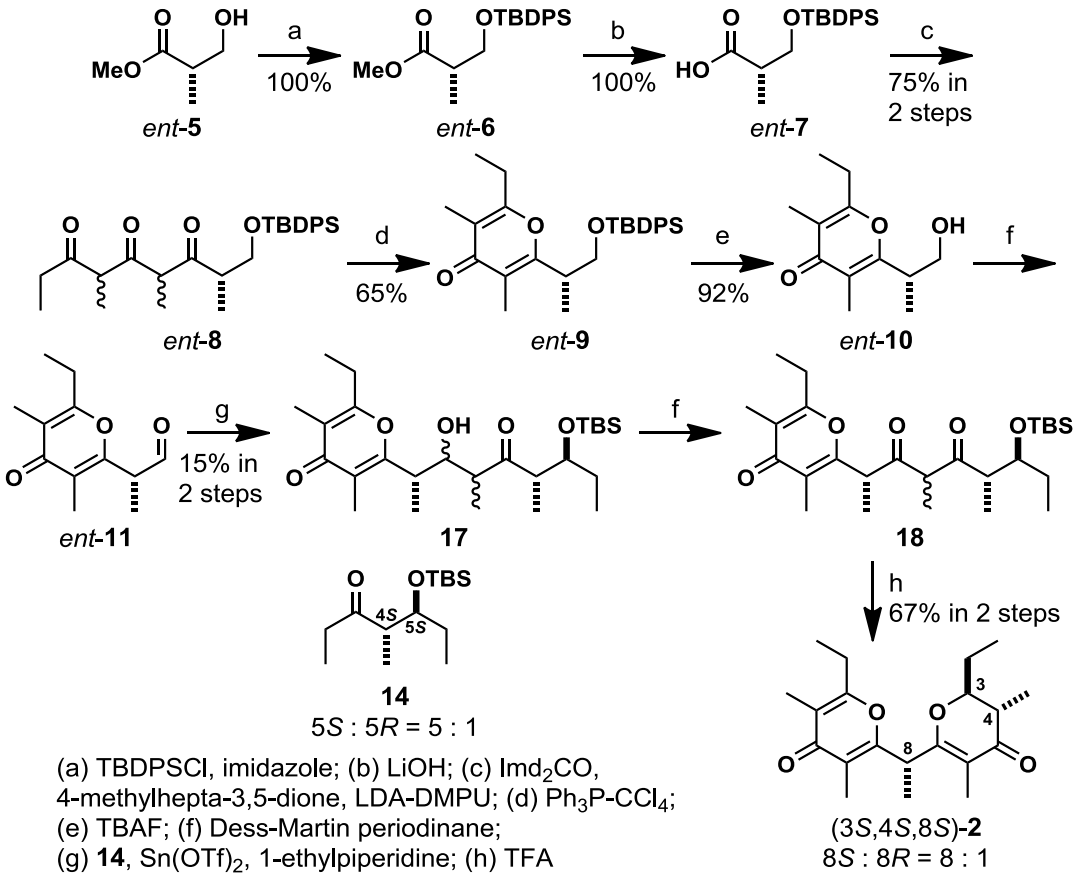
The synthesis of (8*R*)-vallartanone B began with commercially available methyl (*R*)-3-hydroxy-2-methylpropionate (**5**). After protection of the alcohol group in **5** and hydrolysis of the ester, the resulting carboxylic acid **7** was converted to the triketone **8** by reaction of the *in situ* generated mixed anhydride

with the dilithium dienolate of 4-methyl-hepta-3,5-dione. Under their optimized conditions, **8** was transformed into the γ-pyrone **9** without loss of enantiopurity. Deprotection of **9** gave the alcohol **10** that was oxidized with DMP to afford the aldehyde **11** in moderate yield. This aldehyde was found to be configurationally unstable and, without purification or characterization, it was immediately subjected to a tin-mediated aldol reaction with the known ketone **14**[3] to give **15** as an unspecified mixture of diastereomers in modest yield. The mixture of diastereomers **15** was oxidized to give the diketones **16** that were subjected to excess TFA to obtain a 8:1 mixture of (8*R*)-**2** and its C-8 epimer. The origin of the C-8 epimer could hypothetically come from several places during the synthesis: 1) racemization of aldehyde **11** before or during the tin-mediated aldol reaction, 2) isomerization at C-8 in **16** or **2** during the TFA-mediated cyclization and 3) isomerization at C-4 in the product resulting from the minor diastereomer of **14**. Among the mixture of epimers in the final product, the spectral data corresponding to the minor isomer ((8*S*)-**2**) matched with those reported for isolated **2**.

1.4 Arimoto synthesis of (3*S*,4*S*,8*S*)-vallartanone B

The preparation of (3*S*,4*S*,8*S*)-vallartanone B was accomplished in a similar fashion to that used for the (3*S*,4*S*,8*R*) diastereomer by starting with *ent*-**5** with slight changes in the reaction conditions of the tin-mediated aldol reaction (*N*-ethylpiperidine vs triethylamine) and the overall yield (Scheme 1.3).[2] The diastereoselectivity of the aldol reaction of **14** with *ent*-**5** was again not reported and the final product was also obtained as a mixture with its C-8 epimer. (8*S*)-Vallartanone B was obtained free from its (8*R*)-epimer by chiral HPLC and was found to match all the physical data reported for the vallartanone B isolated by Faulkner and Manker.

Scheme 1.3 Arimoto synthesis of (3*S*,4*S*,8*S*)-vallartanone B.



1.5 Revision of absolute configuration of vallartanone B

Arimoto proposed that the discrepancy in absolute configuration assignment could arise from Faulkner's assumption that the conformation of **1** was solely governed by the configuration of C-8, but in fact it should be influenced by C-3 and C-4 as well. To further elaborate this hypothesis, theoretical calculations on the two C-8 epimers of vallartanone A were made via the MOPAC program, an eigenvector following method under the PM3 Hamiltonian. Results showed that the conformation of (8*R*)-**1** was different from that proposed by Faulkner and Manker and suggested the configurations at C-3 and C-4 also influence the conformation (Figure 1.3). Because the calculated models of the epimers looked alike but were different from those proposed by Faulkner, Arimoto concluded that it was unreliable to assign the absolute configuration through CD spectra.

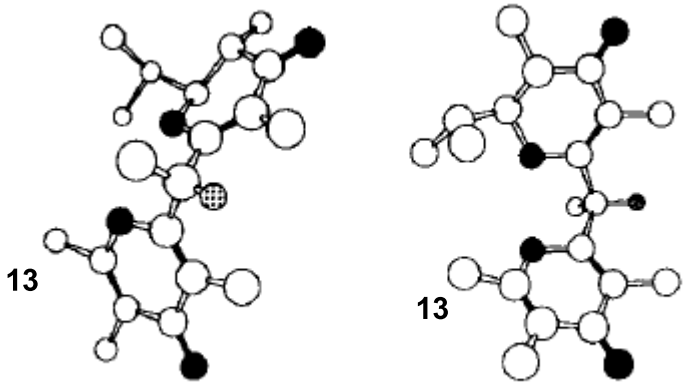


Figure 1.3 Calculated energy minima of (8*R*)-vallartanone A (left) and (8*S*)-vallartanone A (right); an ethyl group adjacent to C-13 was changed to a methyl for simplification. Adapted from *Tetrahedron*, 52, Arimoto H., Yokoyama, R., Nakamura, K., Okumura, Y., Uemura, D., Vallartanone B: Synthesis and Related Studies, 13901-13908, Copyright (1996), with permission from Elsevier.

Arimoto also explained why the relative configuration should be revised – presuming that Faulkner had proposed the (3*S**,4*S**,8*R**) configuration – through investigating the C-8 epimers of 6,7-dihydrovallartanone A (**3** and **4**). The two most stable conformers of each epimer were obtained through

identical computational parameters as mentioned above and their dihedral angles between HC-7 and HC-8 were translated to coupling constants. Because the relationship between the three stereocenters were based on the coupling constants between HC-7 and HC-8 in **3** and **4**, coupling constants based on dihedral angles of the computed models were compared with the reported values. The calculated coupling constants were 3.3 Hz (8*S*) and 10.1 Hz (8*R*) (Figure 1.4) were in good agreement with the experimental values of 4.0 Hz and 9.8 Hz (Figure 1.4) respectively for **3** and **4**. Given that the data for the synthetic (8*S*)-vallartanone B matched with those for the natural product, Arimoto concluded the absolute configuration of vallartanone B was (3*S*,4*S*,8*S*). As noted above, Faulkner and Manker also proposed this relative configuration for vallartanone B (3*R*,4*R*,8*R*).

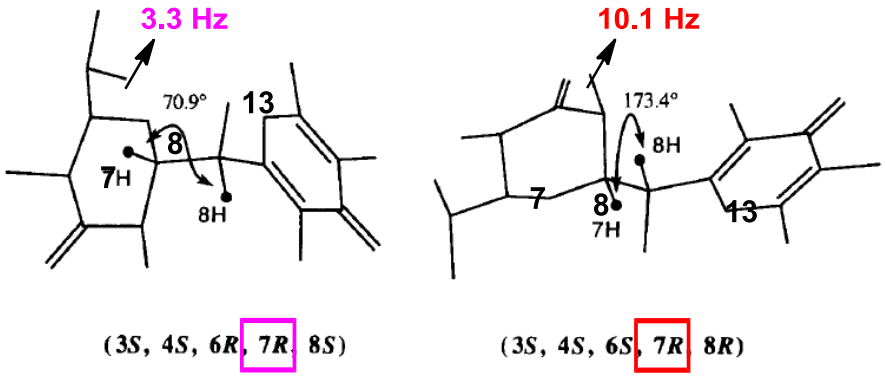


Figure 1.4 Calculated energy minima of (8*S*)-**3** (left) and (8*R*)-**4** (right); an ethyl group adjacent to C-13 was changed to a methyl for simplification. Adapted from *Tetrahedron*, 52, Arimoto H., Yokoyama, R., Nakamura, K., Okumura, Y., Uemura, D., Vallartanone B: Synthesis and Related Studies, 13901-13908, Copyright (1996), with permission from Elsevier.

It should be noted that a better way to determine the relative configurations of **3** and **4** was through securing the 3D spatial arrangement of C-18 via nOe experiments. Because the C-7–C-8 torsion is expected to be governed by minimization of the steric interactions particularly avoidance of *syn*-pentane interactions between C-18 and C-19, the predominant conformer of **3** will have HC-8 synperiplanar with C-19 regardless of the absolute configuration of C-8 (Figure 1.5).

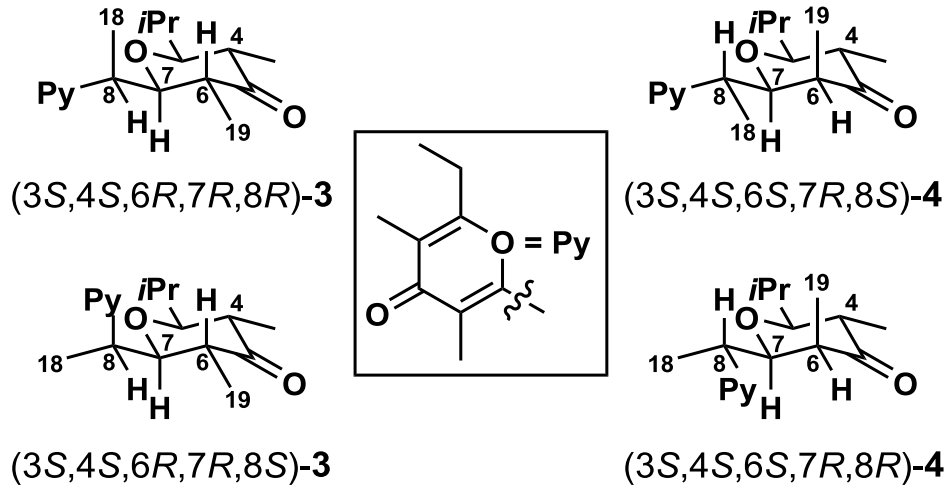


Figure 1.5 Energy minima of **3** and **4** based on avoidance of *syn*-pentane interactions.

Similarly, due to avoidance of *syn*-pentane interactions between C-18 and C-19, the predominant conformer of **4** will have HC-6 synperiplanar with C-18 regardless of the absolute configuration of C-8 (Figure 1.5). In **3**, a positive nOe observation between HC-8 and C-19 would suggest the (3*S**,4*S**,8*S**) relative configuration. In contrast, the observation of a positive nOe between HC-8 and C-19 in **4** would suggest a (3*S**,4*S**,8*R**) relative configuration.

1.6 Conclusion

The configuration of vallartanone A (**1**) was proposed to be (3*R*,4*R*,8*R*) based on analyses of CD and NMR spectra and those of two dihydro derivatives. The same configuration was assigned to vallartanone B (**2**) based on the close correspondence of its spectral data and specific rotation with those of **1**. Unfortunately, there is some discrepancy about the proposed configurations of **1** and **2** because structural drawings in the paper illustrates a (3*S*,4*S*,8*R*) configuration and while the text discusses a (3*R*,4*R*,8*R*) configuration. Through total synthesis, Arimoto established that the absolute configuration of **2** is (3*S*,4*S*,8*S*). Consequently, it is plausible that **1** also possesses the (3*S*,4*S*,8*S*) configuration (Figure 1.6).

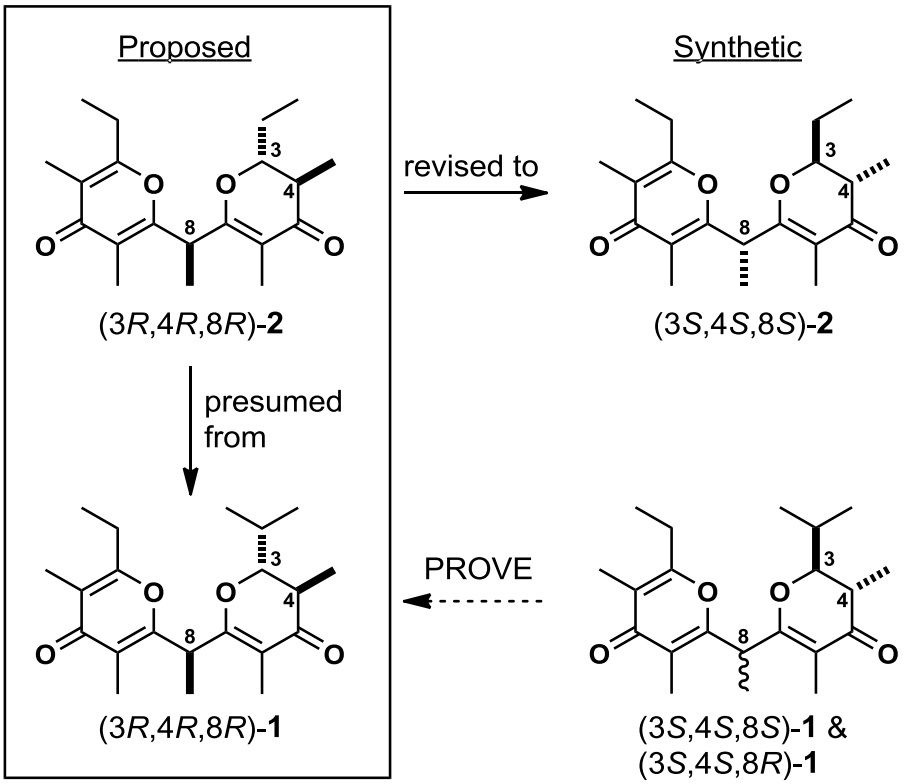


Figure 1.6 Vallartanone A initiative.

2. RESULTS AND DISCUSSION

2.1 Research Objectives

The objective of this research project was to achieve the first total enantioselective syntheses of (3*S*,4*S*,8*S*)-**1** and (3*S*,4*S*,8*R*)-**1** epimer thereby establishing the relative and absolute configurations of vallartanone A. Retrosynthetic analysis of (3*S*,4*S*,8*S*)-**1** is illustrated in Figure 2.1. Thus, retrosynthetic hydration of the dihydropyrone ring in **1** produces hemi-acetal **19** that can undergo ring-chain tautomerization to give the linear form **20**. The β-diketone moiety in **20** could be derived by oxidation of a beta-hydroxy-ketone **21**. Because the configurations of C-6 and C-7 in **21** are irrelevant to the final product, control of the configuration of C-8 in **21** was considered the key to this synthetic project.

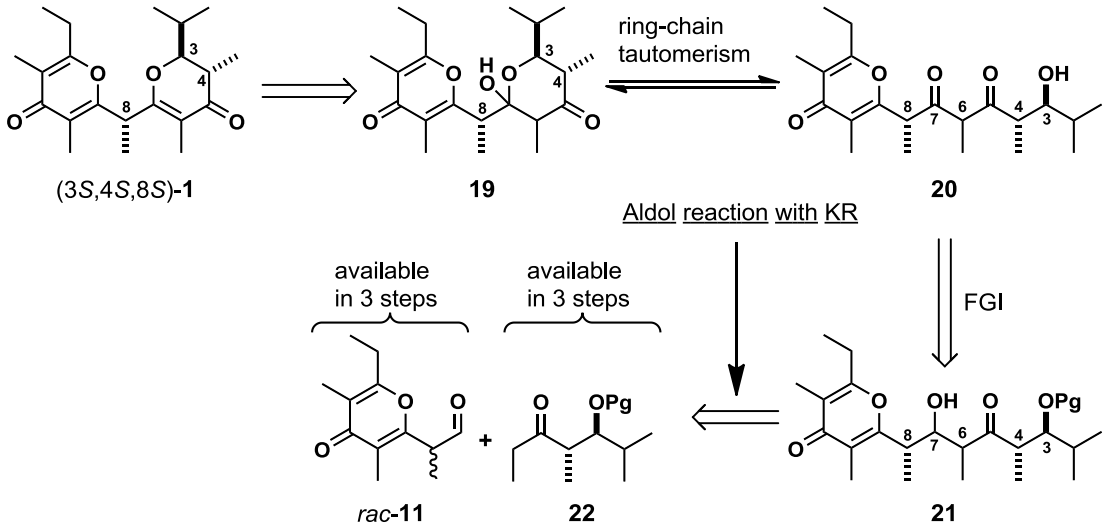
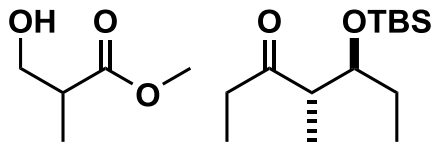


Figure 2.1 Retrosynthetic analysis of (3*S*,4*S*,8*S*)-vallartanone A.

Arimoto obtained (3*S*,4*S*,8*S*)-**2** and (3*S*,4*S*,8*R*)-**2** in separate synthetic sequences starting with the two enantiomers of methyl 3-hydroxy-2-methylpropionate (**5**) and chiral ketone **14** (Figure 2.2).



5 14

Figure 2.2 Starting materials of Arimoto syntheses of vallartanone B's.

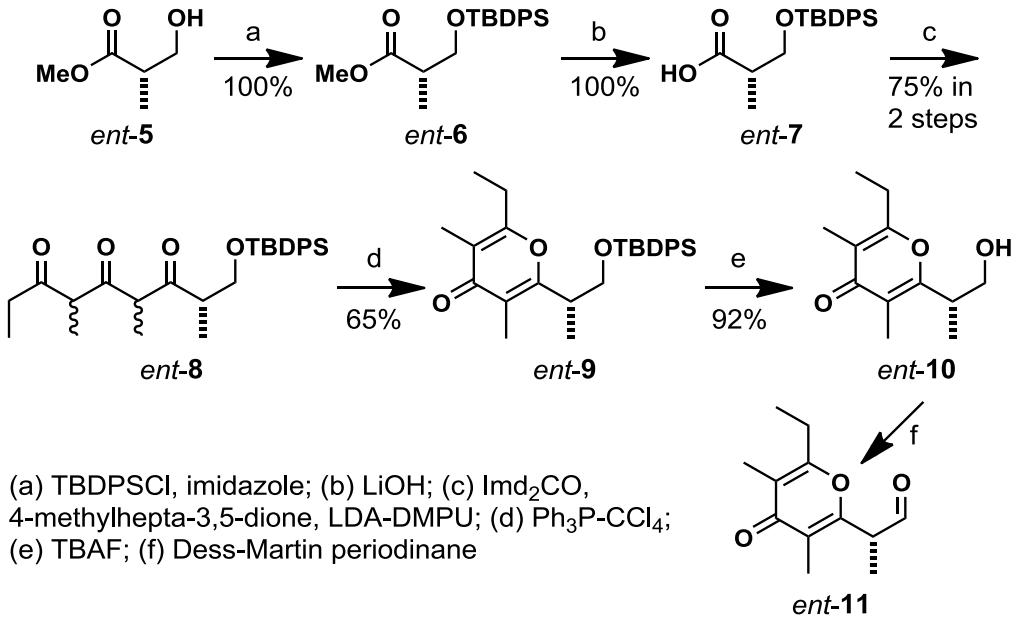
However, the same outcome might be accomplished if an enantiopure fragment was coupled with a racemic fragment with kinetic resolution. Kinetic resolution takes advantage of the fact that the two enantiomers possess different reactivity in a chiral environment thereby allowing the preferential reaction of one enantiomer in the presence of both. One way to form the beta-hydroxy-ketone functional group in **21** is through an aldol reaction. Recent research in the Ward group has involved the design and application of aldol reactions that proceed via kinetic resolution. Coupling chiral fragments using the concept of kinetic resolution allows the use of an enantiopure fragment and a racemic fragment which is advantageous in a total synthesis that follows a convergent pathway. According to the multiplicativity rule,[4] an aldol reaction proceeding with kinetic resolution is expected when the three stereocontrol elements are highly biased; i.e., the relative topicity of the reaction and the diastereoface selectivities of the enolate and aldehyde. Even though the configurations of C-6 and C-7 in **21** are not present in the final product, they will be used to control the C-8 configuration. Once the diastereoface selectivities for additions to aldehyde *rac*-**11** and the enolate derived from ketone **22** have been firmly established, an aldol reaction can be designed with the required relative topicity to afford the (8*S*) configuration.

2.2 Syntheses of aldehyde 11

2.2.1 Previous protocols

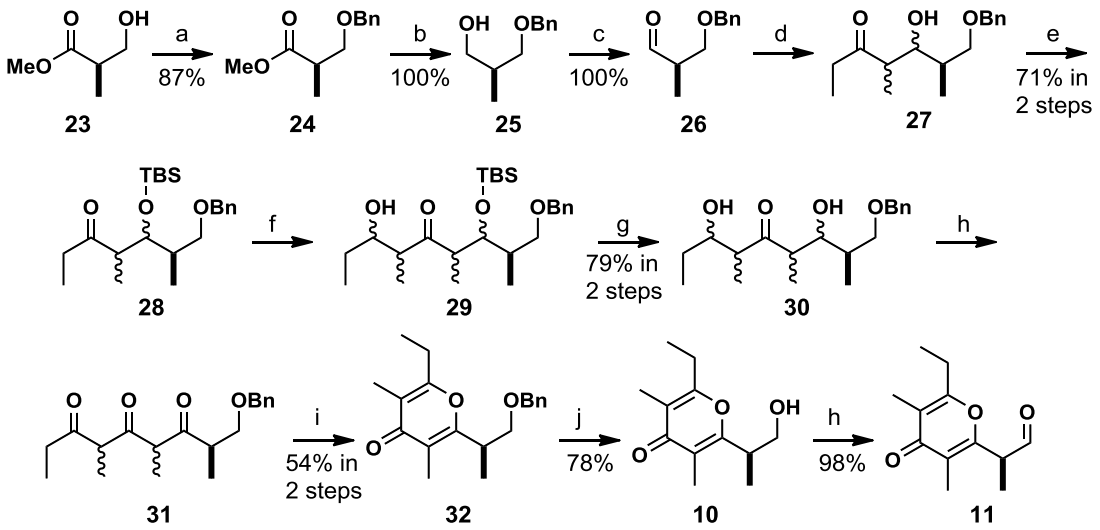
The synthesis of enantiomerically enriched **11** has been reported previously (discussed in Section 1.3 and 1.4); however, **11** has never been characterized. Arimoto and coworkers prepared both **11** and *ent*-**11** in seven steps starting with **5** and *ent*-**5**, respectively (Scheme 2.1).[2]

Scheme 2.1 Arimoto synthesis of *ent*-**11**.



Paterson and coworkers reported the synthesis of the **11** in their total synthesis of baconipyrone C (Scheme 2.2).[5] The only difference from Arimoto's approach was how the tri-ketone **31** was constructed. Instead of coupling 4-methylhepta-3,5-dione with carboxylic acid **7**, Paterson used a total of eight steps to obtain the analogous precursor **31** from **23**, 3-pentanone, and propanal.

Scheme 2.2 Paterson synthesis of **11**.

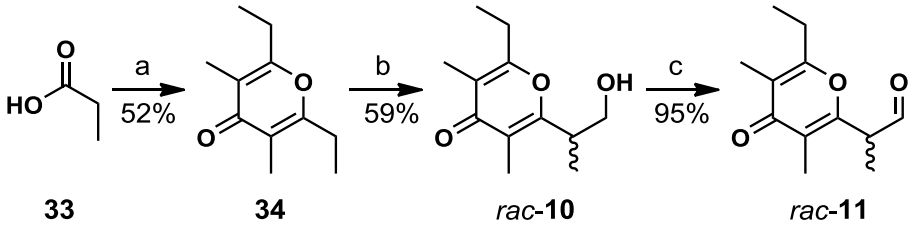


(a) $Cl_3CC(=NH)OBn$, TfOH; (b) $LiAlH_4$; (c) Swern [O]; (d) Et_2CO, $TiCl_4$, *i*-Pr_2NEt; (e) TBSOTf, 2,6-lutidine; (f) $TiCl_4$, *i*-Pr_2NEt, EtCHO; (g) HF; (h) Dess-Martin periodinane; (i) $(COCl)_2$, DMSO; (j) H_2, 10% Pd/C

2.2.2 Ward protocol

The aldehyde *rac*-**11** was accessed in three simple steps. Four molecules of propanoic acid condense to produce 2,6-diethyl-3,5-dimethylpyrone in the presence of polyphosphoric acid at 200 °C (Scheme 2.3). This procedure was adapted from the known protocol developed by Mullock and Suschitzky[6] by modifying the extraction procedure where dichloromethane was used instead of chloroform. Pyrone **34** was deprotonated by NaHMDS and reacted with paraformaldehyde to afford the chiral primary alcohol *rac*-**10**. The deprotonation of **34** was developed by Sengoku and co-workers and the optimal base was found to be NaHMDS (cf. LDA, LTMP, LiHMDS and KHMDS) at -78 °C.[7] These authors also studied reaction of the resulting anion with several alkyl and aryl aldehydes (but not paraformaldehyde), obtaining adducts with low stereoselectivity. After optimizing Sengoku's conditions, the anion of **34** reacted with paraformaldehyde at 0 °C to afford *rac*-**10** in modest yield. Oxidation of *rac*-**10** with IBX gave aldehyde *rac*-**11**.

Scheme 2.3 Ward synthesis of *rac*-**11**.



33 **34** ***rac*-10** ***rac*-11**

(a) PPA; (b) NaHMDS, $HO(CH_2O)_nH$; (c) IBX

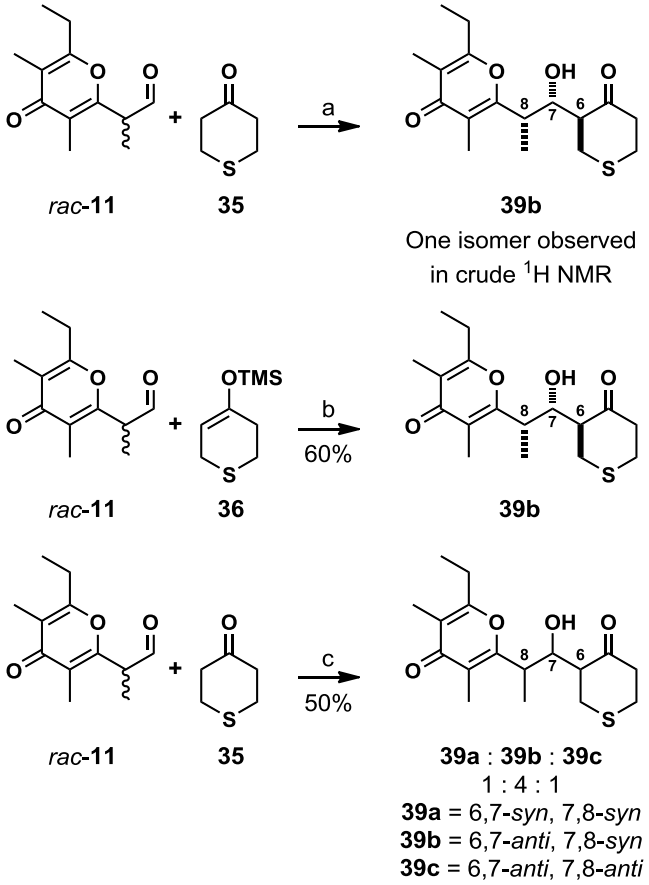
It has been reported that aldehyde **11** is easily racemized even in the presence of silica gel. Because the enantiopurity of the aldehyde was crucial to the syntheses of vallartanone B[2] and baconipyrone C,[5] it was prepared by oxidation of enantiopure **10** with Dess-Martin periodinane and used immediately without characterization.

This synthesis of aldehyde *rac*-**11** has numerous advantages (Scheme 2.3). The approach took fewer steps compared to all known precedents and price difference between the starting materials is over 300-fold. Additionally, the aforementioned configurational instability is not a concern because the racemic aldehyde would be used.

2.3 Establishment of the diastereoface selectivity of *rac*-11

To determine the diastereoface selectivity of aldehyde *rac*-**11**, aldol reactions with the enol dicyclohexylborinate and amine-free lithium enolate[8] of ketone **35** were attempted. In both cases, only one aldol adduct diastereomer (**39b**) was observed in the ^{1}H NMR spectra of the crude products. Adduct **39b** was found to have the relative configuration of (6*S**,7*S**,8*S**) (the structure elucidation of **39b** is described in the following section). Proline-catalyzed aldol reaction between *rac*-**11** and **35** was also attempted but low diastereoselectivity was observed (Scheme 2.4). The *anti* relative configuration of C-6 and C-7 in **39b** is rationalized by a chair-like Zimmermen-Traxler transition state.[9] The *syn* relative configuration between C-7 and C-8 can be explained by the Felkin-Anh model.[10] The highly stereoselective formation of **39b** from reaction of *rac*-**11** with the enol borinate and the lithium enolate of thiopyran ketone **35** suggests the diastereoface bias for aldol addition to *rac*-**11** is highly Felkin-selective.

Scheme 2.4 Reactions of *rac*-**11** with enol borinate, lithium enolate and enamine of ketone **35**.



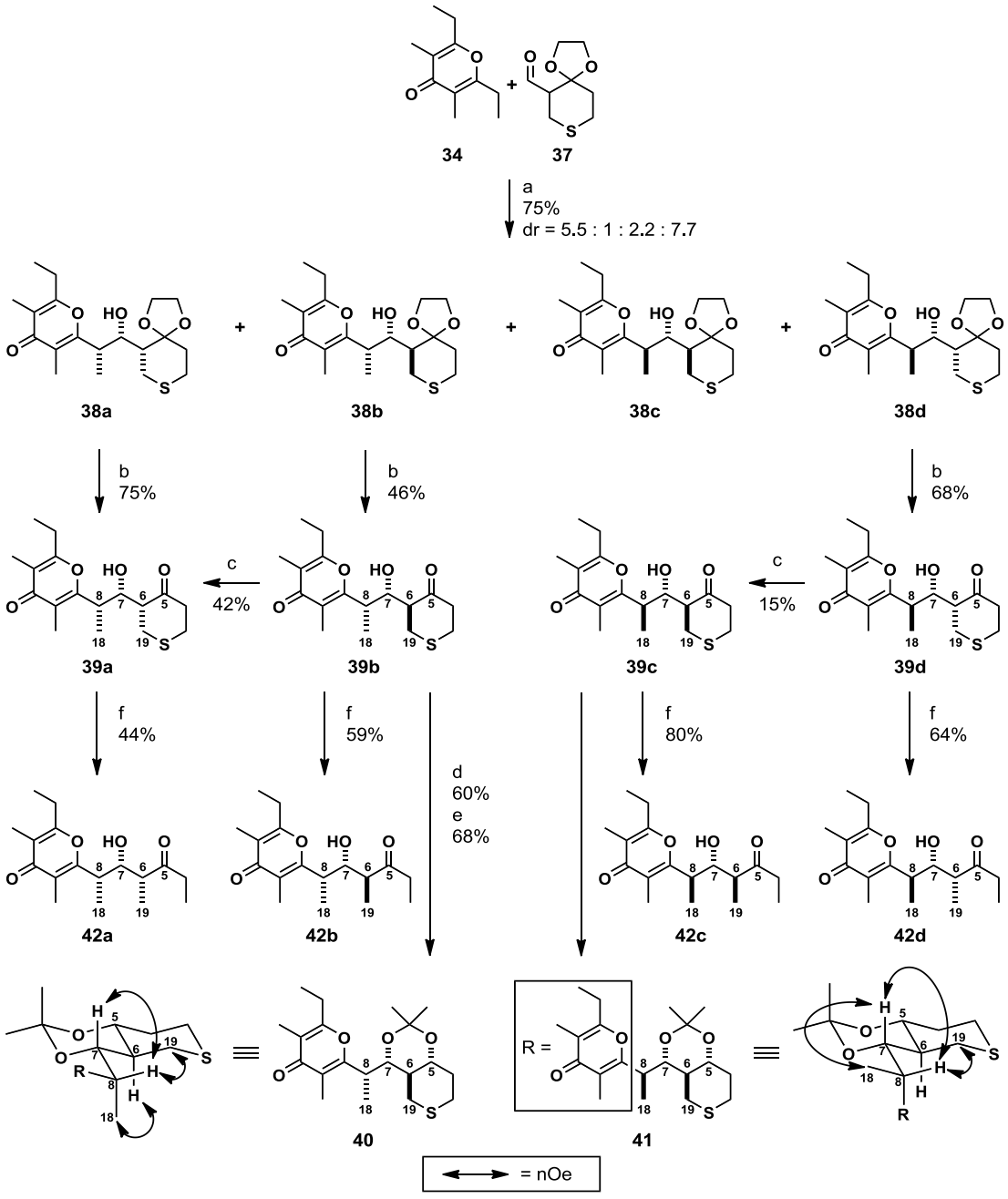
2.4 Characterizations of aldol adducts

2.4.1 Structural elucidations

Model studies were carried out in order to unambiguously assign the relative configuration of the aldol adducts **39a-d** (Scheme 2.5). Given that the reactions of *rac*-**11** with **35** and **36** each gave a single adduct (**39b**), an alternate route was undertaken to obtain all four possible diastereomers (Scheme 2.5). Deprotonation of pyrone **34** with NaHMDS followed by addition of aldehyde **37** to gave a 5.5 : 1 : 2.2 : 7.7 mixture of the four possible adducts **38a**, **38b**, **38c**, and **38d**, respectively. Separate treatment of **38a**, **38b** and **38d** with $FeCl_3 \cdot 6H_2O$ resulted in hydrolysis of the ketal moieties to give **39a**, **39b**, and **39d**, respectively.[11] The fourth diastereomer, **39c**, was obtained from **39d** by isomerization (*vide infra*).[12]

Structural analysis began by transforming the diastereomers **39b** and **39c** into their respective *syn* 1,3-diols via a well-established protocol (Et_2BOMe, $NaBH_4$)[13] followed by conversion into the corresponding acetonides **40** and **41**, respectively. Both **40** and **41** had two characteristic peaks in the ^{13}C NMR spectra corresponding to the methyl groups of an acetonide from a *syn* 1,3-diol (i.e., at *ca.* 20 and 30 ppm).[14] Because the acetonides are conformationally rigid, the relative configurations at C-5, C-6 and C-7 in **40** and **41** could be established by ^1H NMR through the analysis of coupling constants. Large vicinal coupling constants between H-C5–C6-H and H-C6–C7-H observed both in **40** (10.5 and 10 Hz) and in **41** (10.5 and 10.5 Hz) suggested *anti* relationships and supported the assignment of (5*R**,6*R**,7*S**) relative configurations.

Scheme 2.5 Relative configuration verifications on aldol adducts.



(a) NaHMDS; (b) $FeCl_3 \cdot 6H_2O$; (c) imidazole; (d) Et_2BOMe, $NaBH_4$; (e) 2,2-dimethoxypropane, *p*-TsOH; (f) Raney Ni

Assignments of the relative configurations of C-8 in **40** and **41** were based on nOe experiments. The hypothesis was that the C-7–C-8 torsion angle would be governed by minimization of steric interactions particularly avoidance of *syn*-pentane interactions between C-18 and H_2C-19. Thus, the

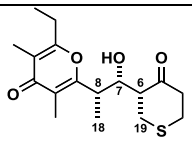
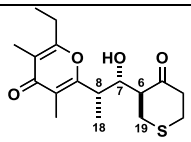
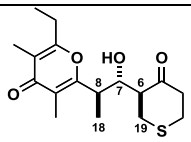
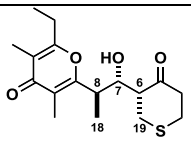
predominant conformer should have the HC-8 synperiplanar with H_2C-19 and this assumption was supported by the observation of small H-C7–C8-H coupling constants (4 Hz for **40**, 3 Hz for **41**) and positive nOe's between HC-8 and H_2C-19 in both **40** and **41**. In **40**, the positive nOe observed between HC-6 and H_3C-18 suggests the (5*R**,6*R**,7*S**,8*S**) relative configuration. In contrast, the observation of a positive nOe between HC-7 and H_3C-18 in **41** suggests a (5*R**,6*R**,7*S**,8*R**) relative configuration. Through the above analysis, a (6*S**,7*S**,8*S**) relative configuration can be assigned to **39b** thereby establishing that the addition of the enol borinate and lithium enolate of thiopyran ketone **37** to *rac*-**11** is Felkin-selective (discussed in Section 2.3).

Structures **39a** and **39d** are the C-6 epimers of **39b** and **39c**, respectively, and these relationships were established by isomerization reactions starting with **39b** and **39c**, respectively. Based on previous work of Ward group,[12] aldol adducts that are derived from thiopyran ketones can undergo *syn-anti* isomerization in the presence of imidazole via keto-enol tautomerism. Separate treatment of aldol adducts **39b** and **39d** with imidazole afforded **39a** and **39c**, respectively, thereby establishing the epimeric relationship at C-6 between **39a** and **39b** as well as **39c** and **39d**. The results of the isomerization reactions allowed **39a** and **39d** to be assigned the relative configuration (6*R**,7*S**,8*S**) and (6*R**,7*S**,8*R**), respectively. After the unambiguous assignments of the relative configurations of **39a-d**, each was subjected to desulfurization to afford **42a-d**, respectively. Due to difficulty of separation, compounds **42b-d** were characterized as a mixture of diastereomers (see experimental section for details).

2.4.2 Correlation between structural features and spectral data

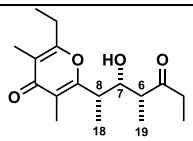
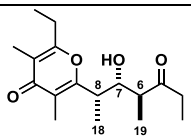
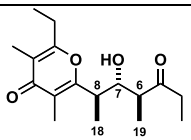
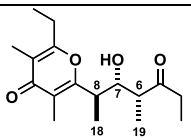
The NMR data for **39a-d** and **42a-d** were collected and analyzed to identify trends that might be used to assign the relative configurations of related aldol adducts. The discussion will begin with **39a-d** (Table 2.1). Structures that have a *syn* relative configuration between C-7 and C-8 (**39a**, **39b**) consistently have a H_3C-18 ^1H NMR chemical shift that is ≥ 1.35 ppm. In contrast, structures that have an *anti* relative configuration between C-7 and C-8 (**39c**, **39d**) have a ^1H NMR chemical shift of H_3C-18 that is ≤ 1.20 ppm. Three carbon nuclei (C-8, C-7 and C-19) have chemical shifts that consistently change with the relative configuration between C-6 and C-7. Structures that have a *syn* relative configuration between C-6 and C-7 (**39a**, **39d**) consistently possess the ^{13}C NMR chemical shifts ≤ 37.8 ppm, ≤ 71.1 ppm and ≤ 30.3 ppm for C-8, C-7 and C-19, respectively. On the other hand, structures that have an *anti* relative configuration between C-6 and C-7 (**39b**, **39c**) consistently possess the ^{13}C NMR chemical shifts ≥ 39.7 ppm, ≥ 76.5 ppm and ≥ 35.7 ppm for C-8, C-7 and C-19, respectively.

Table 2.1 Unique characteristic NMR features of **39a**-**d** with corresponding structural features.

		 **39a**	 **39b**	 **39c**	 **39d**
Relative configuration	C-6–C-7	*syn*	*anti*	*anti*	*syn*
	C-7–C-8	*syn*	*syn*	*anti*	*anti*
Chemical shift (ppm)	δ_H, C-18	1.35	1.36	1.20	1.16
	δ_C, C-8	37.8	40.4	39.7	37.5
	δ_C, C-7	71.0	76.5	76.7	71.1
	δ_C, C-19	30.3	35.7	35.7	29.7

The spectral features that correspond to the relative configuration of structures **42a-d** are identical with those of **39a-d** (Table 2.2). Structures that have a *syn* relative configuration between C-7 and C-8 (**42a**, **42b**) consistently have a H_3C-18 ^1H NMR chemical shift that is ≥ 1.32 ppm. In contrast, structures that have an *anti* relative configuration between C-7 and C-8 (**42c**, **42d**) displays constantly with a ^1H NMR chemical shift of H_3C-18 that is ≤ 1.23 ppm. Three carbon nuclei (C-8, C-7 and C-19) have chemical shifts that consistently vary with the relative configuration between C-6 and C-7. Structures that have a *syn* relative configuration between C-6 and C-7 (**42a**, **42d**) consistently possess the ^{13}C NMR chemical shifts ≤ 38.8 ppm, ≤ 72.5 ppm and ≤ 10.0 ppm for C-8, C-7 and C-19, respectively. On the other hand, structures that have an *anti* relative configuration between C-6 and C-7 (**42b**, **42c**) consistently possess the ^{13}C NMR chemical shifts ≥ 40.0 ppm, ≥ 77.0 ppm and ≥ 15.9 ppm for C-8, C-7 and C-19, respectively.

Table 2.2 Unique characteristic NMR features of **42a**-**d** with corresponding structural features.

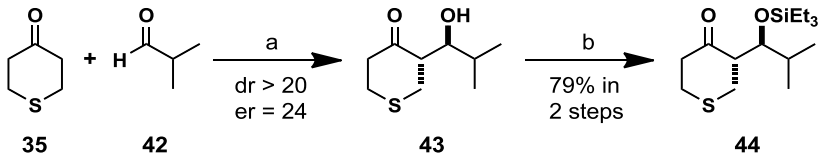
		 **42a**	 **42b**	 **42c**	 **42d**
Relative configuration	C-6–C-7	*syn*	*anti*	*anti*	*syn*
	C-7–C-8	*syn*	*syn*	*anti*	*anti*
Chemical shift (ppm)	δ_H, C-18	1.33	1.32	1.23	1.13
	δ_C, C-8	38.8	40.5	40.0	38.2
	δ_C, C-7	72.4	77.0	77.6	72.5
	δ_C, C-19	10.0	15.9	15.9	9.3

2.5 Synthesis of ketone 44

2.5.1 Enantioselective proline-catalyzed intermolecular aldol reaction

It has been established that the enol dicyclohexylborinate of thiopyran ketone **35** adds to *rac*-**11** with high Felkin selectivity and *anti*-selective relative topicity (discussed in Section 2.3). According to the multiplicativity rule, reaction of *rac*-**11** with an enol dicyclohexylborinate that possesses high biased diastereoface selectivity should proceed via kinetic resolution with synthetically useful selectivity. Based on previous work of Ward group[15], aldol reactions of enol dicyclohexylborinates derived from thiopyran ketones show high levels of *anti* relative topicity and *trans* ketone enol(ate) face selectivity. Consequently, ketone **44** emerged as a viable candidate for reaction with *rac*-**11**. Enantioenriched ketone **44** was synthesized in two steps starting with aldehyde **42** and ketone **35**, a readily available material in the Ward group that is also available commercially (Scheme 2.6). The first reaction was a proline-catalyzed intermolecular aldol reaction that was previously optimized with ketone **35** in excess to afford aldol adduct **43** in dr > 20 and > 98% ee.[16] For this work, aldehyde **42** was used in excess and the resulting aldol adduct **43** was obtained in dr > 20 (by ^{1}H NMR of the crude reaction mixture) and with slightly lower enantiopurity (92% ee by optical rotation) for unknown reasons. Aldol adduct **43** was protected as a triethylsilyl ether to afford **44**.

Scheme 2.6 Synthesis of ketone **44**.



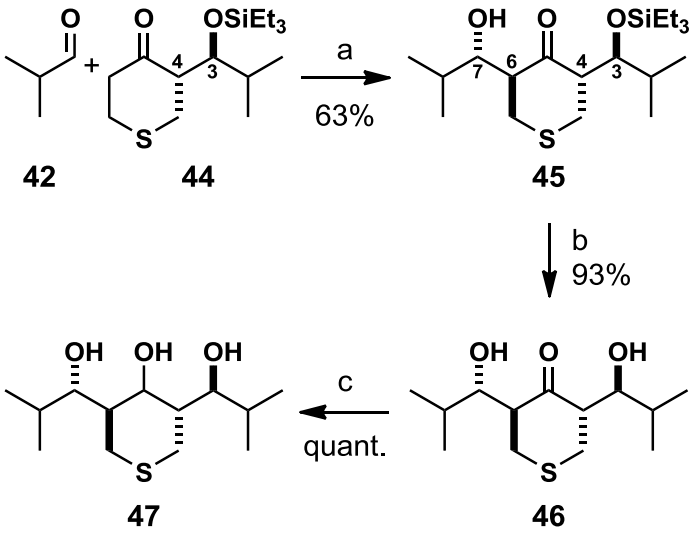
35 42 43 44

(a) L-proline (50 mol %); (b) $TfOSiEt_3$, 2,6-lutidine

2.5.2 Establishment of the diastereoface selectivity of enol(ate) of ketone 44

In order to establish the diastereoface selectivity of **44**, aldol reaction with isobutyraldehyde **42** was investigated (Scheme 2.7). Reaction of **44** with chlorodicyclohexylborane and triethylamine followed by the addition of **42** afforded adduct **45** (dr > 20 by ^{1}H NMR of the crude reaction mixture). In order to determine its relative configuration, **45** was desilylated to afford diol **46**. The ^{13}C spectrum of **46** had seven signals suggesting a structure with either C_S (*cis-anti* relative configuration) or C_2 (*trans-anti* relative configuration) symmetry. Reduction of **46** gave unsymmetric triol **47** in quantitative yield (thirteen signals in the ^{13}C NMR spectrum) thereby establishing that **46** was C_2 symmetric. Because ketone **44** has the (3*S*,4*S*) absolute configuration, an absolute configuration of (3*S*,4*S*,6*S*,7*S*) can be assigned to **45**. The exclusive formation of **45** from reaction of isobutyraldehyde with enol borinate of **44** suggests the diastereoface bias of **44** for addition to aldehyde is highly *trans*-selective.

Scheme 2.7 Establishment of the relative configuration of aldol adduct **45**.



(a) (*c*-Hex)$_2$BCl, Et$_3$N; (b) 10 wt. % HF; (c) NaBH$_4$

2.6 Total synthesis of (3*S*,4*S*,8*S*)-vallartanone A

2.6.1 Aldol reaction with kinetic resolution

It has been established that the enol borinate of thiopyran ketone **35** adds to *rac*-**11** with high Felkin selectivity and *anti*-selective relative topicity (discussed in Section 2.3). The enol borinate of chiral ketone **44** undergoes aldol reaction with *trans* diastereoface selectivity and *anti*-selective relative topicity (discussed in Section 2.5.2). Based on previous work of the Ward group,[16] it is expected that the reaction of enol borinate of **44** with *rac*-**11** will afford **49**, a synthetic precursor of vallartanone A, that has the required absolute configuration (3*S*,4*S*,8*S*) and the configurations at C-6 (6*S*) and C-7 (7*S*) set to aid the desired aldol coupling (Figure 2.3).

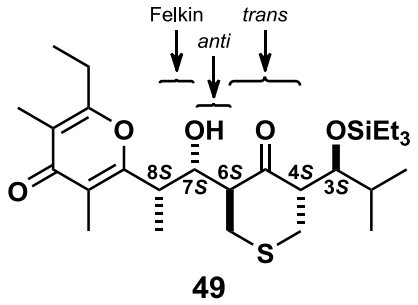
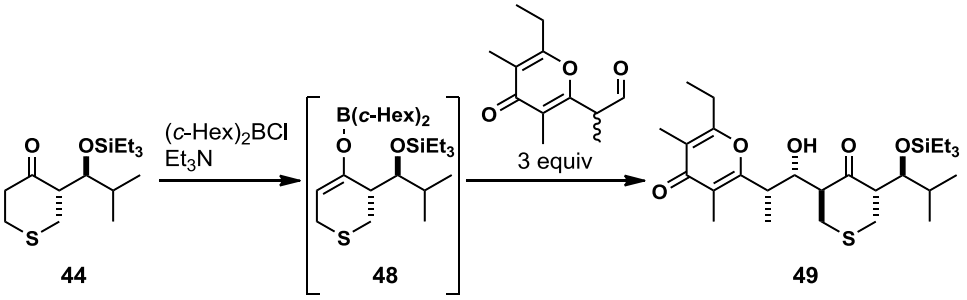


Figure 2.3 A synthetic precursor that can be transformed into (3*S*,4*S*,8*S*)-vallartanone A.

Reaction of **44** with chlorodicyclohexylborane and triethylamine followed by the addition of three equivalents of *rac*-**11** afforded adduct **49** (dr = 10 by ^{1}H NMR of the crude reaction mixture) (Scheme 2.8). Generally in a kinetic resolution, the enantiomeric ratio of an initially racemic reactant increases with conversion and the ratio of stereoisomeric products decreases.[17] In order to preserve both yield and selectivity of product, an excess amount of *rac*-**11** was used in the reaction between enol borinate **48** and aldehyde *rac*-**11**. The relative configuration of **49** was analyzed through conformational and spectral analyses.

Scheme 2.8 Aldol reaction with kinetic resolution.



2.6.2 Structural elucidation of aldol adduct 49

If **49** is a *cis*-1,3-substituted tetrahydropyran ring (**50**), substituents R^1 and R^2 would both be in equatorial orientations (Figure 2.4). Consequently a single chair conformer would dominate and the expected coupling constants for H-C4–C20-H_2 are 0-5/6-14 Hz and 0-5/6-14 Hz for H-C6–C19-H_2 (Table 2.3). If **49** is a *trans*-1,3-substituted tetrahydropyran ring, two chair conformers are possible, **51a** and **51b**, that will differ in energy according to the difference in conformational energies of the two substituents, R^1 and R^2. The expected coupling constants in **51a** for H-C4–C20-H_2 are 0-5/0-5 Hz and 0-5/6-14 Hz for H-C6–C19-H_2 (Table 2.3). In **51b**, the expected coupling constants for H-C4–C20-H_2 are 0-5/6-14 Hz and 0-5/0-5 Hz for H-C6–C19-H_2, respectively. The observed coupling constants of H-C4–C20-H_2 and H-C6–C19-H_2 are 5/10.5 Hz and 5/6 Hz, respectively, thereby establishing **49** has a *trans* relative configuration between C-4 and C-6 with **51a** as the predominant conformer.

Table 2.3 Proton spin-coupling constants comparison of **49-51**.

	50	**51a**	**51b**	**49**
	Coupling constants (Hz)			
	Expected	Expected	Expected	Observed
C-4–C-20	0-5, 6-14	0-5, 6-14	0-5, 0-5	5, 10.5
C-6–C-19	0-5, 6-14	0-5, 0-5	0-5, 6-14	5, 6

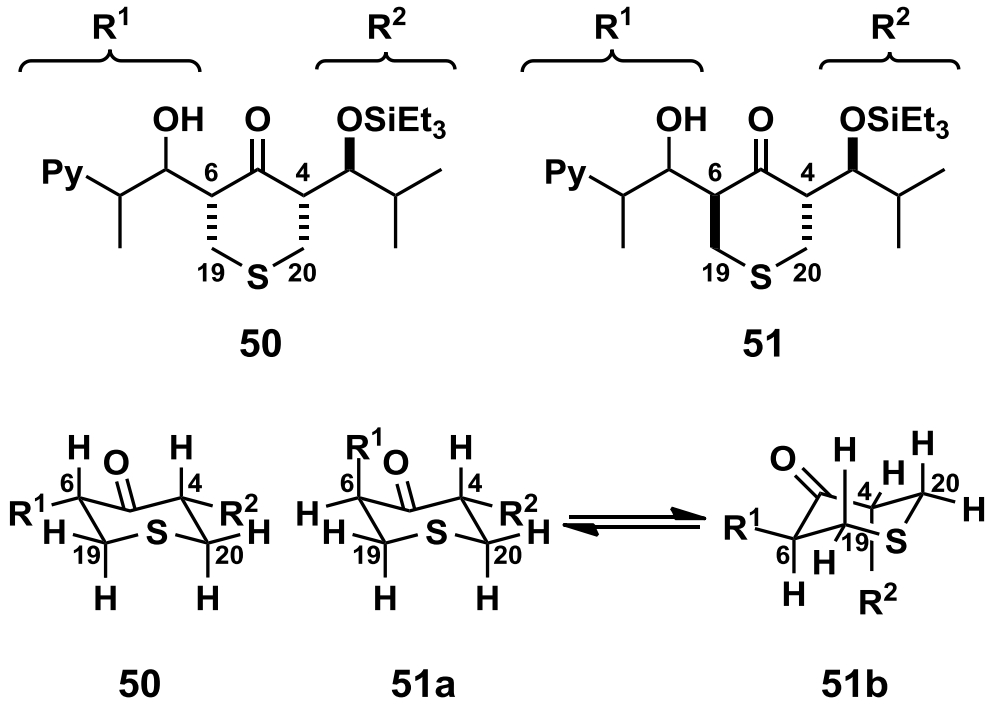
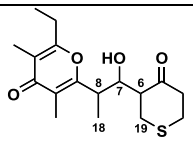
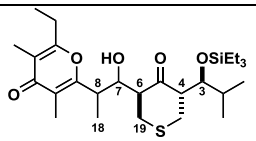


Figure 2.4 Conformational analyses of **50** and **51**.

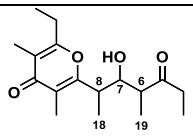
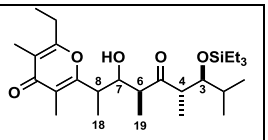
The NMR data of **39a-d** was used to assign the remaining relative configurations of **49**. Aldol adduct **49** was assigned a *syn* relative configuration between C-7 and C-8 based on its observed H_3C-18 ^1H NMR chemical shift, 1.29 ppm (Table 2.4). The *anti* relative configuration between C-6 and C-7 was assigned based on the observed ^{13}C NMR chemical shifts of C-8 (39.4 ppm) and C-7 (74.8 ppm). To further validate the above assignment, **49** was desulfurized and the corresponding acyclic aldol adduct **52**, was investigated.

Table 2.4 Comparison of chemical shifts between **39a-d** and **49**.

 **39a-d**					 **49**
Relative configuration					Observed chemical shift (ppm)
C-6–C-7	*syn*	*anti*	*anti*	*syn*	
C-7–C-8	*syn*	*syn*	*anti*	*anti*	
Chemical shift (ppm)					
δ_H, C-18	1.35	1.36	1.20	1.16	1.29
δ_C, C-8	37.8	40.4	39.7	37.5	39.4
δ_C, C-7	71.0	76.5	76.7	71.1	74.8
δ_C, C-19	30.3	35.7	35.7	29.7	30.8

The relative configuration of aldol adduct **52** was assigned by the comparison of its NMR data with those of **42a-d**. The *syn* relative configuration between C-7 and C-8 was assigned based on the observed H_3C-18 ^1H NMR chemical shift (1.36 ppm) of **52** (Table 2.5). The *anti* relative configuration between C-6 and C-7 was assigned based on the observed ^{13}C NMR chemical shifts of C-8 (40.0 ppm), C-7 (76.1 ppm) and C-19 (14.7 ppm) in **52**. In conclusion, the relative configuration of **49** was assigned *trans* (C-4–C-6), *anti* (C-6–C-7) and *syn* (C-7–C-8) based on the conformational analysis of **49** and the spectral analyses of **49** and **52**. Because the starting ketone **44** has the (3*S*,4*S*) absolute configuration, a (3*S*,4*S*,6*S*,7*S*,8*S*) absolute configuration can be assigned to **49**.

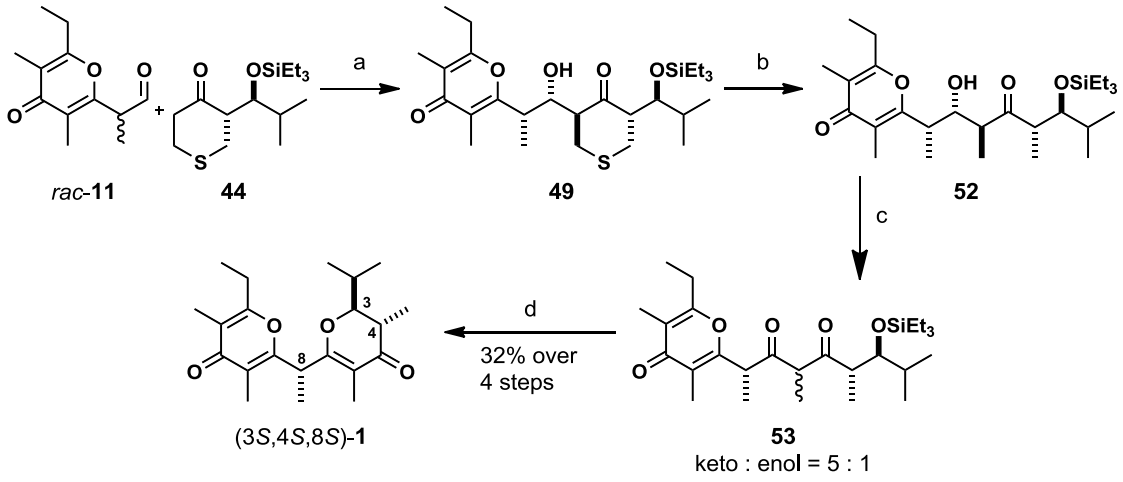
Table 2.5 Comparison of chemical shifts between **42a-d** and **52**.

 **42a-d**					 **52**
Relative configuration					Observed chemical shift (ppm)
C-6–C-7	*syn*	*anti*	*anti*	*syn*	
C-7–C-8	*syn*	*syn*	*anti*	*anti*	
Chemical shift (ppm)					
δ_H, C-18	1.33	1.32	1.23	1.13	1.36
δ_C, C-8	38.8	40.5	40.0	38.2	40.0
δ_C, C-7	72.4	77.0	77.6	72.5	76.1
δ_C, C-19	10.0	15.9	15.9	9.3	14.7

2.6.3 Endgame

Aldol adduct **52** was oxidized with IBX in DMSO at room temperature and without characterization, the oxidized products were treated with 10 wt. % HF to afford (3*S*,4*S*,8*S*)-vallartanone A as a single compound suggesting that no epimerization had occurred throughout those two transformations. Due to difficulty of separation after the aldol reaction, a telescoped procedure was also developed starting with ketone **44** and *rac*-**11**(Scheme 2.9).

Scheme 2.9 Completion of the total synthesis of (3*S*,4*S*,8*S*)-vallartanone A.



(a) *c*-$(Hex)_2BCl$, Et_3N; (b) Raney Ni; (c) IBX; (d) 10 wt. % HF

2.7 Total synthesis of 8-*epi*-vallartanone A

2.7.1 Strategic switch of one stereocontrol element

Similar to the efficient total synthesis of (3*S*,4*S*,8*S*)-vallartanone A, synthetic precursors of 8-*epi*-vallartanone A (**54-57**) can also be assembled through an aldol reaction that proceeds via kinetic resolution (Figure 2.5). The precursors **54**, **55**, and **56** emerge by inverting the C-4–C-6, C-6–C-7, or C-7–C-8 relative configuration of **49,** respectively (Table 2.6). Precursor **57** arises by inverting the C-4–C-6, C-6–C-7, and C-7–C-8 relative configurations of **49**. The key to switch the enantioselectivity of the reaction is to selectively reverse one or all of the three stereocontrol elements by modification of the reaction conditions.

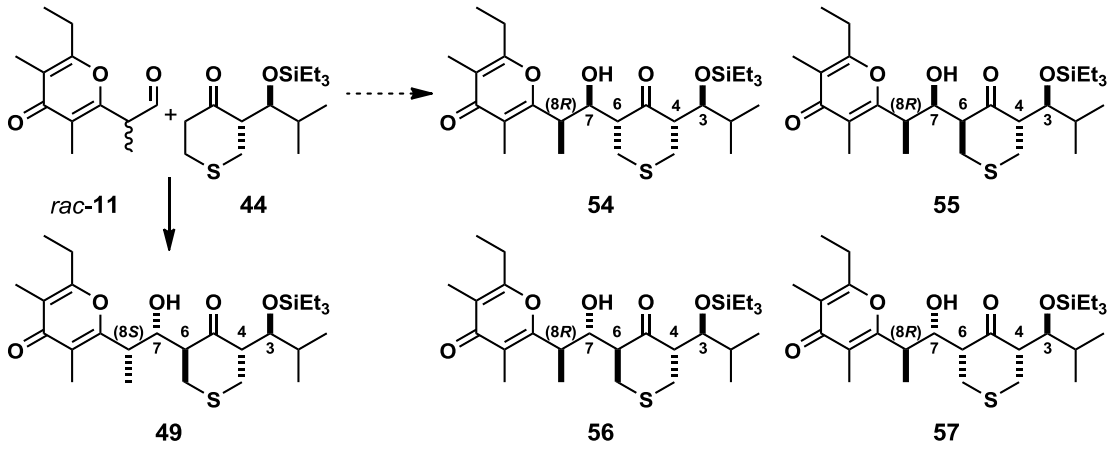


Figure 2.5 Possible synthetic precursors (**54-57**) for 8-*epi*-vallartanone A.

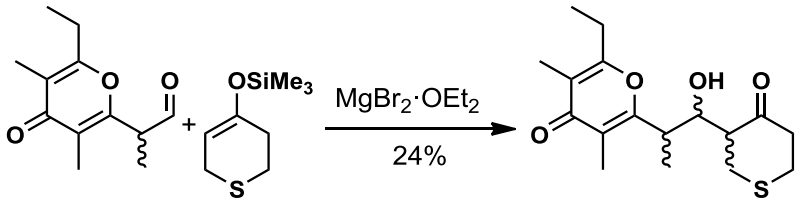
Table 2.6 Configurational relationship between **49** and **54-57**.

	(8*S*)-**49**	(8*R*)-**54**	(8*R*)-**55**	(8*R*)-**56**	(8*R*)-**57**
Relative configuration					
C-4–C-6[a]	*trans*	*cis*	*trans*	*trans*	*cis*
C-6–C-7[b]	*anti*	*anti*	*syn*	*anti*	*syn*
C-7–C-8[c]	*syn*	*syn*	*syn*	*anti*	*anti*

Controlled by [a]diastereoface selectivity of enolate, [b]relative topicity of reaction and [c]diastereoface selectivity of aldehyde.

Based on previous work of Ward group,[18] the diastereoface selectivity of an aldehyde can be modulated in the presence of a chelating Lewis acid, leading to non-Felkin addition to the aldehyde. Attempting to reverse the diastereoface selectivity of *rac*-**11**, it was allowed to react with enolsilane **36** in the presence of $MgBr_2 \cdot OEt_2$ (Scheme 2.10). After purification, a mixture of four diastereomers was isolated in low yield.

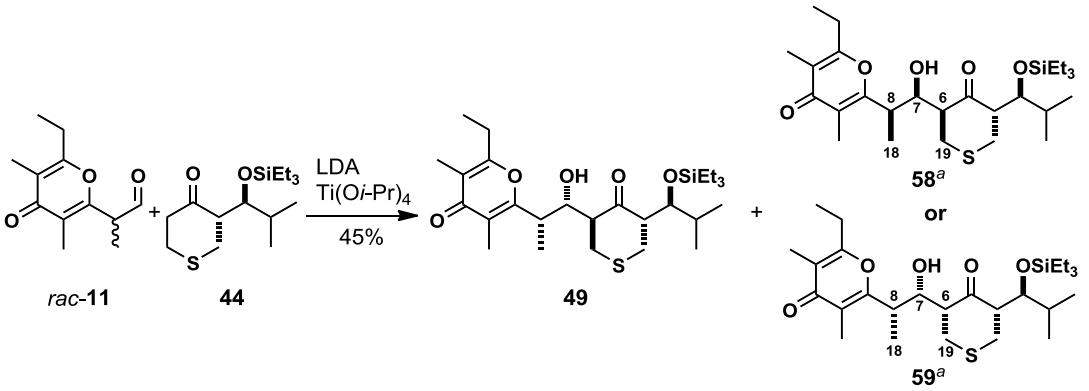
Scheme 2.10 Modulation of diastereoselectivity in the presence of a chelating Lewis acid.



rac-**11** **36** **39a-d**

Based on previous work of Ward group[16], aldol reactions of thiopyran ketones show high levels of *anti* and *syn* relative topicities using enol borinates and titanium enolates, respectively. Thus, an aldol reaction between the *in situ* generated titanium enolate of ketone **44** and *rac*-**11** was attempted in an effort to obtain *syn* relative topicity (Scheme 2.11). After purification, a mixture of two diastereomers (dr = 1.4 by ^{1}H NMR in favor of **49**) was obtained in low yield.

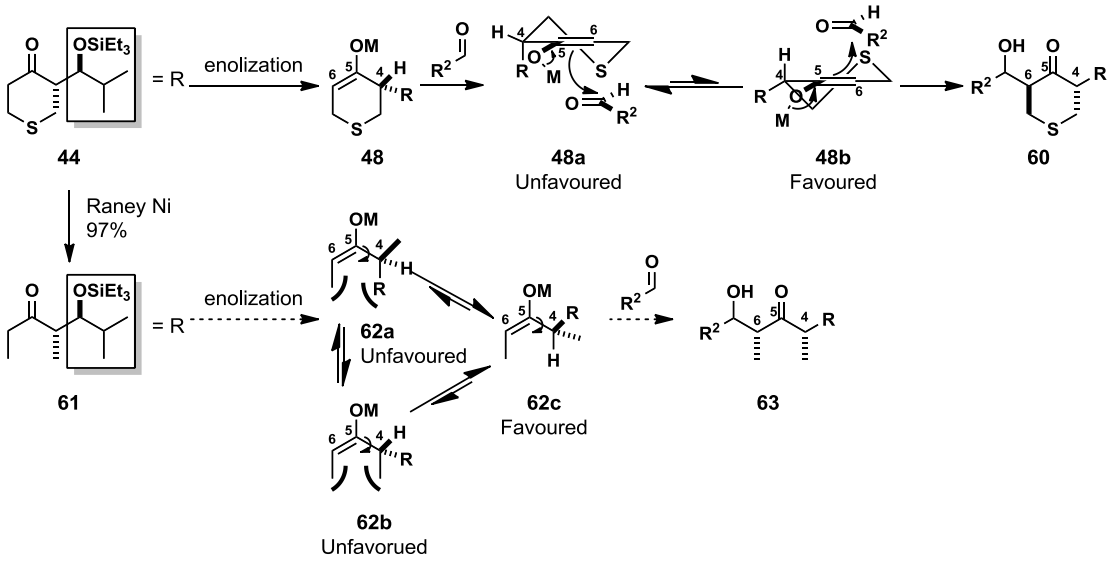
Scheme 2.11 Modulation of diastereoselectivity through titanium enolate.



[a]Utilizing the NMR data of **39a-d**, aldol adduct **58**/**59** was assigned a *syn* relative configuration between C-7 and C-8 based on its observed H_3C-18 ^1H NMR chemical shift, 1.31 ppm. The *syn* relative configuration between C-6 and C-7 was assigned based on the observed ^{13}C NMR chemical shifts of C-8 (38.0 ppm), C-7 (71.0) and C-19 (29.9 ppm).

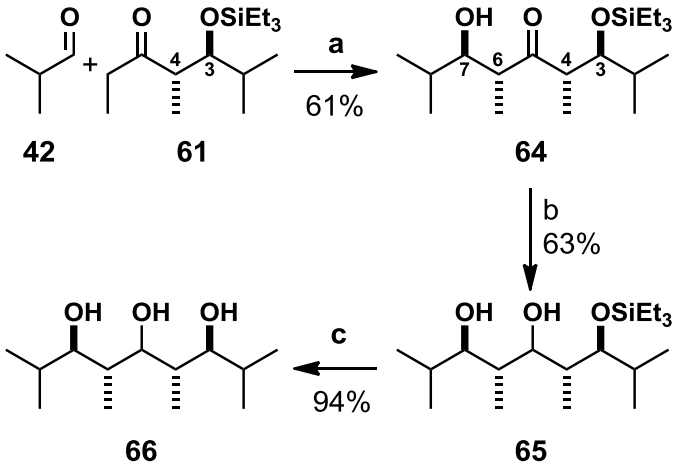
The diastereoface selectivity of enol borinate **48** was rationalized through conformational analysis (Scheme 2.12). The diastereoface selectivity of aldol reactions of chiral ethyl ketones is influenced by the geometry of the enolate as well as the preferred torsion angle C4–C5. Enol borinate **48** is a six-membered ring with limited C4–C5 rotation; moreover, only an (*E*)-enol borinate can be formed. As a result, the most stable conformer of **48** will have the R substituent in an equatorial orientation (**48b**) when the aldehyde undergoes a pseudo-axial attack. On the other hand, torsion C4–C5 will be influenced by minimization of 1,3-allylic strain in (*E*)-enol borinate **62**, now that it lacks the cyclic sulfide. The most stable conformer of **62** will have H-C4 eclipsing with the vinyl methyl group (**62c**) with the diastereotopic faces differentiated by methyl and R groups. The aldehyde should approach on the rear face of **62** to afford 4,6-*syn*-**63** due to steric effect, hence reversing the diastereoface selectivity of the ketone enol(ate).

Scheme 2.12 Rationalization of opposite diastereoface selectivity of enol borinates **48** and **62**.



Thus, ketone **44** was desulfurized to afford the acyclic analogue, **61** (Scheme 2.12), and the aforementioned hypothesis was tested by reacting the (*E*)-enol borinate of ketone **61** and aldehyde **42** (Scheme 2.13). The reaction afforded one aldol adduct, **64**, after purification (dr > 20 by ^{1}H NMR of the crude reaction mixture). In order to determine its relative configuration, **64** was reduced to afford one diol **65**. Desilylation of **65** gave symmetric triol **66** (seven signals in the ^{13}C NMR spectrum) thereby establishing its C_S symmetry. Because ketone **61** has the (3*S*,4*S*) absolute configuration, an absolute configuration of (3*S*,4*S*,6*R*,7*R*) can be assigned to **64**. The exclusive formation of **64** from reaction of isobutyraldehyde with enol borinate of **61** suggests it undergoes aldol reaction with 4,6-*syn* diastereoface selectivity and *anti*-selective relative topicity.

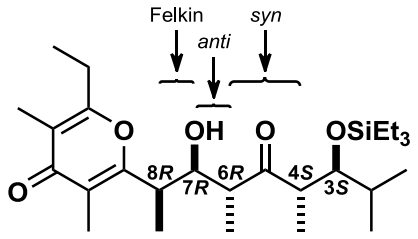
Scheme 2.13 Establishment of the relative configuration of aldol adduct **64**.



(a) (c-Hex)$_2$BCl, EtNMe$_2$; (b) Et$_2$BOMe, NaBH$_4$; (c) 10 wt. % HF

2.7.2 Aldol reaction with kinetic resolution (sequel)

Similar to the aldol reaction between aldehyde *rac*-**11** and enol borinate **48**, it is expected the reaction of *rac*-**11** and enol borinate **62** will also proceed with kinetic resolution. As a result, a synthetic precursor of 8-*epi*-vallartanone A (**67**) would be assembled that has the required absolute configuration (3*S*,4*S*,8*R*), and the configuration at C-6 (6*R*) and C-7 (7*R*) set to aid the desired aldol coupling (Figure 2.6).

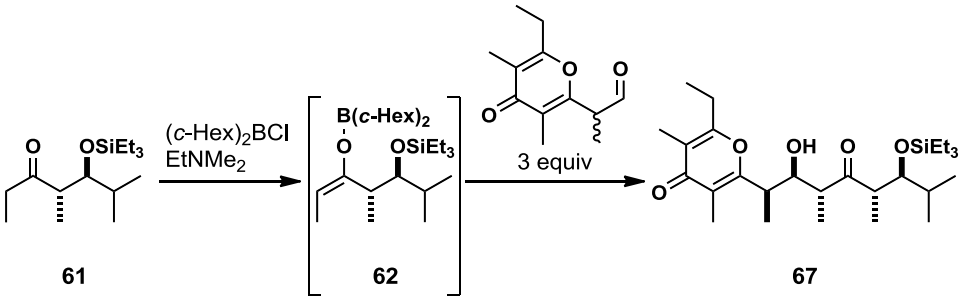


67

Figure 2.6 A synthetic precursor that can be transformed into 8-*epi*-vallartanone A.

Reaction of **61** with chlorodicyclohexylborane and *N*,*N*-dimethylethylamine followed by the addition of three equivalents of *rac*-**11** afforded adduct **67** (dr = 10 by ^{13}C NMR of the crude reaction mixture) (Scheme 2.14). The relative configuration of **67** was assigned through spectral analyses.

Scheme 2.14 Aldol reaction with kinetic resolution (sequel).

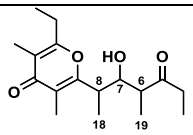
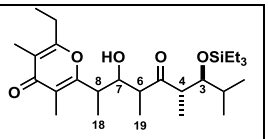


61 **62** **67**

2.7.3 Structural elucidation of aldol adduct 67

The relative configuration of **67** was assigned by comparison of its NMR data with those of **42a-d**. Aldol adduct **67** was assigned with *syn* relative configuration between C-7 and C-8 based on the observed H_3C-18 ^1H NMR chemical shift, 1.28 ppm (Table 2.7). The *anti* relative configuration between C-6 and C-7 was assigned based on the observed ^{13}C NMR chemical shifts of C-8 (38.9 ppm), C-7 (76.0 ppm) and C-19 (14.7 ppm) in **67**. The NMR data of **67** are different from those of **52**; however, the relative configurations at C-6–C-7 and C-7–C-8 in **67** are identical to those of **52**. Because, the 4,6-*anti* relative configuration was assigned in aldol adduct **67** based on NMR analysis of the precursor **49**, the 4,6-*syn* relative configuration was assigned to **67**. In conclusion, the relative configuration of **67** was assigned *syn* (C-4–C-6), *anti* (C-6–C-7) and *syn* (C-7–C-8) based on spectral analysis of **67**. Because the starting ketone **61** has the (3*S*,4*S*) absolute configuration, a (3*S*,4*S*,6*R*,7*R*,8*R*) absolute configuration can be assigned to **67**.

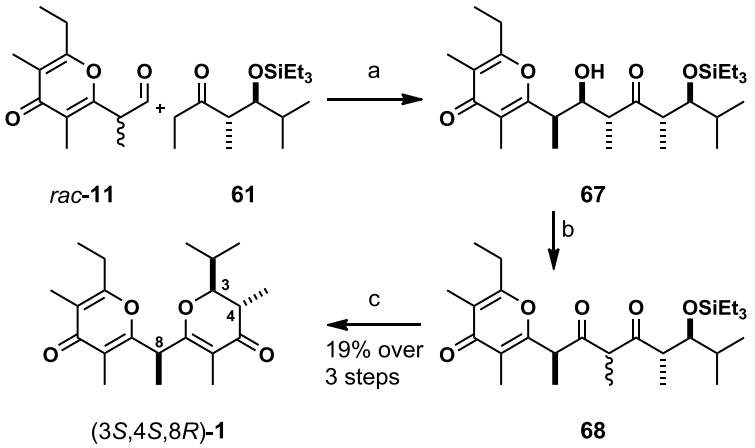
Table 2.7 Comparison of chemical shifts between **42a-d** and **67**.

 **42a-d**					 **67**
Relative configuration					Observed chemical shift (ppm)
C-6–C-7	*syn*	*anti*	*anti*	*syn*	
C-7–C-8	*syn*	*syn*	*anti*	*anti*	
Chemical shift (ppm)					
δ_H, C-18	1.33	1.32	1.23	1.13	1.28
δ_C, C-8	38.8	40.5	40.0	38.2	38.9
δ_C, C-7	72.4	77.0	77.6	72.5	76.0
δ_C, C-19	10.0	15.9	15.9	9.3	14.7

2.7.4 Endgame

Aldol adduct **67** was oxidized with IBX in DMSO at room temperature and without characterization, the oxidized products were treated with 10 wt. % HF to afford a mixture of 8-*epi*-**1** and **1** (dr = 15 by ^{1}H NMR) suggesting epimerization had occurred throughout those two transformations. Even though **1** was obtained free of its C-8 epimer under identical condition, the origin of epimerization for the formation of 8-*epi*-**1** was unknown. Due to difficulty of separation after the aldol reaction, a telescoped procedure was also developed starting with ketone **61** (Scheme 2.15).

Scheme 2.15 Completion of the total synthesis of 8-*epi*-vallartanone A.



(a) *c*-$(Hex)_2BCl$, $EtNMe_2$; (b) IBX; (c) 10 wt. % HF

2.8 Explanation of stereochemical outcome of aldol reactions

The diastereoface selectivities of the enol borinates **48** and **62** (*trans* and *syn*, respectively) were governed by steric effects (discussed in Section 2.7.1). The diastereoface selectivity of aldehyde *rac*-**11** can be rationalized using the Felkin-Anh model.[10] The *anti* relative topicity of the aldol reactions originate from (*E*)-enol borinates (**48** and **62**) that react with *rac*-**11** via chair-like Zimmerman-Traxler transition states.[9] The relative configurations of aldol adducts **49** and **67** essentially arise from the simultaneous cooperation of the three stereocontrol elements: 1) diastereoface selectivity of the ketone enol(ate), 2) relative topicity of the reaction and 3) diastereoface selectivity of the aldehyde (Figure 2.7).

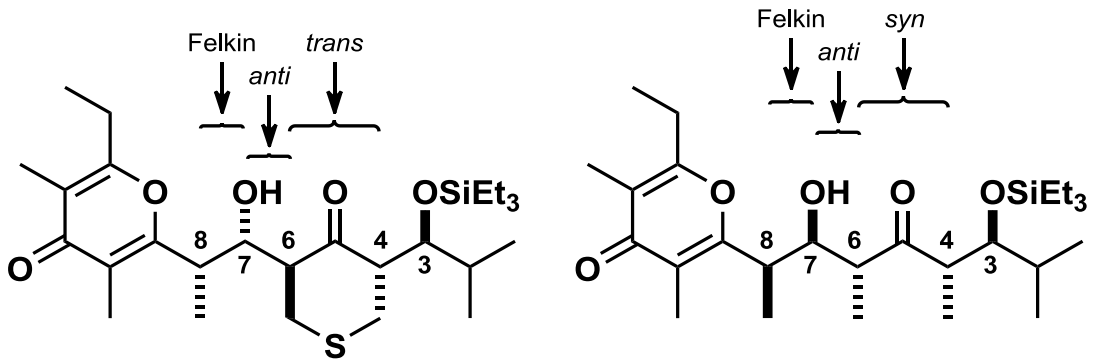


Figure 2.7 Aldol adducts **49** and **67**.

In the presence of both enantiomers of **11**, enol borinates **48** and **62** preferentially reacted with (*R*)-**11** and (*S*)-**11**, respectively. This enantiomer selective reaction can be rationalized through the conformational analyses of their respective chair-like transition states (Figure 2.8). The hypothesis was that the C-7–C-8 torsion in **69** would be governed by minimization of steric interactions particularly avoidance of *syn*-pentane interactions between C-18 and C-19. Assuming the pyrone group of (*R*)-**11** resembles a phenyl group, the lowest energy transition state should have HC-8 synperiplanar with H_2C-19, at the same time, C-18 synperiplanar with HC-6.

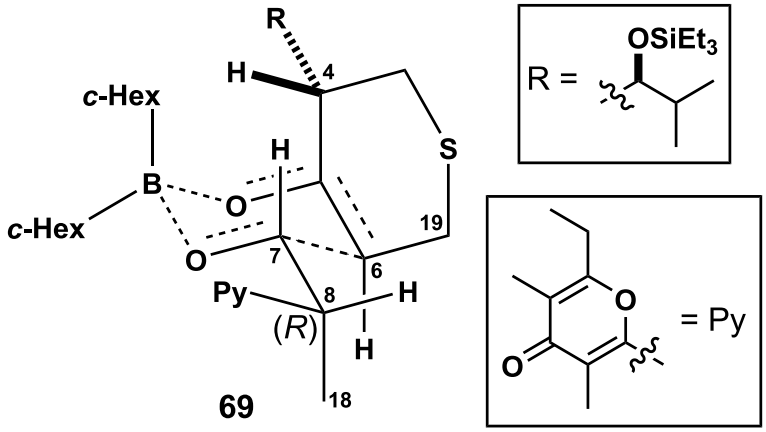


Figure 2.8 Proposed transition state for aldol reaction between **48** and (*R*)-**11**.

Similarly, the preferred C-7–C-8 torsion in transition state **70** would be strongly biased by steric repulsion between C-18 and C-19 (Figure 2.9). With the assumption that the pyrone group of (*S*)-**11** resembles a phenyl group, the lowest energy transition state should have HC-8 synperiplanar with H_3C-19, and C-18 synperiplanar with HC-6.

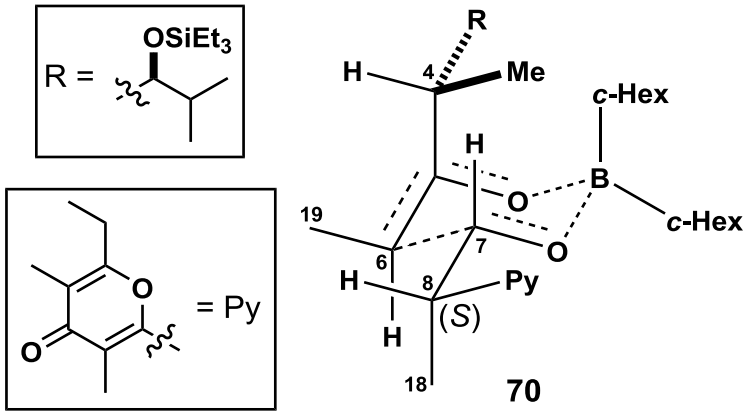
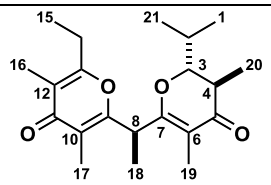
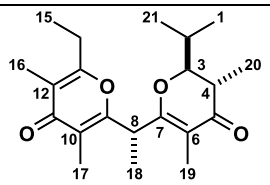


Figure 2.9 Proposed transition state for aldol reaction between **62** and (*S*)-**11**.

2.9 Comparison of physical data

Synthetic (3*S*,4*S*,8*S*)-**1** ($[\alpha]_D$ = -180 (*c* 0.50, $CHCl_3$) gave spectroscopic data (MS and ^1H) that matched with those reported[1] for isolated **1** ($[\alpha]_D$ = -176 (*c* 0.68, $CHCl_3$)) (Table 2.8).

Table 2.8 Comparison of ^1H NMR spectra ($CDCl_3$) between natural **1** and synthetic (3*S*,4*S*,8*S*)-**1**.

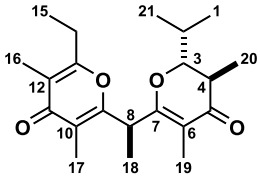
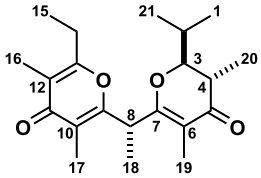
 (3*R*,4*R*,8*R*)-**1**		assignment[a]	 (3*S*,4*S*,8*S*)-**1**	
natural[a]			synthetic	
δ_H (360 MHz)	multiplicity (*J*'s in Hz)		δ_H (500 MHz)	multiplicity (*J*'s in Hz)
4.17	q (7.1)	C-8	4.17	q (7)
3.79	dd (2.6, 12.9)	C-3	3.78	dd (2.5, 13)
2.62	q (7.6)	C-14	2.68-2.56	m
2.38	dq (12.9, 6.8)	C-4	2.38	dq (13, 7)
1.96	s	C-16	1.95	s
1.94	s	C-17	1.94	s
1.85[b]	m	C-2	1.99-1.95	m
1.75	s	C-19	1.74	s
1.47	d (7.1)	C-18	1.46	d (7)
1.23	t (7.6)	C-15	1.22	t (7.5)
1.08	d (6.8)	C-1	1.08	d (7)
1.07	d (6.8)	C-20	1.06	d (7)
0.84	d (6.8)	C-21	0.83	d (7)

[a]Data and assignment according to Faulkner (ref. 1). [b]Discrepancy was assumed to be caused by artifact during isolation, based on matching data (^{13}C NMR, specific rotation and circular dichroism) between isolated **1** and synthetic **1**.

Because Faulkner used a 2D $^1H/^{13}C$ HSC experiment to assign the ^{13}C NMR spectrum of **1**, signals that correspond to the quaternary carbons were assigned based on chemical shift and were considered interchangeable (Table 2.9).[1] In this work, all ^{13}C NMR spectra were assigned and confirmed by gHSQC and gHMBC experiments. ^{13}C Chemical shifts for synthetic **1** are consistently higher (average = 0.14 ppm)

than those reported for the natural **1**, except for C-10, presumably due to a different reference standard; this work used δ_C $CDCl_3$ = 77.23 ppm.

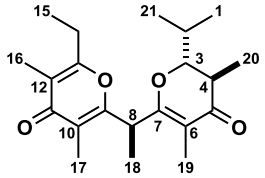
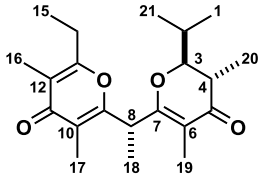
Table 2.9 Comparison of ^{13}C NMR spectra ($CDCl_3$) between natural **1** and synthetic (3*S*,4*S*,8*S*)-**1**.

 (3*R*,4*R*,8*R*)-**1**	assignment[a]	 (3*S*,4*S*,8*S*)-**1**
natural[a]		synthetic
δ_C (50 MHz)		δ_C (125 MHz)
195.2	C-5	195.7
179.4	C-11	179.8
168.4[b,d]	C-7	168.8
164.4[b,e]	C-13	164.7
160.8[f]	C-9	161.0
119.4[c]	C-10	119.1
118.3[c]	C-12	118.5
108.7	C-6	108.8
87.4	C-3	87.4
41.0	C-4	41.1
38.8	C-8	38.9
28.9	C-2	29.0
24.8	C-14	25.0
19.6	C-1	19.8
14.6	C-21	14.7
14.2	C-18	14.5
11.2	C-15	11.6
10.1	C-20	10.2
9.4	C-16	9.8
9.2	C-17	9.5
8.9	C-19	9.3

[a]Data and assignment according to Faulkner (ref. 1). [b,c]Signals maybe interchanged (ref. 1). [d]Originally assigned as C-13 (ref. 1). [e]Originally assigned as C-9 (ref. 1). [f]Originally assigned as C-7 (ref. 1).

Although the ^1H NMR spectrum of 8-*epi*-**1** was the only physical data provided by Faulkner, the ^1H NMR spectrum of synthetic (3*S*,4*S*,8*R*)-**1** ($[\alpha]_D$ = -100 (*c* 0.30, $CHCl_3$)) matched with those reported[1] for 8-*epi*-**1** (Table 2.10).

Table 2.10 Comparison of ^1H NMR spectra ($CDCl_3$) between isolated 8-*epi*-**1** and synthetic (3*S*,4*S*,8*R*)-**1**.

 (3*R*,4*R*,8*S*)-**1**		assignment[a]	 (3*S*,4*S*,8*R*)-**1**	
isolated[a]			synthetic	
δ_H (360 MHz)	multiplicity (*J*'s in Hz)		δ_H (500 MHz)	multiplicity (*J*'s in Hz)
4.14	q (7.0)	C-8	4.14	q (7)
3.71	dd (2.8, 12.8)	C-3	3.71	dd (2, 13)
2.61	q (7.7)	C-14	2.67-2.54	m
2.45	dq (12.8, 6.9)	C-4	2.45	dq (13, 7)
2.00	m	C-2	1.99-1.91	m
1.95	s	C-16	1.95	s
1.94	s	C-17	1.94	s
1.73	s	C-19	1.73	s
1.49	d (7.0)	C-18	1.49	d (7)
1.23	t (7.7)	C-15	1.22	t (7.5)
1.07	d (6.9)	C-20	1.06	d (7)
0.96	d (6.9)	C-1	0.96	d (7)
0.95	d (6.9)	C-21	0.95	d (7)

[a]Data and assignment according to Faulkner (ref. 1).

The circular dichroism spectra of (3*S*,4*S*,8*S*)-**1** and (3*S*,4*S*,8*R*)-**1** were acquired for further structural validation (Figure 2.10). The negative split Cotton effect exhibited by (3*S*,4*S*,8*S*)-**1** (max @ 235 nm and min @ 276 nm) matched with those reported[1] for **1** (max @ 237 nm and min @ 274 nm).

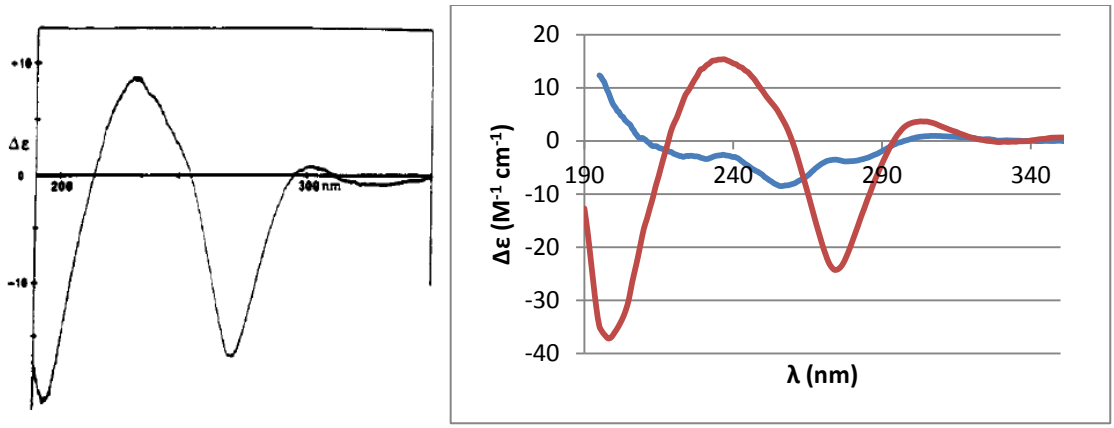


Figure 2.10 Circular dichorism spectra of isolated **1** (left), (3*S*,4*S*,8*S*)-**1** (red), and (3*S*,4*S*,8*R*)-**1** (blue). Copied with permission from Manker, D. C.; Faulkner, D. J. Vallartanone A and B, polypropionate metabolites of *Siphonaria maura* from Mexico. *J. Org. Chem.* **1989**, *54*, 5374-5377. Copyright 1989 American Chemical Society.

2.10 Conclusion

The first total syntheses of (3*S*,4*S*,8*S*)-**1** and its C-8 epimer were accomplished starting with commercially available materials: ketone **35**, isobutyraldehyde and propanoic acid (Figure 2.11). The syntheses of **49** and **67**, the synthetic precursors for (3*S*,4*S*,8*S*)-**1** and (3*S*,4*S*,8*R*)-**1**, respectively, were achieved by coupling *rac*-**11** with specific enantioenriched ketones via aldol reactions designed to proceed with kinetic resolution but with opposite enantioselectivity. In the presence of *rac*-**11**, the enol borinate of **44** reacted preferentially with (*R*)-**11** (i.e., enantiomer selective) in a highly diastereoselective manner (*trans* ketone enol(ate) diastereoface selectivity, *anti* relative topicity and Felkin aldehyde diastereoface selectivity) to afford (3*S*,4*S*,6*S*,7*S*,8*S*)-**49** (dr =10). The enantioselectivity of the reaction was switched by a tactical change of the ketone enol(ate) diastereoface selectivity (*trans* to *syn*) through the usage of ketone **61**, the desulfurized analogue of **44**. In the presence of *rac*-**11**, the enol borinate of **61** reacted preferentially with (*S*)-**11** in a highly diastereoselective manner (*syn* ketone enol(ate) diastereoface selectivity, *anti* relative topicity and Felkin aldehyde diastereoface selectivity) to afford (3*S*,4*S*,6*R*,7*R*,8*R*)-**67** (dr =10). Both aldol adducts, **49** and **67**, were individually transformed into (3*S*,4*S*,8*S*)-**1** and (3*S*,4*S*,8*R*)-**1**, respectively. Physical data (MS, CD, NMR, $[\alpha]_D$) of (3*S*,4*S*,8*S*)-**1** and ^{1}H NMR of (3*S*,4*S*,8*R*)-**1** was found to matched with those reported[1] for naturally occurring **1** and 8-*epi*-**1**, respectively. Base on the unambiguous configurational assignments of **49** and **67**, the absolute configuration of vallartanone A should be revised from (3*R*,4*R*,8*R*) to (3*S*,4*S*,8*S*).

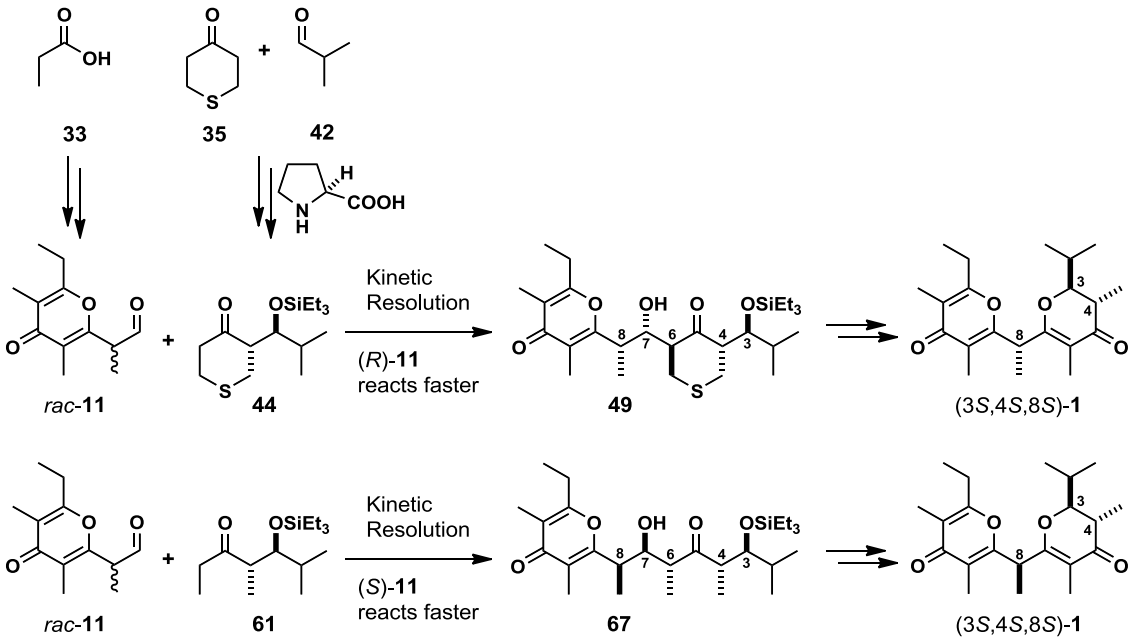


Figure 2.11 Summary of total syntheses of vallartanone A and 8-*epi*-vallartanone A.

3. EXPERIMENTAL

3.1 General Methods

Anhydrous solvents were distilled under argon atmosphere as follows: tetrahydrofuran (THF) from benzophenone sodium ketyl; Et_2O from benzophenone sodium ketyl; CH_2Cl_2 from CaH_2; DMSO from CaH_2 at reduced pressure (stored over 4Å molecular sieves); MeOH from $Mg(OMe)_2$. Unless otherwise noted, all experiments involving air- and/or moisture-sensitive compounds were conducted in an oven dried round-bottom flask (RBF) capped with a rubber septum, and attached via a needle and connecting tubing to an argon manifold equipped with mercury bubbler (ca. 5 mm positive pressure of argon). Low temperature baths were: ice/water (0 °C), $CO_{2(s)}$/MeCN (-50 °C), and $CO_{2(s)}$/AcMe (-78 °C). Unless otherwise noted, reaction temperatures refer to that of the bath.

Concentration refers to removal of volatiles at water aspirator pressure on a rotary evaporator. Preparative TLC (PTLC) was carried out on glass plates (20x20 cm) pre-coated (0.25 mm) with silica gel 60 F_{254}. Materials were detected by visualization under an ultraviolet lamp (254 nm) and/or by treating a 1 cm vertical strip removed from the plate with a solution of phosphomolybdic acid (5%) containing a trace of ceric sulphate in aqueous sulfuric acid (5% v/v) followed by charring on a hot plate. Flash column chromatography (FCC) was performed according to Still et al.[19] with silica gel 60 (40-63 μm). All mixed solvent eluents were reported as v/v solutions. Unless otherwise noted, all reported compounds were homogeneous by thin layer chromatography (TLC) and by ^{1}H NMR.

3.2 Spectral data

High resolution mass spectra (HRMS) and low resolution mass spectra (LRMS) were obtained on a double focussing high resolution spectrometer; only partial data are reported. Electron impact (EI) ionization was accomplished at 70 eV, chemical ionization (CI) at 50 eV with ammonia as the reagent gas; only partial data are reported. Alternatively, HRMS were obtained on an LC-MS/MS time-of-flight high resolution spectrometer with electrospray ionization (ESI) from acetonitrile solution. Infrared (IR) spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and/or intense peaks are reported. Unless otherwise noted, NMR spectra were measured in $CDCl_3$ solution at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Signals due to the solvent (^{13}C NMR) or residual protonated solvent (^{1}H NMR) served as the internal standard: $CDCl_3$ (7.26 δ_H, 77.23 δ_C); C_6D_6 (7.16 δ_H, 128.39 δ_C). The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), ap (apparent); the list of couplings constants (*J*) corresponds to the order of the multiplicity assignment. Coupling constants are reported to the nearest 0.5 Hz (i.e. ±0.25 Hz as consistent with the digital resolution 0.2 Hz/pt). The ^{1}H NMR assignments were made on the basis of chemical shift, multiplicity and were confirmed by homonuclear decoupling and/or two-dimensional correlation experiments (gCOSY, gHSQC, gHMBC).[20] The multiplicity of ^{13}C NMR signals refers to the number of attached H's (i.e., s = C, d = CH, t = CH_2, q = CH_3). The ^{13}C assignments were made on the basis of chemical shift and multiplicity (as determined by gHSQC) and confirmed by two-dimensional $^{1}H/^{13}C$ correlation experiments (gHSQC and gHMBC).[20] Specific rotations ($[\alpha]_D$) were the average of five determinations at ambient temperature using a 1 mL, 10 dm cell; the units are (deg·mL)/(g·dm) and/or (10^{-1}·deg·cm^2)/g), and the concentrations (*c*) are reported in g/100 mL, and the values were rounded to reflect the accuracy of the measured concentrations (the major source of error).

3.3 Materials

The following compounds and reagents were prepared as described previously: **35**,[21] **36**,[21] **37**,[22] **43**,[16] W-2 Raney nickel,[23] IBX[24] and (*c*-Hex)$_2$BCl.[25] 2,6-Lutidine and Et_3N were distilled from CaH_2 under argon and stored over KOH under argon. Isobutyraldehyde was distilled from anhydrous Na_2SO_4 and stored under argon. All other reagents were commercially available and unless otherwise noted, were used as received.

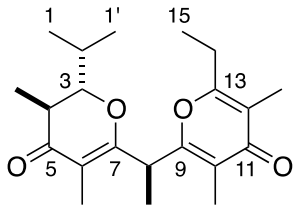
3.4 General experimental procedures

3.4.1 General procedure for desulfurization of aldol adducts[26]

A suspension of Raney Ni (W-2)[23] (ca. 1 mL settled volume/50 mg of substrate) in ethanol was added in one portion to a stirred solution of substrate in ethanol (0.01 M) and the reaction mixture was heated under reflux. The reaction was monitored by TLC and when complete, the mixture was decanted and the solid was suspended in ethanol and heated under reflux with vigorous stirring for several min. The above washing procedure was repeated with ethyl acetate and with acetone. The supernatants were filtered through a pad of Celite® and the combined filtrates were concentrated to give the crude product.

3.5 Experimental procedures and spectral data for compounds

2-Ethyl-6-((*S*)-1-((2*S*,3*S*)-2-isopropyl-3,5-dimethyl-4-oxo-3,4-dihydro-2*H*-pyran-6-yl)ethyl)-3,5-dimethyl-4*H*-pyran-4-one (vallartanone A) (1).



(1)

Aldol reaction of **44** (101 mg, 0.33 mmol) with *rac*-**11** (220 mg, 1.1 mmol) according to the procedure described for the preparation of **49** gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 10:1 mixture of diastereoisomeric aldol adducts. The crude was fractionated by SCC (packed and loaded with PhMe, eluted with 30% Et_2O in PhMe) to give a 2.6:1 mixture of **49** and **72**, respectively (107 mg; ca. 55% yield of **49**). Reaction of the above mixture (107.5 mg) with Raney Ni (1.5 mL settled volume) in THF (3 mL) for 30 minutes according to the general procedure gave, after work up, the crude desulfurization product (107 mg, complete conversion by ^{1}H NMR). IBX (125.5 mg, 0.45 mmol) was added to a stirred solution of the above crude ketone (107 mg) in DMSO (2.2 mL) at ambient temperature. After 14 h, the reaction was quenched by addition of sat. aqueous $NaHCO_3$. The mixture was diluted with ethyl acetate, washed with water and brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (30% EtOAc in hexanes) to give the crude dione (49.5 mg) as mixture of keto-enol tautomers by ^{1}H NMR. Aqueous HF (20% (w/w); 0.5 mL) was added to a stirred solution of the crude diketone (49.5 mg) in MeCN (1 mL) at ambient temperature. After 14 h, the reaction was quenched by addition of sat. aqueous $NaHCO_3$. The mixture was diluted with ethyl acetate, washed with water and brine, dried over Na_2SO_4, concentrated to give the title compound (36 mg, 31% over 4 steps; dr >19:1).

white amorphous solid, TLC R_f = 0.38 (50% ethyl acetate in hexane, developed thrice), $[\alpha]_D$ –170 (*c* 0.5, $CHCl_3$) (lit.[1] –176; *c* 0.68, $CHCl_3$)

IR (DRIFT) ν_{max} 1655, 1616 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.17 (1H, q, *J* = 7 Hz, HC-8), 3.78 (1H, dd, *J* = 2.5, 13 Hz, HC-3), 2.63 (2H, dq, *J* = 15, 7.5 Hz, HC-14), 2.60 (1H, dq, *J* = 15, 7.5 Hz, HC-14), 2.38 (1H, dq, *J* = 13, 7 Hz, HC-4), 1.99-1.92 (1H, m, HC-2), 1.95 (3H, s, H_3CC-12), 1.94 (3H, s, H_3CC-10), 1.74 (3H, s, H_3CC-6), 1.46 (3H, d, *J* = 7 Hz, H_3CC-8),

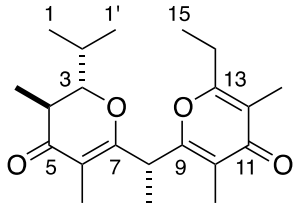
1.22 (3H, t, *J* = 7.5 Hz, H_3C-15), 1.08 (3H, d, *J* = 7 Hz, H_3C-1), 1.06 (3H, d, *J* = 7 Hz, H_3CC-4), 0.83 (3H, d, *J* = 7 Hz, H_3C-1').

^{13}C NMR (125 MHz, $CDCl_3$) δ 195.7 (s, C-5), 179.8 (s, C-11), 168.8 (s, C-7), 164.7 (s, C-13), 161.0 (s, C-9), 119.1 (s, C-10), 118.5 (s, C-12), 108.8 (s, C-6), 87.4 (d, C-3), 41.1 (d, C-4), 38.9 (d, C-8), 29.0 (d, C-2), 25.0 (t, C-14), 19.8 (q, C-1), 14.7 (q, C-1'), 14.5 (q, CH_3C-8), 11.6 (q, C-15), 10.2 (q, CH_3C-4), 9.8 (q, CH_3C-12), 9.5 (q, CH_3C-10), 9.3 (q, CH_3C-6).

LRMS (EI), *m/z* (relative intensity): 346 ($[M]^+$, 100), 317 (12), 263 (44), 234 (12), 206 (19), 180 (64).

HRMS *m/z* calcd. for $C_{21}H_{30}O_4$ 346.2144, found 346.2146 (EI).

2-Ethyl-6-((*R*)-1-((2*S*,3*S*)-2-isopropyl-3,5-dimethyl-4-oxo-3,4-dihydro-2*H*-pyran-6-yl)ethyl)-3,5-dimethyl-4*H*-pyran-4-one (8-*epi*-vallartanone A) (8-*epi*-1).



(8-*epi*-1)

From **67**. IBX (15 mg, 0.054 mmol) was added to a stirred solution of **67** (12 mg, 0.025 mmol) in DMSO (0.3 mL) at room temperature. After 48 hours, the mixture was diluted with ethyl acetate and washed sequentially with $NaHCO_3$, water, and brine. The organic phase was dried over Na_2SO_4, concentrated, and fractionated by PTLC (30% ethyl acetate in hexanes) to give **68** (9 mg, 75%) as a mixture of keto-enol tautomers (by ^{1}H NMR). 10% aqueous HF (0.2 mL) was added to a stirred solution of the above **68** (8 mg, 0.02 mmol) in MeCN (0.4 mL) at room temperature. After 51 hours, the reaction mixture was diluted with ethyl acetate and washed sequentially with $NaHCO_3$, water, and brine. The organic phase was dried over Na_2SO_4, concentrated, and fractionated by PLTC (30% ethyl acetate in hexane, multiple developments) to give the title compound (4 mg, 70%). From **61**. (*c*-Hex)$_2$BCl (1.0 M in hexane; 0.30 mL, 0.30 mmol) and Me_2NEt (40 µL, 27 mg, 0.37 mmol) were added to a stirred solution of **61** (40 mg, 0.15 mmol) in Et_2O (0.45 mL) at room temperature. After 3 h, the mixture was cooled to –78 °C and a solution of *rac*-**11** (94 mg, 0.45 mmol) in Et_2O (0.75 mL) was added. After 1 day, the reaction was quenched by sequential addition of phosphate buffer (pH = 7; 1 mL), MeOH (1 mL) and 30% aq H_2O_2 (0.5 mL) with vigorous stirring. After stirring at 0 °C for 15 min, sat. aqueous Na_2SO_3 was added and the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (30% ethyl acetate in hexane) to give a 3:1 mixture of **67**

and **72**, respectively (28 mg; ca. 35% of **67**). IBX (31 mg, 0.11 mmol) was added to a stirred solution of the above mixture (28 mg) in DMSO (0.60 mL)at room temperature. After 14 h, the reaction was quenched by addition of sat. aqueous $NaHCO_3$. The resulting suspension was diluted with ethyl acetate and washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude (23 mg) that was taken up in in MeCN (0.50 mL) and 20% HF in H_2O (0.25 mL) was added with stirring. After 36 h, the reaction was quenched buy addition of sat. aqueous $NaHCO_3$. The mixture was diluted with ethyl acetate and washed with water and brine. The organic phase was dried over Na_2SO_4, concentrated, and fractionated by PTLC (40% ethyl acetate in hexane) to give the title compound (10 mg, 19% over 3 steps; dr 17:1).

colorless oil, TLC R_f = 0.23 (30% ethyl acetate in hexane), $[\alpha]_D$ –100 (*c* 0.4 $CHCl_3$)

IR (DRIFT) ν_{max} 1657, 1616 cm^{-1}.

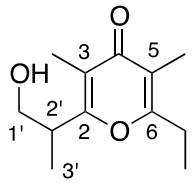
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.13 (1H, q, *J* = 7 Hz, HC-8), 3.70 (1H, dd, *J* = 2.5, 13 Hz, HC-3), 2.62 (1H, dq, *J* = 15, 7.5 Hz, HC-14), 2.59 (1H, dq, *J* = 15, 7.5 Hz, HC-14), 2.44 (1H, dq, *J* = 13, 7 Hz, HC-4), 1.99-1.91 (1H, m, HC-2), 1.945 (3H, s, H_3CC-10 or H_3CC-12), 1.937 (3H, s, H_3CC-10 or H_3CC-12), 1.72 (3H, s, H_3CC-6), 1.48 (3H, d, *J* = 7 Hz, H_3C-8), 1.22 (3H, t, *J* = 7.5 Hz, H_3C-15), 1.06 (3H, d, *J* = 7 Hz, H_3CC-4), 0.95 (3H, d, *J* = 7 Hz, H_3C-1), 0.94 (3H, d, *J* = 7 Hz, H_3C-1').

^{13}C NMR (125 MHz, $CDCl_3$) δ 195.7 (s, C-5), 179.8 (s, C-11), 168.9 (s, C-7), 164.7 (s, C-13), 161.3 (s, C-9), 118.9 (s, C-10), 118.5 (s, C-12), 109.1 (s, C-6), 87.2 (d, C-3), 41.1 (d, C-4), 39.0 (d, C-8), 28.9 (d, C-2), 25.1 (t, C-14), 19.6 (q, C-1), 14.9 (q, C-1'), 14.6 (q, CH_3C-8), 11.7 (q, C-15), 10.3 (q, CH_3C-4), 9.7 (q, CH_3C-12), 9.5 (q, CH_3C-10), 9.1 (q, CH_3C-6).

LRMS (EI), *m/z* (relative intensity): 346 ($[M]^+$, 78), 263 (36), 180 (73).

HRMS *m/z* calcd. for $C_{21}H_{30}O_4$ 346.2144, found 346.2149 (EI).

2-Ethyl-6-(1-hydroxypropan-2-yl)-3,5-dimethyl-4*H*-pyran-4-one (10).



(10)

Adapting the procedure of Kigoshi,[7a] NaHMDS (1.0 M in THF; 7.1 mL, 7.1 mmol) was added to a stirred solution of pyrone **34** (1.061g, 5.89 mmol) in THF (20 mL) at 0 °C under Ar. After 1 min, solid paraformaldehyde (360 mg; 2 equiv of CH_2O) was added. After 7 min, the reaction was quenched by addition of saturated aq NH_4Cl. The mixture was diluted with ethyl acetate, washed with saturated aq NH_4Cl, dried over Na_2SO_4, concentrated, and fractionated by FCC (ethyl acetate) to give the title compound (727 mg 59%). NMR data for **10** were consistent with those previously reported.[2,5b]

white amorphous solid, TLC R_f = 0.24 (100% ethyl acetate)

IR (DRIFT) ν_{max} 2974, 2940, 2878, 1656, 1614, 1590 cm^{-1}.

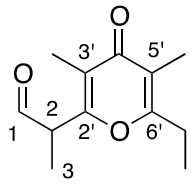
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (1, m, HC-1'), 3.72 (1, m, HC-1'), 3.23 (1, m, HC-2'), 2.61 (2, dq, *J* = 2.5, 7.5 Hz, H_2CC-2), 1.98 (3, s, H_3CC-5), 1.93 (3, s, H_3CC-3), 1.83 (1, t, *J* = 6 Hz, HO), 1.22 (3, t, *J* = 7.5 Hz, H_3CC-2), 1.21 (3, d, *J* = 7 Hz, H_3C-3').

^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0 (s, C-4), 164.4 (s, C-2), 163.7 (s, C-6), 119.6 (s, C-5), 118.2 (s, C-3), 65.6 (t, C-1'), 38.5 (d, C-2'), 25.0 (t, CH_2C-2), 14.5 (q, C-3'), 11.5 (q, CH_3C-2), 9.7 (q ×2, CH_3C-3, CH_3C-5).

LRMS (EI), *m/z* (relative intensity): 210 ($[M]^+$, 48), 193 (100), 179 (57), 166 (12).

HRMS *m/z* calcd. for $C_{12}H_{18}O_3$ 210.1256, found 210.1256.

2-(6-Ethyl-3,5-dimethyl-4-oxo-4*H*-pyran-2-yl)propanal (11).



(11)

IBX (600 mg, 2.14 mmol) was added to a solution of **10** (224 mg, 1.07 mmol) in MeCN (3.6 mL) and the mixture was heated under reflux until TLC analysis indicated complete consumption of **10** (ca. 1 h). The suspension was cooled to 0 °C and then filtered through a sintered glass funnel with the aid of ethyl acetate. The combined filtrate and washings were washed with saturated aq $NaHCO_3$, dried over Na_2SO_4, concentrated, and fractionated by FCC (60% ethyl acetate in hexane) to give the title compound (180 mg, 81%).

colorless liquid, TLC R_f = 0.27 (60% ethyl acetate in hexane)

IR (DRIFT) ν_{max} 1737, 1658, 1419 cm^{-1}.

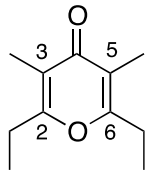
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (1, s, HC-1), 3.79 (1, q, *J* = 7 Hz, HC-2), 2.60 (2, q, *J* = 7.5 Hz, H_2CC-6'), 1.99 (3, s, H_3CC-3'), 1.95 (3, s, H_3CC-5'), 1.45 (3, d, *J* = 7 Hz, H_3C-3), 1.19 (3, t, *J* = 7.5 Hz, H_3CC-6').

^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7 (d, C-1), 179.7 (s, C-4'), 165.2 (s, C-6'), 158.9 (s, C-2'), 121.0 (s, C-3'), 118.7 (s, C-5'), 49.1 (d, C-2), 25.0 (t, CH_2C-6'), 11.7 (q, C-3'), 11.4 (q, CH_3C-6'), 9.9 (q), 9.7 (q).

LRMS (EI), *m/z* (relative intensity): 208 ($[M]^+$, 42), 179 (100), 151 (25).

HRMS *m/z* calcd. for $C_{12}H_{16}O_3$ 208.1099, found 208.1092.

2,6-Diethyl-3,5-dimethyl-4*H*-pyran-4-one (34).



(34)

Adapting the procedure of Mullock,[6a] a mixture of propanoic acid (30 g) and polyphosphoric acid (150 g) were heated under reflux (bath temperature, 200 °C). After 3 h, the mixture was removed from the heating bath and the reaction was quenched by slow addition of ice. The mixture was diluted with

water and extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4, and concentrated. The residue was distilled (150 °C, 0.5 mbar) to give the title compound (9.3 g, 52%).

yellow crystalline solid, TLC R_f = 0.54 (60% ethyl acetate in hexane)

IR (DRIFT) ν_{max} 1664, 1626, 1611 cm^{-1}.

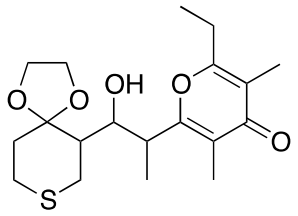
^{1}H NMR (500 MHz, $CDCl_3$) δ 2.59 (4H, q, *J* = 7.5 Hz, H_2CC-2, H_2CC-6), 1.94 (6H, s, H_3CC-3 H_3CC-5), 1.21 (6H, t, *J* = 7.5 Hz, H_3CCC-2, H_3CCC-6).

^{13}C NMR (125 MHz, $CDCl_3$) δ 180.1 (s , C-4), 164.6 (s ×2, C-2, C-6), 118.0 (s ×2, C-3, C-5), 25.0 (t ×2, CH_2C-2, CH_2C-6), 11.6 (q ×2, CH_3CC-2, CH_3CC-6), 9.7 (q ×2, CH_3C-3, CH_3C-5).

LRMS (EI), *m/z* (relative intensity): 180 ($[M]^+$, 69), 179 (100), 137 (13), 113 (15), 57 (15).

HRMS *m/z* calcd. for $C_{11}H_{16}O_2$ 180.1150, found 180.1128 (EI).

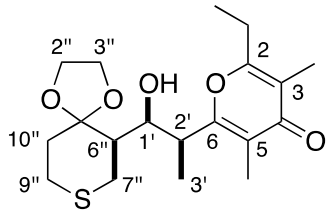
2-Ethyl-6-(1-hydroxy-1-(1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)propan-2-yl-3,5-dimethyl-4*H*-pyran-4-one (38a-d).



(38a-d)

Adapting the procedure of Kigoshi,[7a] NaHMDS (1.0 M in THF; 0.85 mL, 0.85 mmol) was added to a stirred solution of pyrone **34** (177 mg, 0.98 mmol) in THF (1.2 mL) at 0 °C under Ar. After 10 min, the reaction mixture was cooled to –78 °C and a solution of aldehyde **37** (106 mg, 0.56 mmol) in THF (0.5 mL + 0.5 mL rinse) was added via a syringe over 3 min. After 3 h, the reaction was quenched by addition of saturated aq NH_4Cl. The suspension was diluted with ethyl acetate and washed sequentially with saturated aq NH_4Cl, water and brine. The organic layer was dried over Na_2SO_4, and concentrated to give the crude product that contained **34** and **37** and a 1.7:1.3:1 mixture of adducts **38d**, **38a**, and (**38b** + **38c**), respectively. Fractionation of the crude by FCC (70% ethyl acetate in hexanes) gave recovered **34** (94 mg, 53%), **37** (25 mg, 24%), **38a** (52 mg, 25%), and a 7.7:2.2:1 mixture of **38d**, **38c**, and **38b**, respectively (102 mg, 50%). The mixture (69 mg) was further fractionated by PTLC (50% PhMe in ethyl acetate; multiple development) to give **38d** (36 mg, 26%), **38c** (6 mg, 4.3%) and **38b** (3 mg, 2.2%).

2-Ethyl-6-((1*S*,2*S*)-*rel*-1-hydroxy-1-((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)propan-2-yl-3,5-dimethyl-4*H*-pyran-4-one (38a).



(38a)

pale yellow foam, TLC R_f = 0.21 (60% ethyl acetate in hexane)

IR (DRIFT) ν_{max} 1657, 1607 cm^{-1}.

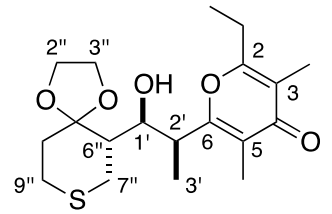
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.39 (1H, br d, *J* = 10 Hz, HC-1'), 4.11-3.92 (4H, m, H_2C-2'', H_2C-3''), 3.19 (1H, s, HO), 3.08 (1H, dq, *J* = 10, 6.5 Hz, HC-2'), 3.03 (1H, dd, *J* = 11.5, 14 Hz, HC-7''), 2.77 (1H, ddd, *J* = 2.5, 12.5, 13.5 Hz, HC-9''), 2.67-2.43 (4H, m, H_2CC-2, HC-7'', HC-9''), 2.10 (1H, ddd, *J* = 3, 4, 14 Hz, HC-10''), 1.97 (3H, s, H_3C-3 or H_3C-5), 1.94 (3H, s, H_3C-3 or H_3C-5), 1.71 (1H, dd, *J* = 3.5, 11.5 Hz, HC-6''), 1.61 (1H, ddd, *J* = 3.5, 12.5, 14 Hz, HC-10''), 1.33 (3H, d, *J* = 6.5 Hz, H_3C-3''), 1.21 (3H, t, *J* = 7.5 Hz, H_3CCC-2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 179.9, 164.7, 163.8, 119.0, 118.0, 110.3, 70.9, 64.8, 64.3, 47.1, 38.9, 36.0, 26.6, 26.1, 24.9, 15.7, 11.2, 9.8, 9.7.

LRMS (EI), *m/z* (relative intensity): 368 ($[M]^+$, 1), 237 (3), 209 (5), 189 (5), 180 (100), 99 (20).

HRMS *m/z* calcd. for $C_{19}H_{28}O_5S$ 368.1657, found 368.1650 (EI).

2-Ethyl-6-((1*S*,2*S*)-*rel*-1-hydroxy-1-((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)propan-2-yl-3,5-dimethyl-4*H*-pyran-4-one (38b).



(38b)

pale yellow foam, TLC R_f = 0.09 (60% ethyl acetate in hexane)

IR (DRIFT) ν_{max} 3489, 1653, 1605 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.26 (1H, ap t, *J* = 5 Hz, HC-1'), 4.20-3.96 (5H, m, HO, H_2C-2''. H_2C-3''), 3.26 (1H, dq, *J* = 5, 7 Hz, HC-2'), 2.91 (1H, dd, *J* = 2.5, 14 Hz, HC-7''), 2.76 (1H, ddd, *J* = 3, 8.5, 13.5 Hz, HC-9''),

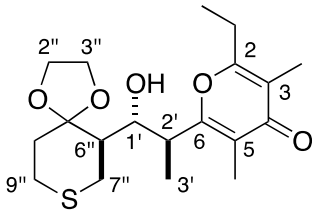
2.73-2.65 (2H, m, HC-7'', HC-9''), 2.62 (2H, ap q, *J* = 7.5 Hz, H_2CC-2), 2.16 (1H, m, *J* = 3.5, 9, 13.5 Hz, HC-10''), 2.02 (3H, s, H_3CC-3 or H_3CC-5), 1.99-1.92 (1H, m, HC-6''), 1.94 (3H, s, H_3CC-3 or H_3CC-5), 1.79 (1H, ddd, *J* = 3.5, 7, 13.5 Hz, HC-10''), 1.27 (3H, d, *J* = 7 Hz, H_3C-3'), 1.22 (3H, t, *J* = 7.5 Hz, H_3CCC-2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 180.2, 165.1, 164.6, 118.6, 118.1, 110.6, 73.4, 64.8, 64.1, 46.5, 38.4, 34.7, 30.2, 26.9, 25.0, 11.5, 11.0, 9.8, 9.8.

LRMS (CI, NH_3), *m/z* (relative intensity): 369 ($[M+1]^+$, 99), 209 (10), 189 (10), 180 (100), 99 (19).

HRMS *m/z* calcd. for $C_{19}H_{28}O_5S$+H 369.1736, found 369.1728 (CI, NH_3).

2-Ethyl-6-((1*R*,2*S*)-*rel*-1-hydroxy-1-((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)propan-2-yl-3,5-dimethyl-4*H*-pyran-4-one (38c).



(38c)

pale yellow foam, TLC R_f = 0.09 (60% ethyl acetate in hexane)

IR (DRIFT) ν_{max} 3489, 1656, 1606 cm^{-1}.

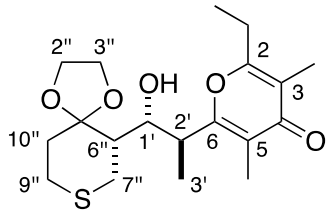
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.11 (1H, ddd, *J* = 5.5, 7, 7 Hz, HC-1'), 4.04-3.95 (4H, m, H_2C-2'', HC-3''), 3.89 (1H, d, *J* = 5.5 Hz, HO), 3.34 (1H, dq, *J* = 7, 7 Hz, HC-2'), 2.84 (1H, dd, *J* = 3, 14 Hz, HC-7''), 2.77 (1H, dd, *J* = 8, 14 Hz, HC-7''), 2.74-2.66 (2H, m, H_2C-9''), 2.61 (2H, ap q, *J* = 7.5 Hz, H_2CC-2), 2.23-2.16 (1H, m, HC-10''), 2.04 (1H, ddd, *J* = 4, 7, 8 Hz, HC-6''), 1.97 (3H, s, H_3CC-3 or H_3CC-5), 1.94 (3H, s, H_3CC-3 or H_3CC-5), 1.81-1.74 (1H, m, HC-10''), 1.29 (3H, d, *J* = 7 Hz, H_3C-3'), 1.22 (3H, t, *J* = 7.5 Hz, H_3CCC-2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0, 165.0, 164.5, 119.4, 118.1, 111.0, 76.0, 64.4, 64.0, 45.2, 39.9, 35.1, 31.1, 26.7, 25.0, 15.3, 11.5, 10.1, 9.7.

LRMS (CI, NH_3), *m/z* (relative intensity): 369 ($[M+1]^+$, 100), 209 (6), 189 (10), 180 (94), 99 (19).

HRMS *m/z* calcd. for $C_{19}H_{28}O_5S$+H 369.1736, found 369.1725 (CI, NH_3).

2-Ethyl-6-((1*R*,2*S*)-*rel*-1-hydroxy-1-((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)propan-2-yl-3,5-dimethyl-4*H*-pyran-4-one (38d).



(38d)

pale yellow foam, TLC R_f = 0.09 (60% ethyl acetate in hexane)

IR (DRIFT) ν_{max} 3416, 1657, 1605 cm^{-1}.

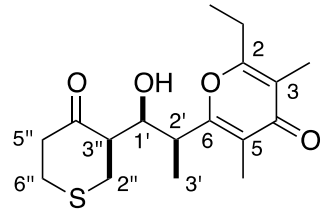
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35 (1H, d, *J* = 10 Hz, HC-1'), 4.15-3.97 (4H, m, H_2C-2''. H_2C-3''), 3.19 (1H, s, HO), 3.09 (1H, dq, *J* = 10, 7 Hz, HC-2'), 3.07 (1H, dd, *J* = 12, 13.5 Hz, HC-7''), 2.84 (1H, ddd, *J* = 2.5, 12.5, 13.5 Hz, HC-9''), 2.65-2.55 (3H, m, H_2CC-2, HC-7''), 2.51 (1H, dddd, *J* = 2.5, 3.5, 3.5 13.5 Hz, HC-9''), 2.19-2.11 (2H, m, HC-6'', HC-10''), 1.95 (3H, s, H_3CC-3 or H_3CC-5), 1.90 (3H, s, H_3CC-3 or H_3CC-5), 1.75 (1H, ddd, *J* = 3.5, 12.5, 14 Hz, HC-10''), 1.19 (3H, t, *J* = 7.5 Hz, H_3CCC-2), 1.12 (3H, d, *J* = 7 Hz, H_3C-3').

^{13}C NMR (125 MHz, $CDCl_3$) δ 179.9, 164.5, 164.1, 119.5, 118.0, 110.5, 71.0, 65.1, 64.3, 46.3, 38.3, 36.6, 26.6, 25.2, 24.9, 14.6, 11.4, 9.8, 9.7.

LRMS (CI, NH_3), *m/z* (relative intensity): 369 ($[M+1]^+$, 100), 189 (10), 180 (79), 99 (17).

HRMS *m/z* calcd. for $C_{19}H_{28}O_5S$+H 369.1736, found 369.1727 (CI, NH_3).

2-Ethyl-6-((1*S*,2*S*)-*rel*-1-hydroxy-1-((*R*)-4-oxotetrahydro-2*H*-thiopyran-3-yl)propan-2-yl)-3,5-dimethyl-4*H*-pyran-4-one (39a).



(39a)

From **39b**. A solution of **39b** (12 mg, 0.037 mmol) and imidazole (28 mg, 0.41 mmol) in $CDCl_3$ (1 mL). After 4 d, ^{1}H NMR suggested the presence of a 1.6:1 equilibrium mixture of **39a** and **39b**, respectively. The mixture was diluted with ethyl acetate, washed with aq citric acid (0.1 M), dried over Na_2SO_4, concentrated, and fractionated by PTLC (70% ether in benzene; multiple development) to give **39b** (4 mg 33%) and the title compound (5 mg 42%). From **38a**. $FeCl_3 \cdot 6H_2O$ (0.50 M in acetone; 0.60 mL,

0.30 mmol) was added to a solution of **38a** (32 mg, 0.086 mmol) in acetone (0.6 mL) and the mixture was heated under reflux. After 1 h, the mixture was diluted with ethyl acetate, washed with water, dried over Na_2SO_4, concentrated, and fractionated by FCC (60% ethyl acetate in hexane) to give the title compound (21 mg 75%).

amorphous white solid, TLC R_f = 0.44 (90% ethyl acetate in hexane)

IR (DRIFT) ν_{max} 3385, 2929, 1706, 1651, 1590 cm^{-1}.

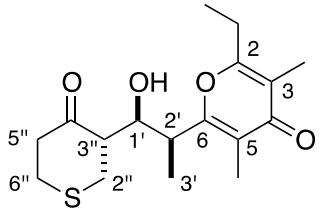
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.55 (1H, ddd, *J* = 2.5, 4, 9 Hz, HC-1'), 3.07 (1H, dd, *J* = 11.5, 13.5 Hz, HC-2''), 3.05 (1H, dq, *J* = 9, 7 Hz, HC-2'), 2.96 (1H, ddd, *J* = 3.5, 11.5, 13.5 Hz, HC-6''), 2.89 (1H, dddd, *J* = 2.5, 5, 4.5, 13.5 Hz, HC-6''), 2.83 (1H, ddd, *J* = 2.5, 4.5, 13.5 Hz, HC-2''), 2.73 (1H, ddd, *J* = 3,5, 4.5, 13.5 Hz, HC-5''), 2.67 (1H, m, *J* = 5, 11.5, 13.5 Hz, HC-5''), 2.64 (1H, d, *J* = 4 Hz, HO), 2.62-2.54 (2H, m, H_2CC-2), 2.51 (1H, ddd, *J* = 2.5, 4.5, 11.5 Hz, HC-3''), 2.00 (3H, s, H_3CC-5), 1.95 (3H, s, H_3CC-3), 1.35 (3H, d, *J* = 7 Hz, H_3C-3'), 1.16 (3H, t, *J* = 7.5 Hz, H_3CCC-2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 211.3 (s, C-4''), 179.9 (s, C-4), 164.6 (s, C-2), 163.4 (s, C-6), 119.1 (s, C-5), 118.5 (s, C-3), 71.0 (d, C-1'), 55.9 (d, C-3''), 45.0 (t, C-5''), 37.8 (d, C-2'), 30.8 (t, C-6''), 30.3 (t, C-2''), 24.9 (t, CH_2C-2), 15.5 (q, C-3'), 11.5 (q, CH_3CC-2), 10.0 (q, CH_3C-5), 9.8 (q, CH_3C-3).

LRMS (EI), *m/z* (relative intensity): 324 ($[M]^+$, 14), 209 (11), 180 (100), 151 (6), 89 (6), 57 (14).

HRMS *m/z* calcd. for $C_{17}H_{24}O_4S$: 324.1395; found: 324.1399 (EI).

2-Ethyl-6-((1*S*,2*S*)-*rel*-1-hydroxy-1-((*S*)-4-oxotetrahydro-2*H*-thiopyran-3-yl)propan-2-yl)-3,5-dimethyl-4*H*-pyran-4-one (39b).



(39b)

From **38b**. A solution of $FeCl_3 \cdot 6H_2O$ (19 mg, 0.070 mmol) and **38b** (7.3 mg, 0.020 mmol) in acetone (0.60 mL) was heated under reflux for 0.75 h. The mixture was diluted with ethyl acetate, washed with water, dried over Na_2SO_4, concentrated, and fractionated by PTLC (ethyl acetate) to give the title compound (3 mg 46%). From **35**. The "amine free" Li enolate of tetrahydro-4*H*-thiopyran-4-one was prepared by reaction of the corresponding TMS enol ether (157.5 mg, 0.84 mmol) in ether (2 mL)

with MeLi (1.6 M in ether; 0.45 mL, 0.72 mmol) at 0 °C to room temperature under argon, as previously described.[8] After 1 h, THF (2 mL) was added to the lithium enolate suspension and the resulting solution was cooled to –78 °C. A solution of pyrone aldehyde *rac*-**11** (104 mg, 0.50 mmol) in THF (0.5 mL) was added via syringe and, after 5 min, the reaction was quenched by addition of a solution of AcOH (0.06 mL, 1 mmol) in THF (0.20 mL). The mixture was diluted with CH_2Cl_2 and washed with saturated aq $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (60% ethyl acetate in hexane) to give the title compound (97 mg, 60%).

amorphorus white solid, TLC R_f = 0.1 (40% ethyl acetate in hexane)

IR (DRIFT) ν_{max} 3399, 1711, 1650, 1591 cm^{-1}.

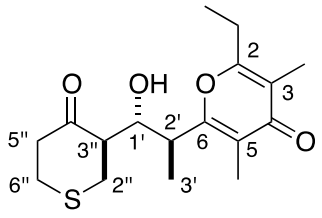
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66 (1H, ddd, *J* = 2.5, 10, 11.5 Hz, HC-1'), 3.37 (1H, dq, *J* = 10, 7 Hz, HC-2'), 3.22 (1H, dd, *J* = 11.5, 13.5 Hz, HC-2''), 3.00 (1H, d, *J* = 11 Hz, HO), 2.97 (1H, ddd, *J* = 3, 11.5, 13.5 Hz, HC-6''), 2.93-2.86 (1H, m, HC-6''), 2.83 (1H, ddd, *J* = 2.5, 4.5, 13.5 Hz, HC-2''), 2.69 (1H, ddd, *J* = 3.5, 4, 13.5 Hz, HC-5''), 2.56-2.66 (4H, m, H_2CC-2, HC-3'', HC-5'',), 1.95 (3H, s, H_3CC-3), 1.85 (3H, s, H_3CC-5), 1.36 (3H, d, *J* = 7 Hz, H_3C-3'), 1.20 (3H, t, *J* = 7.5 Hz, H_3CCC-2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 212.9 (s, C-4''), 179.8 (s, C-4), 164.5 (s, C-2), 163.7 (s, C-6), 119.2 (s, C-5), 118.4 (s, C-3), 76.5 (d, C-1'), 55.1 (d, C-3''), 45.7 (t, C-5''), 40.4 (d, C-2'), 35.7 (t, C-2''), 31.4 (t, C-6''), 24.9 (t, CH_2C-2), 15.2 (q, C-3'), 11.5 (q, CH_3CC-2), 9.72 (q, CH_3C-3 or CH_3C-5), 9.70 (q, CH_3C-3 or CH_3C-5).

LRMS (EI), *m/z* (relative intensity): 324 ([M]$^+$, 3), 235 (1), 208 (7), 180 (100), 149 (10), 89 (8), 57 (14).

HRMS *m/z* calcd. for $C_{17}H_{24}O_4S$: 324.1395; found: 324.1394 (EI).

2-Ethyl-6-((1*R*,2*S*)-*rel*-1-hydroxy-1-((*R*)-4-oxotetrahydro-2*H*-thiopyran-3-yl)propan-2-yl)-3,5-dimethyl-4*H*-pyran-4-one (39c).



(39c)

From **39d**. A solution of **39d** (33.5 mg, 0.10 mmol) and imidazole (163 mg, 2.4 mmol) in CH_2Cl_2 (3.4 mL) was allowed to stand at room temperature in a stoppered flask. After 2 days, the mixture was diluted with aq citric acid (0.1 M) and extracted with CH_2Cl_2. The combined organic layers were dried

over Na_2SO_4 and concentrated to give the crude product as a 2:1 mixture of **39d** and **39c**, respectively (by ^{1}H NMR). The crude was fractionated by PTLC (70% ether in benzene; multiple developments) to give **39d** (3 mg 9%), a 9:1 mixture of **39d** and **39c** (19 mg, 57%), respectively, and the title compound (5 mg 15%).

amorphous white solid, TLC R_f = 0.1 (50% ethyl acetate in hexane)

IR (DRIFT) ν_{max} 3389, 1709, 1655, 1589 cm^{-1}.

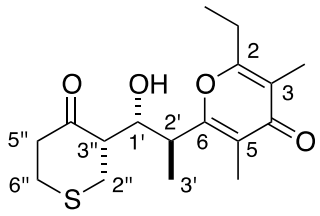
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78 (1H, ddd, *J* = 2.5, 8.5, 10.5 Hz, HC-1'), 3.42 (1H, dq, *J* = 8.5, 7 Hz, HC-2'), 3.21 (1H, ap dd, *J* = 11.5, 15 Hz, HC-2''), 3.02 (1H, d, *J* = 10.5 Hz, HO), 3.06-2.93 (4H, m, HC-2'', HC-3'', H_2C-6''), 2.79-2.74 (2H, m, H_2C-5''), 2.65-2,57 (2H, m, H_2CC-2), 2.00 (3, s, H_3CC-5), 1.94 (3, s, H_3CC-3), 1.22 (3, t, *J* = 7.5 Hz, H_3CC-2), 1.20 (3, d, *J* = 7 Hz, H_3C-3').

^{13}C NMR (125 MHz, $CDCl_3$) δ 212.3 (s, C-4''), 180.0 (s, C-4), 164.4 (s, C-2), 163.6 (s, C-6), 119.8 (s, C-5), 118.2 (s, C-3), 76.7 (d, C-1'), 54.5 (d, C-3''), 45.8 (t, C-5''), 39.7 (d, C-2'), 35.7 (t, C-2''), 31.4 (t, C-6''), 25.0 (t, CH_2C-2), 15.6 (q, C-3'), 11.5 (q, CH_3CC-2), 10.0 (q, CH_3C-5), 9.7 (q, CH_3C-3).

LRMS (EI), *m/z* (relative intensity): 324 ([M]$^+$, 2), 208 (14), 180 (100), 116 (12).

HRMS *m/z* calcd. for $C_{17}H_{24}O_4S$: 324.1395; found: 324.1402 (EI).

2-Ethyl-6-((1*R*,2*S*)-*rel*-1-hydroxy-1-((*S*)-4-oxotetrahydro-2*H*-thiopyran-3-yl)propan-2-yl)-3,5-dimethyl-4*H*-pyran-4-one (39d).



(39d)

A solution of $FeCl_3 \cdot 6H_2O$ (102 mg, 0.38 mmol) and **38d** (39 mg, 0.11 mmol) in acetone (1.6 mL) was heated under reflux for 1 h. The mixture was diluted with EtOAc, washed with water, dried over Na_2SO_4, concentrated, and fractionated by PTLC (ethyl acetate) to give the title compound (24 mg 68%).

amorphorus white solid, TLC R_f = 0.47 (ethyl acetate)

IR (DRIFT) ν_{max} 3385, 1706, 1653, 1591 cm^{-1}.

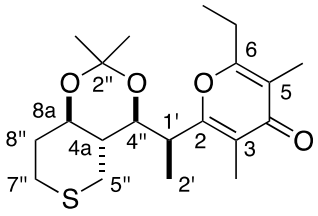
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.40 (1H, ddd, *J* = 3.5, 4.5, 9 Hz, HC-1'), 3.13 (1H, dq, *J* = 9, 7 Hz, HC-2'), 3.10 (1H, dd, *J* = 11.5, 13.5 Hz, HC-2''), 3.00 (1H, ap dt, *J* = 4.5, 13.5 Hz, HC-6''), 2.99 (1H, dd, *J* = 4.5, 13.5 Hz, HC-2''), 2.96-2.90 (1H, m, HC-6''), 2.83 (1H, ddd, *J* = 3.5, 4.5, 11.5 Hz, HC-3''), 2.79-2.70 (2H, m, H_2C-5''), 2.65-2.55 (2H, m, H_3CC-2), 2.58 (1H, d, *J* = 4.5 Hz, HO), 1.92 (6H, s, H_3CC-3, H_3CC-5), 1.20 (3H, t, *J* = 7.5 Hz, H_3CCC-2), 1.16 (3H, d, *J* = 7 Hz, H_3C-3').

^{13}C NMR (125 MHz, $CDCl_3$) δ 211.2 (s, C-4''), 179.9 (s, C-4), 164.3 (s, C-2), 163.7 (s, C-6), 119.8 (s, C-5), 118.2 (s, C-3), 71.1 (d, C-1'), 55.2 (d, C-3''), 45.1 (t, C-5''), 37.5 (d, C-2'), 30.7 (t, C-6''), 29.7 (t, C-2''), 25.0 (t, CH_2C-2), 14.7 (q, C-3'), 11.5 (q, CH_3C-2), 9.9 (q, CH_3C-3 or CH_3C-5), 9.7 (q, CH_3C-3 or CH_3C-5).

LRMS (EI), *m/z* (relative intensity): 324 ($[M]^+$, 7), 208 (12), 180 (100), 151 (6), 116 (9), 89 (6), 57 (9).

HRMS *m/z* calcd. for $C_{17}H_{24}O_4S$: 324.1395; found: 324.1394 (EI).

2-((*S*)-*rel*-1-((4*S*,4a*R*,8a*R*)-2,2-Dimethylhexahydrothiopyrano[4,3-*d*][1,3]dioxin-4-yl)ethyl)-6-ethyl-3,5-dimethyl-4*H*-pyran-4-one (40).



(40)

p-TsOH (14 mg, 0.074 mmol) was added to a stirred solution of **71** (40 mg, 0.12 mmol) and 2,2-dimethoxypropane (0.10 mL, 0.81 mmol) in CH_2Cl_2 (2 mL) at ambient temperature. After 15 min (reaction complete by TLC analysis), the mixture was diluted with ethyl acetate, washed sequentially with saturated aq $NaHCO_3$, water and brine, dried over Na_2SO_4, concentrated, and fractionated by PTLC (60% ethyl acetate in hexane) to give the title compound (30 mg, 68%) that was homogeneous by ^{1}H NMR.

amorphous white solid, TLC R_f = 0.53 (ethyl acetate)

IR (DRIFT) ν_{max} 1655, 1601 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (1H, dd, *J* = 4, 10 Hz, HC-4''), 3.51 (1H, ddd, *J* = 3.5, 10.5, 10.5 Hz, HC-8''a), 3.17 (1H, dq, *J* = 4, 7 Hz, HC-1'), 2.82 (1H, ddd, *J* = 2.5, 12.5, 14 Hz, HC-7''), 2.55-2.65 (3H, m, H_2CC-6, HC-7''), 2.44 (1H, ddd, *J* = 2.5, 3, 13.5 Hz, HC-5''x), 2.36 (1H, dd, *J* = 11.5, 13.5 Hz, HC-5''y), 2.09 (1H,

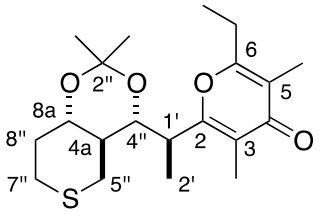
dddd, *J* = 2.5, 3, 3.5, 13 Hz, HC-8''), 1.97 (3H, s, H_3CC-3), 1.95 (3H, s, H_3CC-5), 1.85-1.73 (2H, m, HC-8'', HC-4a), 1.34 (6H, ap s, $(H_3C)_2C$-2''), 1.27 (3H, d, *J* = 7 Hz, H_3C-2'), 1.22 (3H, t, *J* = 7.5 Hz, H_3CC-6).

^{13}C NMR (125 MHz, $CDCl_3$) δ 180.1 (s, C-4), 164.6 (s, C-2), 164.5 (s, C-6), 118.12 (s, C-3 or C-5), 118.08 (s, C-3 or C-5), 98.6 (s, C-2''), 74.0 (d, C-4''), 72.8 (d, C-8a), 45.2 (d, C-4a), 37.5 (d, C-1'), 34.2 (t, C-8''), 30.1 (q, CH_3C-2''), 27.79 (t, C-5'' or C-7''), 27.73 (t, C-5'' or C-7''), 24.9 (t, CH_2C-6), 19.7 (q, CH_3C-2''), 11.6 (q, C-2'), 11.4 (q, CH_3CC-6), 9.76 (q, CH_3C-3 or CH_3C-5), 9.74 (q, CH_3C-3 or CH_3C-5).

LRMS (CI, NH_3), *m/z* (relative intensity): 367 ($[M+1]^+$, 100), 351 (5), 180 (72), 129 (9), 101 (7).

HRMS *m/z* calcd. for $C_{20}H_{30}O_4S$+H: 367.1943; found: 367.1935 (Ci, NH_3).

2-((*S*)-*rel*-1-((4*R*,4a*S*,8a*S*)-2,2-Dimethylhexahydrothiopyrano[4,3-*d*][1,3]dioxin-4-yl)ethyl)-6-ethyl-3,5-dimethyl-4*H*-pyran-4-one (41).



(41)

Water (35 µL, 35 mg, 1.94 mmol) was added to a stirrred suspension of tetrahydro-4*H*-thiopyran-4-one (**35**) (168 mg, 1.45 mmol) and L-proline (15 mg, 0.13 mmol) in DMSO (0.30 mL) under argon at room temperature. After 2 h, the suspension was transferred via syringe to a vial containing aldehyde *rac*-**11** (46 mg, 0.22 mmol). After stirring for 5 days, the mixture was diluted with NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and fractionated by FCC (5-100% ethyl acetate in hexane) to provide a 6.2:1 mixture of **39b** and **39a**, respectively (28 mg; ca. 34 %), and a 3.2:1 mixture of **39c** and **39a**, respectively (8 mg; ca. %). The latter fraction was dissolved in ethanol (0.44 mL) and $NaBH_4$ (6.6 mg, 0.17 mmol) was added to the stirred solution at room temperature. After 15 min, the reaction was quenched by slow addition of 10% aq HCl until effervescence ceased and then the mixture was basified by addition of aq NaOH (3 M). After stirring for 30 min, the mixture was diluted with brine and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, concentrated, and the resulting crude product was fractionated by PTLC (ethyl acetate) to provide a mixture of diols (7 mg). Without further purification, the mixure was taken up in CH_2Cl_2 (0.37 mL) and 2,2-dimethoxypropane (15 µL, 0.12 mmol) and *p*-TsOH (6 mg, 0.03 mmol) were added to the stirred solution. After 20 min, the mixture was diluted with ethyl acetate and washed

sequentially with saturated aq $NaHCO_3$, water and brine. The organic layer was dried over Na_2SO_4, concentrated, and fractionated by PTLC (40% ethyl acetate in hexane, multiple developments) to give the title compound as an amorphous white solid (2.5 mg, 3% over 3 steps).

amorphous white solid, TLC R_f = 0.64 (ethyl acetate)

IR (DRIFT) ν_{max} 1654, 1606 cm^{-1}.

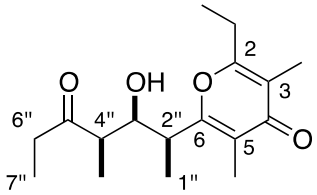
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (1H, dd, *J* = 3, 10.5 Hz, HC-4''), 3.49 (1H, ddd, *J* = 3.5, 10.5, 11 Hz, HC-8a), 3.18 (1H, dq, *J* = 3, 7 Hz, HC-1'), 2.80 (1H, ddd, *J* = 3, 12.5, 14 Hz, HC-7''), 2.63-2.56 (3H, m, H_2CC-6, HC-7''), 2.43 (1H, ddd, *J* = 2.5, 3, 13.5 Hz, HC-5''), 2.31 (1H, dd, *J* = 11.5, 13.5 Hz, HC-5''), 2.06 (1H, dddd, *J* = 3, 3.5, 3.5, 13 Hz, HC-8''x), 1.98 (3H, s, H_3CC-3), 1.96 (3H, s, H_3CC-5), 1.71 (1H, dddd, *J* = 3.5, 11, 12.5, 13 Hz, HC-8''), 1.60 (1H, dddd, *J* = 3, 10.5, 10.5, 11.5 Hz, HC-4''a), 1.45 (3H, s, H_3CC-2''), 1.37 (3H, s, H_3CC-2''), 1.32 (3H, d, *J* = 7 Hz, H_3CC-2'), 1.24 (3H, t, *J* = 7.5 Hz, H_3CC-6).

^{13}C NMR (125 MHz, $CDCl_3$) δ 180.1 (s, C-4), 164.7 (s, C-6), 163.0 (s, C-2), 120.0 (s, C-3), 118.1 (s, C-5), 98.8 (s, C-2''), 75.1 (d, C-4''), 72.9 (d, C-8a), 44.9 (d, C-4a), 38.0 (d, C-1'), 34.1 (t, C-8''), 30.1 (q, CH_3C-2''), 28.1 (t, C-5''), 27.8 (t, C-7''), 25.0 (t, CH_2C-6), 19.5 (q, CH_3C-2''), 14.3 (q, C-2'), 11.6 (q, CH_3CC-6), 10.3 (q, CH_3C-3), 9.8 (q, CH_3C-5).

LRMS (CI, NH_3), *m/z* (relative intensity): 367 ($[M+1]^+$, 100), 180 (73), 129 (9), 101 (8).

HRMS *m/z* calcd. for $C_{20}H_{30}O_4S$: 366.1865; found: 366.1856 (EI).

2-Ethyl-6-((2*S*,3*S*,4*R*)-*rel*-3-hydroxy-4-methyl-5-oxoheptan-2-yl)-3,5-dimethyl-4*H*-pyran-4-one (42a).



(42a)

According to general procedure for desulfurization, reaction of **39a** (183 mg, 0.56 mmol) with Raney nickel (W2) in ethanol for 20 min followed by work up gave the title compound (72 mg, 44%) that was homogeneous by ^{1}H NMR.

amorphous white solid, TLC R_f = 0.3 (40% ethyl acetate in hexane)

IR (DRIFT) ν_{max} 3397, 1712, 1653, 1592 cm^{-1}.

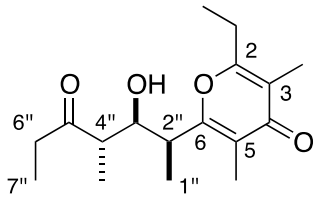
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.18 (1H, ddd, *J* = 2, 2.5, 9.5 Hz, HC-3'), 3.32 (1H, d, *J* = 2.5 Hz, HO), 3.00 (1H, dq, *J* = 9.5, 7 Hz, HC-2'), 2.57 (2H, ap q, *J* = 7.5 Hz, H_2C-2), 2.49 (1H, dq, *J* = 18, 7 Hz, HC-6'), 2.33 (1H, dq, *J* = 18, 7 Hz, HC-6'), 2.32 (1H, dq, *J* = 2, 7 Hz, HC-4'), 1.96 (3H, s, H_3CC-5), 1.92 (3H, s, H_3CC-3), 1.33 (3H, d, *J* = 7 Hz, H_3C-1'), 1.16 (3H, t, *J* = 7.5 Hz, H_3CC-2), 1.08 (3H, d, *J* = 7 Hz, H_3CC-4'), 0.99 (3H, t, *J* = 7 Hz, H_3C-7').

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.3 (s, C-5'), 180.0 (s, C-4), 164.6 (s, C-2), 163.9 (s, C-6), 119.0 (s, C-5), 118.3 (s, C-3), 72.4 (d, C-3'), 47.6 (d, C-4'), 38.8 (d, C-2'), 34.8 (t, C-6'), 24.9 (t, CH_2C-2), 15.7 (q, C-1'), 11.6 (q, CH_3CC-2), 10.0 (q, CH_3C-4'), 9.9 (q, CH_3C-5), 9.7 (q, CH_3C-3), 7.8 (q, C-7').

LRMS (EI), *m/z* (relative intensity): 294 ($[M]^+$, 1), 237 (4), 209 (9), 180 (100), 57 (15).

HRMS *m/z* calcd. for $C_{17}H_{26}O_4$: 294.1831; found: 294.1820 (EI).

2-Ethyl-6-((2*S*,3*S*,4*S*)-*rel*-3-hydroxy-4-methyl-5-oxoheptan-2-yl)-3,5-dimethyl-4*H*-pyran-4-one (42b).



(42b)

According to general procedure for desulfurization, reaction of **39b** (61 mg, 0.019 mmol) with Raney nickel (W2) in ethanol for 20 min gave the title compound (33 mg, 59%) after work up and fractionation of the crude by FCC (60% ethyl acetate hexane).

amorphous white solid, TLC R_f = 0.3 (40% ethyl acetate in hexanes)

IR (DRIFT) ν_{max} 3375, 1700, 1652, 1591 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.68 (1H, ddd, *J* = 3.5, 8.5, 10 Hz, HC-3'), 3.44 (1H, d, *J* = 10 Hz, HO), 3.04 (1H, dq, *J* = 8.5, 7 Hz, HC-2'), 2.58 (2H, ap q, *J* = 7.5 Hz, H_2CC-2), 2.47 (1H, dq, *J* = 3.5, 7 Hz, HC-4'), 2.47 (1H, dq, *J* = 7, 18.5 Hz, HC-6'), 2.21 (1H, dq, *J* = 7, 18.5 Hz, HC-6'), 1.91 (3H, s, H_3CC-3), 1.84 (3H, s, H_3CC-5), 1.32 (3H, d, *J* = 7 Hz, H_3C-1'), 1.22 (3H, d, *J* = 7.5 Hz, H_3CC-4'), 1.18 (3H, t, *J* = 7.5 Hz, H_3CCC-2), 0.95 (3H, t, *J* = 7 Hz, H_3C-7').

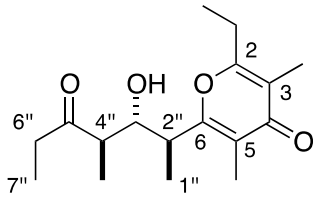
^{13}C NMR (125 MHz, $CDCl_3$) δ 218.0 (s, C-5'), 179.8 (s, C-4), 164.53 (s, C-2 or C-6), 164.50 (s, C-2 or C-6), 118.7 (s, C-5), 118.2 (s, C-3), 77.0 (d, C-3'), 47.0 (d, C-4'), 40.5 (d, C-2'), 36.1 (t, C-6'), 24.9 (t, CH_2C-2), 15.9

(q, CH_3C-4'), 15.2 (q, C-1'), 11.5 (q, CH_3CC-2), 9.67 (q, CH_3C-3 or CH_3C-5), 9.65 (q, CH_3C-3 or CH_3C-5), 7.4 (q, C-7').

LRMS (CI, NH_3), *m/z* (relative intensity): 295 ($[M+1]^+$, 48), 209 (100), 180 (36).

HRMS *m/z* calcd. for $C_{17}H_{26}O_4$+H: 295.1909; found: 295.1906 (CI, NH_3).

2-Ethyl-6-((2*S*,3*R*,4*R*)-*rel*-3-hydroxy-4-methyl-5-oxoheptan-2-yl)-3,5-dimethyl-4*H*-pyran-4-one (42c).



(42c)

According to general procedure for desulfurization, reaction of **39c** (3 mg, 0.009 mmol) with Raney nickel (W2) in ethanol for 20 min gave the title compound (2 mg, 80%) after work up and fractionation of the crude by PTLC (80% ethyl acetate hexane).

amorphous white solid, TLC R_f = 0.2 (50% ethyl acetate in hexane)

IR (DRIFT) ν_{max} 3378, 1698, 1654, 1591 cm^{-1}.

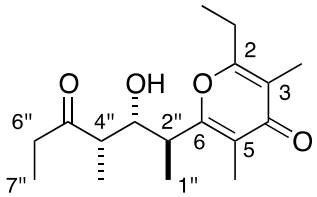
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (1H, ddd, *J* = 4, 7.5, 10 Hz, HC-3'), 3.40 (1H, d, *J* = 10 Hz, HO), 3.12 (1H, dq, *J* = 7.5, 7 Hz, HC-2'), 2.78 (1H, dq, *J* = 4, 7 Hz, HC-4'), 2.65-2.55 (3H, m, H_2CC-2, HC-6'), 2.40 (1H, dq, *J* = 18.5, 7 Hz, HC-6'), 1.97 (3H, s, H_3CC-5), 1.94 (3H, s, H_3CC-3), 1.29 (3H, d, *J* = 7 Hz, H_3CC-4'), 1.23 (3H, t, *J* = 7.5 Hz, H_3CCC-2), 1.23 (3H, d, *J* = 7 Hz, H_3C-1'), 1.02 (3H, t, *J* = 7 Hz, H_3C-7').

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.3 (s, C-5'), 179.9 (s, C-4), 164.5 (s, C-2), 164.1 (s, C-6), 119.5 (s, C-5), 118.2 (s, C-3), 77.6 (d, C-3'), 47.0 (d, C-4'), 40.0 (d, C-2'), 36.2 (t, C-6'), 25.0 (t, CH_2C-2), 15.9 (q, CH_3C-4'), 15.5 (q, C-1'), 11.5 (q, CH_3CC-2), 10.1 (q, CH_3C-5), 9.7 (q, CH_3C-3), 7.5 (q, C-7').

LRMS (CI, NH_3), *m/z* (relative intensity): 295 ($[M+1]^+$, 34), 277 (5), 209 (100), 180 (29), 151 (5).

HRMS *m/z* calcd. for $C_{17}H_{26}O_4$+H: 295.1909; found: 295.1907 (CI, NH_3).

2-Ethyl-6-((2*S*,3*R*,4*S*)-*rel*-3-hydroxy-4-methyl-5-oxoheptan-2-yl)-3,5-dimethyl-4*H*-pyran-4-one (42d).



(42d)

According to general procedure for desulfurization, reaction of **39d** (24 mg, 0.074 mmol) with Raney nickel (W2) in ethanol for 20 min gave the title compound (14 mg, 64%) after work up and fractionation of the crude by PTLC (80% ethyl acetate hexane).

amorphous white solid, TLC R_f = 0.30 (80% ethyl acetate in hexane)

IR (DRIFT) ν_{max} 3374, 1713, 1654, 1591 cm^{-1}.

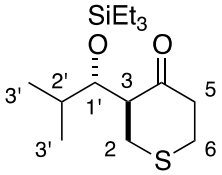
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.20 (1H, ddd, *J* = 2.5, 3.5, 9 Hz, HC-3'), 3.08 (1H, dq, *J* = 9, 7 Hz, HC-2'), 2.95 (1H, d, *J* = 3.5 Hz, HO), 2.71 (1H, dq, *J* = 2.5, 7 Hz, HC-4'), 2.68-2.55 (3H, m, H_2CC-2, HC-6'), 2.49 (1H, dq, *J* = 18, 7 Hz, HC-6'), 1.95 (3H, s, H_3CC-5), 1.92 (3H, s, H_3CC-3), 1.22 (3H, d, *J* = 7 Hz, H_3CC-4'), 1.20 (3H, t, *J* = 7.5 Hz, H_3CC-2), 1.13 (3H, d, *J* = 7 Hz, H_3C-1'), 1.06 (3H, t, *J* = 7 Hz, H_3C-7').

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.3 (s, C-5'), 179.9 (s, C-4), 164.3 (s, C-2), 164.1 (s, C-6), 119.7 (s, C-5), 118.1 (s, C-3), 72.5 (d, C-3'), 46.8 (d, C-4'), 38.2 (d, C-2'), 34.9 (t, C-6'), 25.0 (t, CH_2C-2), 14.7 (q, C-1'), 11.6 (q, CH_3CC-2), 9.8 (q, CH_3C-3 or CH_3C-5), 9.7 (q, CH_3C-3 or CH_3C-5), 9.3 (q, CH_3C-4'), 7.8 (q, C-7').

LRMS (EI), *m/z* (relative intensity): 294 ($[M]^+$, 2), 279 (1), 237 (5), 209 (7), 208 (6), 180 (100), 57 (27).

HRMS *m/z* calcd. for $C_{17}H_{26}O_4$: 294.1831; found: 294.1821 (EI).

(*S*)-3-((*S*)-2-Methyl-1-((triethylsilyl)oxy)propyl)dihydro-2*H*-thiopyran-4(3*H*)-one (44).



(44)

TESOTf (1.5 mL, 6.7 mmol) and 2,6-lutidine (0.89 mL, 7.7 mmol) were added sequentially to a stirred solution of aldol **43** (1.027 g, 5.46 mmol) in CH_2Cl_2 (50 mL) at –78 °C under argon. After 10 min, the reaction was quenched by addition of 10% aq HCl. The mixture was diluted with ethyl acetate, washed sequentially with 10% aq HCl, water and brine, dried over Na_2SO_4 and concentrated. The residue

was filtered through a plug of silica (ca. 15 g) eluting with 5% ethyl acetate in hexane to give the title compound (1.545 g, 94 %).

colorless liquid, TLC R_f = 0.39 (5% ethyl acetate in hexane), $[\alpha]_D$ –99 (*c* 5.2, $CHCl_3$)

IR (DRIFT) ν_{max} 1712 cm^{-1}.

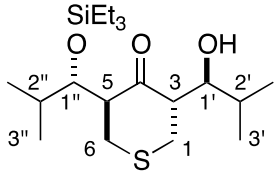
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.20 (1H, dd, *J* = 4, 6 Hz, HC-1'), 2.98-2.88 (3H, m, HC-2, H_2C-6), 2.83-2.73 (3H, m, HC-2, HC-3, HC-5), 2.66 (1H, ap ddd, *J* = 5.5, 8.5, 14 Hz, HC-5), 1.71 (1H, dqq, *J* = 4, 6.5, 6.5 Hz, HC-2'), 0.93 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.89 (3H, d, *J* = 6.5 Hz, H_3C-3'), 0.87 (3H, d, *J* = 6.5 Hz, H_3C-3'), 0.59 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 209.1 (s, C-4), 74.9 (d, C-1'), 58.7 (d, C-3), 44.0 (t, C-5), 31.6 (t, C-2), 30.9 (d, C-2'), 30.5 (t, C-6), 20.6 (q, C-3'), 17.0 (q, C-3'), 7.2 (q ×3, CH_3CSi), 5.5 (t ×3, CH2Si).

LRMS (EI), *m/z* (relative intensity): 302 ($[M]^+$, 2), 273 (100), 239 (21), 201 (39), 182 (29), 171 (31), 153 (30), 115 (34), 100 (52), 57 (84).

HRMS *m/z* calcd. for $C_{15}H_{30}O_2SiS$ 302.1736, found 302.1730 (EI).

(3*S*,5*S*)-3-((*S*)-1-Hydroxy-2-methylpropyl)-5-((*S*)-2-methyl-1-((triethylsilyl)oxy)propyl)dihydro-2*H*-thiopyran-4(3*H*)-one (45).



(45)

This procedure was performed with Schlenk technique and under Ar using freshly distilled Et_2O that was degassed (bubbling Ar into ether for 10 minutes) prior to immediate usage. Ketone **44** was dried by concentration from benzene solution immediately prior to use. (*c*-Hex)$_2$BCl (1.0 M in hexane; 0.18 mL, 0.18 mmol) and Et_3N (0.030 mL, 22 mg, 0.22 mmol) were added to a stirred solution of **44** (37 mg, 0.12 mmol) in Et_2O (1.2 mL) at 0 °C. After 20 min, the mixture was cooled to –78 °C and *i*-PrCHO (0.045 mL, 35 mg, 0.49 mmol) was added. After 20 min, the reaction was quenched by sequential addition of phosphate buffer (pH = 7; 1 mL), MeOH (1 mL) and 30% aq H_2O_2 (0.50 mL) with vigorous stirring. After stirring at 0 °C for 15 min, aq Na_2SO_3 was added and the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to give the title compound (35 mg, 78%).

colorless oil, TLC R_f = 0.40 (10% ethyl acetate in hexane)

IR (DRIFT) ν_{max} 3537, 1699 cm^{-1}.

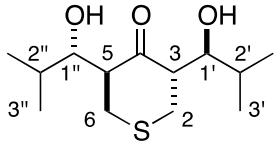
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.13 (1H, dd, *J* = 5, 5 Hz), 3.68 (1H, ddd, *J* = 5, 5, 7 Hz), 3.00-2.83 (6H, m), 2.75-2.67 (1H, m), 1.84-1.74 (2H, m), 1.01 (3H, d, *J* = 7 Hz), 0.96 (9H, t, *J* = 8 Hz, H_3CCSi x3), 0.914 (3H, d, *J* = 7 Hz), 0.905 (3H, d, *J* = 7 Hz), 0.90 (3H, d, *J* = 7 Hz), 0.63 (6H, ap q, *J* = 8 Hz, H_2CSi x3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 213.5, 77.1, 75.9, 57.4, 52.5, 31.9, 30.5, 30.2, 29.8, 20.3, 19.8, 18.1, 15.6, 7.3, 5.6.

LRMS (CI, NH_3), *m/z* (relative intensity): 375 ($[M+1]^+$, 85), 303 (74), 273 (100), 243 (33), 201 (55), 187 (86).

HRMS *m/z* calcd. for $C_{19}H_{38}O_3SSi$+H 375.2389, found 375.2378 (CI, NH_3).

(3*S*,5*S*)-3,5-Bis-((*S*)-1-Hydroxy-2-methylpropyl)dihydro-2*H*-thiopyran-4(3*H*)-one (46).



(46)

Aqueous HF (10% (w/w); 0.10 mL) was added to a stirred solution of **45** (91 mg, 0.24 mmol) in MeCN (2.4 mL) at room temperature. After 25 min, the reaction was quenched by addition of saturated aq $NaHCO_3$ and the resulting mixutre was diluted with EtOAc. The organic phase was sequentially washed with water and brine, and the combined aqueous layers were extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the titled compound (58 mg, 93%).

colorless oil, TLC R_f = 0.19 (20% ethyl acetate in hexane)

IR (DRIFT) ν_{max} 3451, 1699 cm^{-1}.

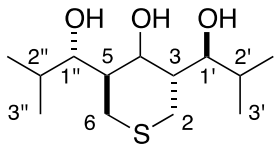
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.79 (2H, dd, *J* = 5, 6.5 Hz), 3.00-2.80 (6H, m), 2.65 (2H, br s), 1.82 (2H, dqq, *J* = 5, 7, 7 Hz), 0.98 (6H, d, *J* = 7 Hz), 0.89 (6H, d, *J* = 7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ 214.7, 76.5, 54.4, 33.4, 30.4, 20.1, 16.7.

LRMS (EI), *m/z* (relative intensity): 260 ([M]$^+$, 20), 242 (13), 217 (26), 199 (26), 187 (26), 170 (21), 145 (100).

HRMS *m/z* calcd. for $C_{13}H_{24}O_3S$ 260.1446, found 260.1449 (EI).

(3*S*,5*S*)-3,5-Bis((*S*)-1-Hydroxy-2-methylpropyl)tetrahydro-2*H*-thiopyran-4-ol (47).



(47)

Sodium borohydride (18 mg, 0.48 mmol) was added to a stirred solution of **46** (56 mg, 0.22 mmol) in EtOH (2.2 mL) at room temperature. After 20 min, aq NaOH (1.0 M; 3 mL, 3 mmol) was added and after 25 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (40% ethyl acetate in hexane then 20% methanol in CH_2Cl_2) to give the title compound (58 mg, quantitative).

white foam, TLC R_f = 0.44 (70% ethyl acetate in hexane)

IR (DRIFT) ν_{max} 3362 cm^{-1}.

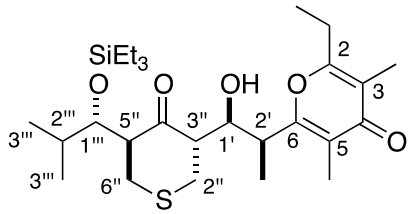
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (1H, br d, *J* = 3.5 Hz), 4.18 (3H, br s), 3.84 (1H, dd, *J* = 2, 9.5 Hz), 3.69 (1H, dd, *J* = 3.5, 8 Hz), 3.03 (1H, br d, *J* = 13 Hz), 2.81 (1H, dd, *J* = 10.5, 13 Hz), 2.29 (1H, br d, *J* = 13.5 Hz), 2.15 (1H, dd, *J* = 5, 13.5 Hz), 2.16-2.07 (1H, m), 2.02-1.95 (1H, m), 1.90-1.75 (2H, m), 1.00 (3H, d, *J* = 7 Hz), 0.98 (3H, d, *J* = 7 Hz), 0.89 (3H, d, *J* = 7 Hz), 0.84 (3H, d, *J* = 7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ 76.7, 75.8, 69.8 (br), 43.6, 40.0, 29.6, 28.9, 26.4, 25.8, 20.4, 20.2, 15.3, 14.0.

LRMS (EI), *m/z* (relative intensity): 262 ([M]$^+$, 64), 244 (11), 219 (36), 201 (52), 183 (62).

HRMS *m/z* calcd. for $C_{13}H_{26}O_3S$ 262.1603, found 262.1593 (EI).

2-Ethyl-6-((1*S*,2*S*)-1-hydroxy-1-((3*S*,5*S*)-5-((*S*)-2-methyl-1-(triethylsilyloxy)propyl)-4-oxotetrahydro-2*H*-thiopyran-3-yl)propan-2-yl)-3,5-dimethyl-4*H*-pyran-4-one (49).



(49)

This procedure was performed with Schlenk technique and under Ar using freshly distilled CH_2Cl_2 that was degassed (bubbling Ar into ether for 10 minutes) prior to immediate usage. Ketone **44** was dried by concentration from benzene solution immediately prior to use. (*c*-Hex)$_2$BCl (1.0 M in hexane; 0.96 mL, 0.96 mmol) and Et_3N (0.16 mL, 120 mg, 1.2 mmol) were added to a stirred solution of **44** (210 mg, 0.64 mmol) in CH_2Cl_2 (3.5 mL) at 0 °C. After 20 min, the mixture was cooled to –78 °C and a solution of *rac*-**11** (432 mg, 2.1 mmol) in CH_2Cl_2 (2.0 mL) was added. After 20 min, the reaction was quenched by sequential addition of phosphate buffer (pH = 7; 4 mL), MeOH (4 mL) and 30% aq H_2O_2 (2 mL) with vigorous stirring. After stirring at 0 °C for 15 min, sat. aqueous Na_2SO_3 was added and the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (40% ethyl acetate in hexane) to give a mixture of aldol adducts and cyclohexanol (329 mg). The cyclohexanol was removed by evaporation (60 °C @ 0.1 torr) to give the aldol adducts (305 mg). A portion of the mixture (28 mg) was further fractionated by FCC (50% ethyl acetate in hexane) to give the titled compound (21 mg, 64%).

white waxy solid, TLC R_f = 0.32 (35% Et_2O in benzene), $[\alpha]_D$ –38 (*c* 0.20, $CHCl_3$)

IR (DRIFT) ν_{max} 3377, 1713, 1653, 1594 cm^{-1}.

^{1}**H NMR** (500 MHz, $CDCl_3$) δ 4.08 (1H, dd, *J* = 4.5, 7.5 Hz, HC-1'), 4.05 (1H, ap dd, *J* = 3, 6 Hz, HC-1'''), 3.25 (1H, dq, *J* = 7.5, 7 Hz, HC-2'), 2.97 (1H, dd, *J* = 5.5, 13 Hz, HC-2''), 2.92-2.82 (4H, m, HC-2'', HC-5'', H_2C-6''), 2.76 (1H, ddd, *J* = 4.5, 5.5, 9 Hz, HC-3''), 2.60 (2H, ap q, *J* = 7.5 Hz, H_2CC-2), 1.94 (3H, s, H_3CC-3 or H_3CC-5), 1.93 (3H, s, H_3CC-3 or H_3CC-5), 1.65 (1H, dqq, *J* = 6, 6.5, 7 Hz, HC-2'''), 1.29 (3H, d, *J* = 7 Hz, H_3C-3'), 1.20 (3H, t, *J* = 7.5 Hz, H_3CCC-2), 0.94 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.87 (3H, d, *J* = 6.5 Hz, H_3C-3'''), 0.78 (3H, d, *J* = 7 Hz, H_3C-3'''), 0.60 (6H, ap q , *J* = 8 Hz, H_2CSi ×3).

^{1}**H NMR** (500 MHz, C_6D_6) δ 4.25 (1H, ddd, *J* = 6, 6, 6.5 Hz, HC-1'), 4.16 (1H, dd, *J* = 5, 5 Hz, HC-1'''), 3.48 (1H, d, *J* = 6 Hz, HO), 3.08 (1H, ddd, *J* = 5, 5, 10.5 Hz, HC-5''), 3.03 (1H, dq, *J* = 6.5, 7 Hz, HC-2'), 2.75 (1H, m, *J* = 5, 6, 7 Hz, HC-3''), 2.67 (1H, ddd, *J* = 1.5, 5, 13.5 Hz, HC-6''), 2.63 (1H, dd, *J* = 5, 13.5 Hz, HC-2''),

2.55 (1H, dd, *J* = 10.5, 13.5 Hz, HC-6''), 2.46 (1H, dd, *J* = 1.5, 7, 13.5 Hz, HC-2''), 2.14 (3H, s, H_3CC-3 or H_3CC-5), 2.12-2.00 (2H, m, H_2CC-2), 1.86 (3H, s, H_3CC-3 or H_3CC-5), 1.57 (1H, dqq, *J* = 5, 7, 7 Hz, HC-2'''), 1.16 (3H, d, *J* = 7 Hz, H_3C-3'), 1.03 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.88 (3H, d, *J* = 7 Hz, H_3C-3'''), 0.87 (3H, t, *J* = 7.5 Hz, H_3CCC-2), 0.84 (3H, d, *J* = 7 Hz, H_3C-3'''), 0.75-0.66 (6H, m, H_2CSi ×3).

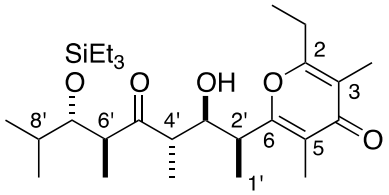
^{13}C NMR (125 MHz, $CDCl_3$) δ 211.3 (s, C-4''), 179.8 (s, C-4), 164.3 (s, C-2 or C-6), 164.1 (s, C-2 or C-6), 119.0 (s, C-5), 118.4 (s, C-3), 76.8 (d, C-1'''), 74.8 (d, C-1'), 58.1 (d, C-5''), 52.4 (d, C-3''), 39.4 (d, C-2'), 32.0 (t, C-2'''), 30.8 (d, C-2''), 28.5 (t, C-6''), 24.9 (t, CH_2C-2), 20.2 (q, C-3'''), 18.7 (q, C-3'''), 14.0 (q, C-3'), 11.5 (q, CH_3CC-2), 9.7 (q, CH_3C-3 or CH_3C-5), 9.6 (q, CH_3C-3 or CH_3C-5), 7.2 (q ×3, CH_3CSi), 5.4 (t ×3, CH_2Si).

^{13}C NMR (125 MHz, C_6D_6) δ 210.2 (s, C-4''), 179.2 (s, C-4), 163.8 (s, C-2 or C-6), 163.6 (s, C-2 or C-6), 119.5 (s, C-3 or C-5), 118.7 (s, C-3 or C-5), 76.9 (d, C-1'''), 75.1 (d, C-1'), 58.5 (d, C-5''), 53.2 (d, C-3''), 39.5 (d, C-2'), 32.1 (t, C-2''), 31.9 (d, C-2'''), 29.6 (t, C-6''), 24.9 (t, CH_2C-2), 20.7 (q, C-3'''), 18.7 (q, C-3'''), 13.6 (q, C-3'), 11.6 (q, CH_3CC-2), 10.12 (q, CH_3C-3 or CH_3C-5), 10.09 (q, CH_3C-3 or CH_3C-5), 7.7 (q ×3, CH_3CSi), 6.0 (t ×3, CH_2Si).

LRMS (EI), *m/z* (relative intensity): 510 ($[M]^+$, 3), 481 (21), 467 (7), 409 (15), 273 (94), 209 (60), 201 (59), 187 (76), 180 (82), 179 (100).

HRMS *m/z* calcd. for $C_{27}H_{46}O_5SSi$ 510.2835, found 510.2835 (EI).

2-Ethyl-6-((2*S*,3*S*,4*S*,6*S*,7*S*)-3-hydroxy-4,6,8-trimethyl-5-oxo-7-((triethylsilyl)oxy)nonan-2-yl)-3,5-dimethyl-4*H*-pyran-4-one (52).



(52)

Desulfurization of **49** (18 mg, 0.035 mmol) with Raney nickel (W2, 1.0 mL settled volume) in refluxing EtOH (2 mL) for 20 minutes according to the general procedure and fractionation of the crude product by PTLC (40% ethyl acetate in hexane) gave the title compound (12.5 mg, 74%).

colorless liquid, TLC R_f = 0.37 (40% ethyl acetate in hexane), $[\alpha]_D$ –25 (*c* 0.25, $CHCl_3$)

IR (DRIFT) ν_{max} 3385, 1715, 1652, 1596 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83-3.78 (2H, , HC-3', HC-7'), 3.37 (1H, br s, HO), 3.11 (1H, dq, *J* = 8, 7 Hz, HC-2'), 2.75 (1H, dq, *J* = 9, 7 Hz, HC-6'), 2.60 (2H, ap q, *J* = 7.5 Hz, H_2CC-2), 2.55 (1H, dq, *J* = 4, 7.5 Hz, HC-4'), 1.93 (3H, s, H_3CC-3), 1.87 (3H, s, H_3CC-5), 1.70 (1H, dqq, *J* = 2.5, 7, 7 Hz, HC-8'), 1.33 (3H, d, *J* = 7 Hz, H_3C-1'), 1.25 (3H, d, *J* = 7.5 Hz, H_3CC-4'), 1.20 (3H, t, *J* = 7.5 Hz, H_3CCC-2), 0.93 (6H, t, *J* = 8 Hz, H_3CCSi ×3), 0.92 (3H, d, *J* = 7 Hz, H_3C-9'), 0.81 (6H, ap d, *J* = 7 Hz, H_3CC-6', H_3C-9'), 0.64 (6H, q, *J* = 8 Hz, H_2CSi ×3).

^{1}H NMR (500 MHz, C_6D_6) δ 3.90-3.82 (2H, m, HC-3', HC-7'), 3.32 (1H, d, *J* = 9 Hz, HO), 3.00 (1H, dq, *J* = 7.5, 7 Hz, HC-2'), 2.60 (1H, dq, *J* = 8.5, 7 Hz, HC-6'), 2.50 (1H, dq, *J* = 4.5, 7.5 Hz, HC-4'), 2.09-1.94 (2H, m, H_2CC-2), 1.97 (3H, s, H_3CC-5), 1.92 (3H, s, H_3CC-3), 1.57-1.49 (1H, dqq, *J* = 2, 7, 7 Hz, HC-8'), 1.28 (3H, d, *J* = 7 Hz, H_3C-1'), 1.22 (3H, d, *J* = 7.5 Hz, H_3CC-4'), 1.05 (9H, t, *J* = 8 Hz, H_3CCSi x3), 0.90 (3H, d, *J* = 7 Hz, H_3C-9'), 0.82 (3H, t, *J* = 7.5 Hz, H_3CC-2), 0.79 (3H, d, *J* = 7 Hz, H_3C-9'), 0.75-0.67 (6H, m, H_2CSi x3), 0.67 (3H, d, *J* = 7 Hz, H_3CC-6').

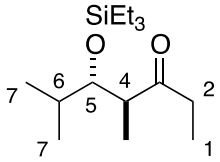
^{13}C NMR (125 MHz, $CDCl_3$) δ 218.3 (s, C-5'), 179.7 (s, C-4), 164.9 (s, C-6), 164.4 (s, C-2), 118.7 (s, C-5), 118.3 (s, C-3), 77.3 (d, C-7'), 76.1 (d, C-3'), 50.0 (d, C-6'), 47.1 (d, C-4'), 40.0 (d, C-2'), 30.9 (d, C-8'), 24.9 (t, CH_2C-2), 20.1 (q, C-9'), 16.0 (q, C-9'), 15.1 (q, C-1'), 14.7 (q, CH_3C-4'), 14.1 (q, CH_3C-6'), 11.5 (q, CH_3CC-2), 9.8 (q, CH_3C-3 or CH_3C-5), 9.7 (q, CH_3C-3 or CH_3C-5), 7.2 (q ×3, CH_3CSi), 5.6 (t ×3, CH_2Si).

^{13}C NMR (125 MHz, C_6D_6) δ 217.5 (s, C-5), 179.1 (s, C-4), 164.5 (s, C-6), 163.7 (s, C-2), 119.1 (s, C-5), 118.6 (s, C-3), 77.8 (d, C-7'), 76.4 (d, C-3'), 50.7 (d, C-6'), 47.5 (d, C-4'), 40.3 (d, C-2'), 31.2 (d, C-8'), 24.9 (t, CH_2C-2), 20.6 (q, C-9'), 16.2 (q, C-9'), 15.0 (q, CH_3C-4'), 14.9 (q, C-1'), 14.1 (q, CH_3C-6'), 11.6 (q, CH_3C-2), 10.2 (q, CH_3C-3 or CH_3C-5), 10.0 (q, CH_3C-3 or CH_3C-5), 7.8 (q ×3, CH_3CSi), 6.2 (t ×3, CH_2Si).

LRMS (EI), *m/z* (relative intensity): 480 ($[M]^+$, 6), 451 (27), 379 (94), 243 (52), 199 (38), 187 (61), 180 (100), 179 (60), 171 (47), 115 (55).

HRMS *m/z* calcd. for $C_{27}H_{48}O_5Si$ 480.3271, found 480.3258 (EI).

(4*S*,5*S*)-4,6-Dimethyl-5-((triethylsilyl)oxy)heptan-3-one (61).



(61)

A suspension of Raney nickel (W2; 5.0 mL settled volume) in EtOH (5 mL plus 2× 5 mL rinses) was added to **44** (591 mg, 1.96 mmol) and the resulting mixture was heated under reflux with vigorous

stirring. After for 20 min (reaction was complete by TLC analysis), the mixture was decanted and the solid was suspended in EtOH (15 mL) and heated under reflux with vigorous stirring for several min. This washing procedure was repeated with ethyl acetate and with acetone. The combined organic layers were filtered through Celite®, concentrated to give the title compound (518 mg, 97%)[27] that was homogeneous by ^{1}H NMR.

colorless liquid, TLC R_f = 0.22 (20% ethyl acetate in hexane), $[\alpha]_D$ +11 (*c* 9.1, $CHCl_3$)

IR (DRIFT) ν_{max} 1720 cm^{-1}.

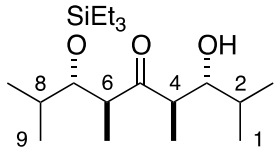
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (1H, dd, *J* = 3, 8 Hz, HC-5), 2.73 (1H, dq, *J* = 8, 7 Hz, HC-4), 2.53 (1H, dq, *J* = 18.5, 7, HC-2), 2.45 (!H, dq, *J* = 18.5, 7 Hz, H_2C-2), 1.72 (1H, dqq, *J* = 3, 7, 7 Hz, HC-6), 1.02 (3H, t, *J* = 7 Hz, H_3C-1), 0.94 (3H, d, *J* = 7 Hz, H_3CC-4), 0.93 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.91 (3H, d, *J* = 7 Hz, H_3C-7), 0.85 (3H, d, *J* = 7 Hz, H_3C-7), 0.56 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 214.7 (s, C-3), 78.8 (d, C-5), 50.3 (d, C-4), 37.0 (t, C-2), 30.9 (d, C-6), 20.2 (q, C-7), 15.9 (q, C-7), 14.1 (q, CH_3C-4), 7.6 (q, C-1), 7.2 (q ×3, CH_3CSi), 5.5 (t ×3, CH2Si).

LRMS (CI, NH_3), *m/z* (relative intensity): 273 ($[M+1]^+$, 100), 243 (42), 58 (40).

HRMS *m/z* calcd. for $C_{15}H_{32}O_2Si$ 273.2250, found 273.2245 (CI, NH_3).

(3*R*,4*R*,6*S*,7*S*)-3-Hydroxy-2,4,6,8-tetramethyl-7-((triethylsilyl)oxy)nonan-5-one (64).



(64)

This procedure was performed with Schlenk technique and under Ar using freshly distilled Et_2O that was degassed (bubbling Ar into ether for 10 minutes) prior to immediate usage. (*c*-Hex)$_2$BCl (1.0 M in hexane; 0.64 mL, 0.64 mmol) and $EtMe_2N$ (0.080 mL, 54 mg, 0.74 mmol) were added to a stirred solution of **61** (88 mg, 0.32 mmol) in Et_2O (1.0 mL) at rt. After 3 h, the mixture was cooled to –78 °C and *i*-PrCHO (0.058 mL, 46 mg, 0.64 mmol) was added. After 3 h, the reaction was quenched by sequential addition of phosphate buffer (pH = 7; 2 mL), MeOH (2 mL) and 30% aq H_2O_2 (0.50 mL) with vigorous stirring. After stirring at 0 °C for 15 min, aq Na_2SO_3 was added and the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (5% ethyl acetate in hexane) to give the title compound (67.5 mg, 61%).

colorless liquid, TLC R_f = 0.5 (10% ethyl acetate in hexane)

IR (DRIFT) ν_{max} 3454, 1714 cm^{-1}.

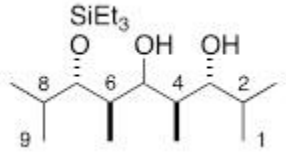
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.89 (1H, dd, *J* = 2.5, 8 Hz), 3.45 (1H, dd, *J* = 3, 8.5 Hz), 3.12 (1H, dq, *J* = 8, 7 Hz), 2.82 (1H, dq, *J* = 8.5, 7 Hz), 1.83-1.75 (2H, m), 1.004 (3H, d, *J* = 7 Hz), 0.999 (3H, d, *J* = 7 Hz), 0.98 (3H, d, *J* = 7 Hz), 0.96 (9H, t, *J* = 8 Hz), 0.95 (3H, d, *J* = 7 Hz), 0.0904 (3H, d, *J* = 7 Hz), 0.0898 (3H, d, *J* = 6.5 Hz), 0.62 (6H, ap q, *J* = 8 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ 219.1, 79.2, 78.2, 51.0, 50.1, 31.5, 29.6, 20.4, 19.7, 17.3, 14.5, 13.8, 13.7, 7.2, 5.4.

LRMS (EI), *m/z* (relative intensity): 344 ($[M]^+$, 0.3), 329 (0.6), 243 (100).

HRMS *m/z* calcd. for $C_{19}H_{40}O_3Si$ 344.2747, found 344.2743 (EI).

(3*R*,4*R*,6*R*,7*S*)-2,4,6,8-Tetramethyl-7-((triethylsilyl)oxy)nonane-3,5-diol (65).



(65)

Et_2BOMe (0.007 mL, 5 mg, 0.05 mmol) was added to stirred solution of **64** (11 mg, 0.032 mmol) in abs. EtOH (0.35 mL) at –78 °C under argon. The reaction vessel was removed from the cooling bath and after 15 min, powdered $NaBH_4$ (6 mg, 0.2 mmol) was added at –78 °C. The reaction vessel was removed from the cooling bath and after 2.5 h, the reaction mixture was concentrated. The residue was taken up in MeOH (0.5 mL) and 30% (w/w) aq H_2O_2 (0.05 mL) and aq NaOH (1 M; 0.45 mL) was added with vigorous stirring. After 10 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over NaSO4, concentrated, and fractionated by PTLC (10% ethyl acetate in hexane) to give the title compound (7 mg, 63%).

colorless liquid, TLC R_f = 0.44 (10% ethyl acetate in hexane)

IR (DRIFT) ν_{max} 3396 cm^{-1}.

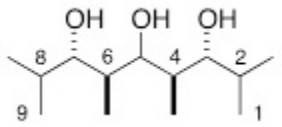
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.50 (1H, bs), 3.76 (1H, bs), 3.49 (1H, dd, *J* = 4.5, 7.5 Hz), 3.45 (1H, dd, *J* = 3.5, 8.5 Hz), 3.42 (1H, dd, *J* = 4, 6 Hz), 2.09 (1H, ddq, *J* = 4, 7.5, 7 Hz), 1.93 (1H, ddq, *J* = 6, 8.5, 7 Hz), 1.86-1.77

(2H, m), 1.00 (3H, d, *J* = 7 Hz), 0.99 (9H, t, *J* = 8 Hz), 0.97 (3H, d, *J* = 7 Hz), 0.92 (3H, d, *J* = 6.5 Hz), 0.91 (3H, d, *J* = 6.5 Hz), 0.90 (3H, d, *J* = 6.5 Hz), 0.89 (3H, d, *J* = 6.5 Hz), 0.67 (6H, ap q, *J* = 8 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ 85.2, 82.0, 79.8, 39.4, 38.5, 34.0, 30.4, 20.7, 19.5, 18.93, 18.90, 17.3, 15.2, 7.1, 5.4.

HRMS *m/z* calcd. for $C_{19}H_{42}O_3Si+Na^+$ 369.2795, found 369.2808 (ESI).

(3*R*,4*R*,6*S*,7*S*)-2,4,6,8-Tetramethylnonane-3,5,7-triol (66).



(66)

Aqueous HF (10% (w/w); 0.05 mL) was added to a stirred solution of **65** (16.5 mg, 0.048 mmol) in MeCN (0.48 mL) at rt. After 5 min, the reaction was quenched by addition of saturated aq $NaHCO_3$. The mixture was diluted with ethyl acetate and washed sequentially with aq. NaHCO3, water and brine, dried over Na_2SO_4, and concentrated to give the title compound (10.5 mg, 94%) as flakey white solid.

white solid, TLC R_f = 0.50 (50% ethyl acetate in hexane)

IR (DRIFT) ν_{max} 3331 cm^{-1}.

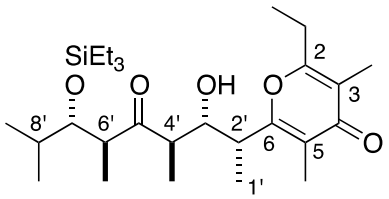
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.55 (1H, t, *J* = 5.5 Hz, HC-5), 3.53 (3H, br s, HO x3), 3.46 (2H, dd, *J* = 3, 8.5 Hz, HC-3, HC-5), 1.97 (2H, ddq, *J* = 5.5, 8.5, 7 Hz, HC-4, HC-6), 1.89 (2H, dqq, *J* = 3, 7, 7 Hz, HC-2, HC-8), 0.98 (6H, d, *J* = 7 Hz, H_3C-1, H_3C-9), 0.91 (6H, d, *J* = 7 Hz, H_3CC-4, H_3CC-6), 0.87 (6H, d, *J* = 7 Hz, H_3CC-2, H_3CC-8).

^{13}C NMR (125 MHz, $CDCl_3$) δ 83.9, 81.0 (×2), 39.5 (×2), 30.3 (×2), 20.5 (×2), 16.3 (×2), 14.8 (×2).

LRMS (CI, NH_3), *m/z* (relative intensity): 233 ($[M+1]^+$, 100), 215 (6), 197 (25), 171 (6), 125 (8).

HRMS *m/z* calcd. for $C_{13}H_{28}O_3$+H 233.2117, found 233.2110 (CI, NH_3).

2-Ethyl-6-((2*R*,3*R*,4*R*,6*S*,7*S*)-3-hydroxy-4,6,8-trimethyl-5-oxo-7-((triethylsilyl)oxy)nonan-2-yl)-3,5-dimethyl-4*H*-pyran-4-one (67).



(67)

This procedure was performed with Schlenk technique and under Ar using freshly distilled CH_2Cl_2 that was degassed (bubbling Ar into ether for 10 minutes) prior to immediate usage. Ketone **61** was dried by concentration from benzene solution immediately prior to use. (*c*-Hex)$_2$BCl (1.0 M in hexane; 0.51 mL, 0.51 mmol) and Me_2NEt (66 μL, 45 mg, 0.61 mmol) were added to a stirred solution of **61** (46 mg, 0.17 mmol) in Et_2O (1.7 mL) at room temperature. After 24 h, the mixture was cooled to –78 °C and a solution of *rac*-**11** (124 mg, 0.60 mmol) in Et_2O (1.0 mL) was added. After 20 min, the reaction was quenched by sequential addition of phosphate buffer (pH = 7; 1 mL), MeOH (1 mL) and 30% aq H_2O_2 (0.5 mL) with vigorous stirring. After stirring at 0 °C for 15 min, sat. aqueous Na_2SO_3 was added and the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (30% ethyl acetate in hexane) to give a 2.5:1 mixture of **67** and **72**, respectively (18 mg). Fractionation of the mixture by PTLC (4% methanol in toluene, multiple developments) gave the title compound (12 mg, 15%).

amorphous white solid, TLC R_f = 0.30 (30% ethyl acetate in hexane), $[\alpha]_D$ +98 (*c* 0.35, $CHCl_3$)

IR (DRIFT) ν_{max} 3389, 1697, 1651, 1590 cm^{-1}.

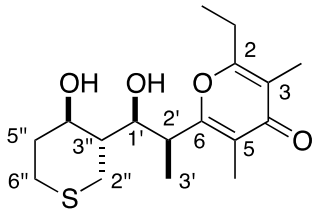
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90-3.85 (2H, m, HC-3', HC-7'), 3.39 (1H, bs, HO), 3.11 (1H, dq, *J* = 5, 7 Hz, HC-2'), 2.98 (1H, dq, *J* = 7.5, 7 Hz, HC-6'), 2.80 (1H, dq, *J* = 7, 7 Hz, HC-4'), 2.66-2.53 (2H, m, H_2CC-2), 1.96 (3H, s, H_3CC-5), 1.94 (3H, s, H_3CC-3), 1.72 (1H, dqq, *J* = 3, 7, 7 Hz, HC-8'), 1.28 (3H, d, *J* = 7 Hz, H_3C-1'), 1.20 (3H, t, *J* = 7.5 Hz, H_3CC-2), 1.11 (3H, d, *J* = 7 Hz, H_3CC-4'), 0.97 (3H, d, *J* = 7 Hz, H_3CC-6'), 0.91 (3H, d, *J* = 7 Hz, H_3C-9'), 0.91 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.87 (3H, d, *J* = 7 Hz, H_3C-9'), 0.57 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.2 (s, C-5'), 180.0 (s, C-4), 165.0 (s, C-6), 164.5 (s, C-2), 118.3 (s, C-5), 118.1 (s, C-3), 78.9 (d, C-7'), 76.0 (d, C-3'), 51.3 (d, C-6'), 49.2 (d, C-4'), 38.9 (d, C-2'), 31.5 (d, C-8'), 24.9 (t, CH_2C-2), 19.8 (q, C-9'), 17.2 (q, C-9'), 14.7 (q, CH_3C-4'), 13.7 (q, CH_3C-6'), 12.1 (q, C-1'), 11.5 (q, CH_3CC-2), 9.7 (q, CH_3C-3, CH_3C-5), 7.1 (q ×3, CH_3CSi), 5.4 (t ×3, CH_2Si).

LRMS (EI), *m/z* (relative intensity): 480 ([M]$^+$, 5), 451 (38), 379 (54), 209 (52), 199 (100), 180 (27).

HRMS *m/z* calcd. for $C_{27}H_{48}O_5Si$ 480.3271, found 480.3257 (EI).

2-Ethyl-6-((1*S*,2*S*)-*rel*-1-hydroxy-1-((3*R*,4*R*)-4-hydroxytetrahydro-2*H*-thiopyran-3-yl)propan-2-yl)-3,5-dimethyl-4*H*-pyran-4-one (71).



(71)

Et_2BOMe (0.030 mL, 23 mg, 0.23 mmol) was added to a stirred solution of **39b** (53 mg, 0.17 mmol) in THF (4.1 mL) and MeOH (0.8 mL) at –78 °C under Ar. The cloudy mixture became clear upon warming to ambient temperature. The resulting solution was cooled to –78 °C and $NaBH_4$ (16 mg, 0.43 mmol) was added. After 1 h, MeOH (1 mL) was added and, after allowing the mixture to warm to ambient temperature, aq NaOH (1 M; 3 mL) was added. After 1.5 hours, the suspension was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (ethyl acetate) to give the title compound (40 mg, 73%).

amorphous white solid, TLC R_f = 0.2 (ethyl acetate)

IR (DRIFT) ν_{max} 3395, 1692, 1650, 1597 cm^{-1}.

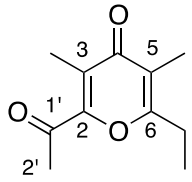
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88-3.84 (1, m, HOC-4'', HC-1'), 3.69 (1, ddd, *J* = 3.5, 9.5, 9.5 Hz, HC-4''), 3.32 (1, dq, *J* = 6.5, 7 Hz, HC-2'), 2.67-2.55 (4, m, H_2CC-2, H_2C-6''), 2.55-2.50 (2, m, H_2C-2''), 2.26 (1, ap dddd, *J* = 3.5, 3.5, 4, 13 Hz, HC-5''), 1.96 (3, s, H_3CC-5), 1.92 (3, s, H_3CC-3), 1.80-1.71 (2, m, HC-3'', HC-5''), 1.30 (3, d, *J* = 7 Hz, H_3C-3'), 1.22 (3, t, *J* = 7.5 Hz, H_3CCC-2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 180.2 (s, C-4), 165.3 (s, C-6), 164.9 (s, C-2), 118.7 (s, C-5), 118.3 (s, C-3), 78.1 (d, C-1'), 72.4 (d, C-4''), 47.5 (d, C-3''), 40.0 (d, C-2'), 36.7 (t, C-5''), 30.7 (t, C-2''), 27.3 (t, C-6''), 25.0 (t, CH_2C-2), 12.4 (q, C-3'), 11.5 (q, CH_3CC-2), 9.8 (q ×2, CH_3C-3, CH_3C-5).

LRMS (EI), *m/z* (relative intensity): 326 ([M]$^+$, 1), 210 (16), 193 (30), 160 (100), 84 (27).

HRMS *m/z* calcd. for $C_{17}H_{26}O_4S$ 326.1552, found 326.1554 (EI).

2-Acetyl-6-ethyl-3,5-dimethyl-4*H*-pyran-4-one (72).



(72)

IBX (107.5 mg, 0.38 mmol) was added to a solution of **10** (40.5 mg, 0.19 mmol) in MeCN (2 mL) and the mixture was heated under reflux. After 15 h, the suspension was cooled to 0 °C and filtered through a sintered glass funnel with the aid of ethyl acetate. The combined filtrate and washings were washed with saturated aq $NaHCO_3$, dried over Na_2SO_4, concentrated, and fractionated by FCC (40% ethyl acetate in hexane) to give the title compound (10 mg, 27%).

White amorphous solid, mp 79-81 °C, TLC R_f = 0.53 (60% ethyl acetate in hexane)

IR (DRIFT) ν_{max} 1711, 1638, 1618 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.70 (2H, q, *J* = 7.5 Hz, H_2CC-6), 2.53, (3H, s, H_3C-1'), 2.27 (3H, s, H_3CC-3'), 2.00 (3H, s, H_3CC-5'), 1.30 (3H, t, *J* = 7.5 Hz, H_3CC-6).

^{13}C NMR (125 MHz, $CDCl_3$) δ 195.3 (s, C-1'), 180.2 (s, C-4), 164.4 (s, C-6), 152.5 (s, C-2), 125.2 (s, C-3), 119.9 (s, C-5), 28.1 (q, C-2'), 25.1 (t, CH_2C-6), 11.4 (q, CH_3C-6), 10.0 (q, CH_3C-5), 9.7 (q, CH_3C-3).

LRMS (EI), *m/z* (relative intensity): 194 ($[M]^+$, 100), 165 (18), 151 (41).

HRMS *m/z* calcd. for $C_{11}H_{14}O_3$ 194.0943, found 194.0493 (EI).

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