Total Synthesis and Absolute Configuration of Pseudosemiglabrin, a Platelet Aggregation Antagonist, and Its Diastereomer Semiglabrin

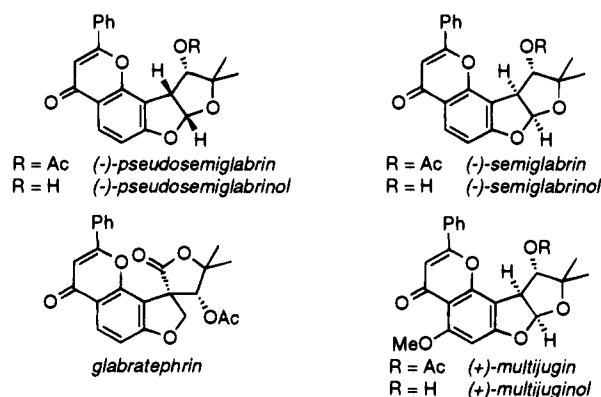## Michael C. Pirrung*,[1] and Yong Rok Lee[2]

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Abstract: A general approach to the synthesis of the flavone−furo[2,3-*b*]furan ring system present in numerous biologically-active secondary metabolites of *Tephrosia* sp. has been developed and applied in one racemic synthesis and two asymmetric syntheses of four members of the family. It uses 2-diazo-1,3-cyclohexanedione as the keystone of the ring system, uniting it with a dihydrofuran through a rhodium-mediated dipolar cycloaddition. The enolate of this tricyclic intermediate is then utilized to elaborate a salicylate that is subjected to a concise annulation protocol with benzaldehyde to produce the tetracycle. Stereochemical control is accomplished by the use of three strategies. Reduction of a ketone from the more accessible face of a folded bicyclooctane ring system produces the *endo* stereochemistry. Steric hindrance by a bulky allylic siloxy group directs the cycloaddition to the opposite face of the prochiral alkene to generate the *exo* stereochemistry. Finally, a novel hydroxyl-directed cycloaddition simultaneously produces the *endo* stereochemistry and accesses the opposite enantiomeric series.

Introduction

A number of flavonoid metabolites have been isolated from the subtropical plant genus *Tephrosia*, which is widely distributed in the southern part of Africa. Shown below are several compounds that were discovered by examination of folkloric medicines (only relative stereochemistry is significant in these structures).[3]

R = Ac   (-)-pseudosemiglabrin
R = H   (-)-pseudosemiglabrinol

R = Ac   (-)-semiglabrin
R = H   (-)-semiglabrinol

glabratephrin

R = Ac   (+)-multijugin
R = H   (+)-multijuginol

Both pseudosemiglabrin and semiglabrin have shown desirable properties in inhibiting aggregation of human platelets induced by the thromboxane-mimetic drug U46619, with the former being more potent; its actions are fully expressed at 6 μg/mL. The latter also has weak antimalarial activity. The structures of these materials have been determined by spectroscopic analysis,[4] but none of their absolute configurations are

known. An interesting feature of this class of natural products is that enantiomeric compounds (multijugins) have been isolated from different sources.[5] Previous synthetic approaches to the *Tephrosia* metabolites are few. A model study toward multijuginol has been reported,[6] but the route produces the incorrect diastereomeric alcohol for a synthesis of multijuginol.

Previous work from our laboratory concerning the dipolar cycloaddition of cyclic rhodium carbenoids to aromatic heterocycles and vinyl ethers[7] suggested a concise approach to the synthesis of *Tephrosia* metabolites involving a cyclohexanedione as a synthon for the core benzene ring of these tetracyclic natural products. This report describes first a preparation of pseudosemiglabrin (in racemic form) featuring a concise flavone annulation we have used in the syntheses of several tricyclic furanoflavones.[8] The use of materials derived from the chiral pool in a cycloaddition featuring relative asymmetric induction enabled the preparation of negatively-rotating semiglabrin and permitted the assignment of the absolute configuration of the natural product as 3*R*,3a*R*,8a*R*. Finally, *syn* direction by an allylic hydroxyl group,[9] a novelty in dipolar cycloadditions, permitted the chiral pool intermediates to be used also in a synthesis of a positively-rotating sample of pseudosemiglabrin, enabling the assignment of the absolute configuration of the natural product as 3*S*,3a*R*,8a*R*.

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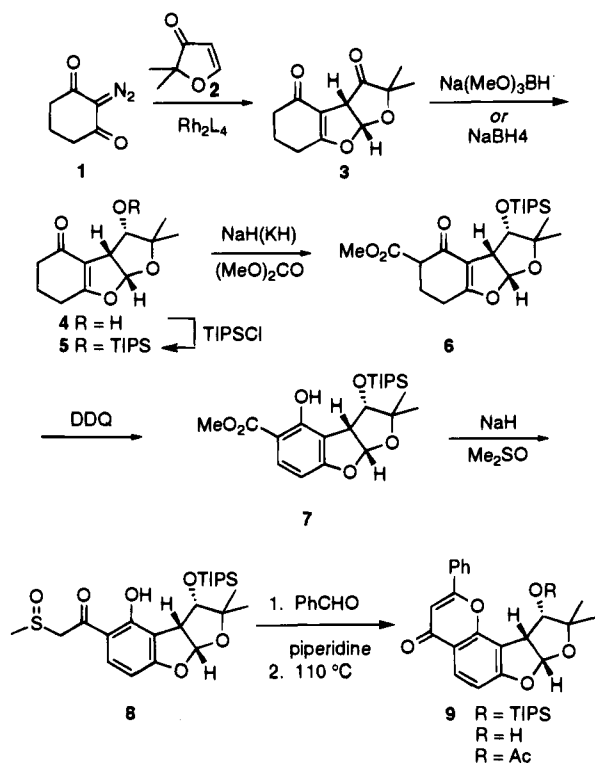[⊗] Abstract published in *Advance ACS Abstracts*, April 15, 1995.

(1) Fellow of the John Simon Guggenheim Memorial Foundation, 1994−95.

(2) Postdoctoral fellow of the Korea Science and Engineering Foundation.

(3) Jonathan, L. T.; Gbeassor, M.; Che, C.-T.; Fong, H. H. S.; Farnsworth, N. R.; LeBreton, G. C.; Venton, D. L. *J. Nat. Prod.* **1990**, *53*, 1572−1574.

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Synthesis and Configuration of Pseudosemiglabrin

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Scheme 1

Table 1

	C-3	C-3a	C-8a	C-2-Me	C-2-Me'
pseudosemiglabrin	5.60	4.63	6.53	1.16	1.40
semiglabrin	5.68	4.32	6.67	1.11	1.33
pseudosemiglabrinol[b]	4.44	4.44	6.42	1.02	1.30
semiglabrinol[b]	4.22	4.22	6.53	0.92	1.42
multijugin	5.56	4.20	6.57	1.10	1.27
multijuginol	4.29	4.20	6.57	1.04	1.37
purpurin	5.46	3.95	6.35	1.01	1.18
synthetic pseudosemiglabrin	5.56	4.61	6.50	1.12	1.37
synthetic pseudosemiglabrinol	4.48	4.48	6.46	1.30	1.44
synthetic pseudosemiglabrinol[b]	4.40	4.40	6.36	1.00	1.27
synthetic semiglabrin	5.64	4.29	6.63	1.09	1.32
synthetic semiglabrinol	4.36	4.29	6.63	1.05	1.41
synthetic semiglabrinol[b]	4.29	4.29	6.59	1.00	1.38

[a] Spectra run in $CDCl_3$ unless otherwise indicated. [b] Run in $CDCl_3$–DMSO-d_6 (3:1).

Results

The first approach to pseudosemiglabrin was to rely on a stereoselective reduction to install a hydroxyl functionality on the *endo* face of its dioxabicyclo[3.3.0]octane ring system. A tricyclic intermediate was readily assembled toward this goal from 2-diazo-1,3-cyclohexanedione (**1**) and dihydrofuranone **2** (2 equiv) with catalysis by rhodium acetate in fluorobenzene (Scheme 1). Other catalysts examined for this process included rhodium pivalate, rhodium acetamide, and rhodium trifluoroacetate[10] but rhodium acetate was superior. The resulting substance **3** was fairly unstable, undergoing β-elimination of the diketone enolate, but the ease with which rhodium-mediated diazo decomposition processes can be conducted proved a significant advantage. The reaction mixture in fluorobenzene could simply be concentrated and the product directly reduced with sodium trimethoxyborohydride in THF or sodium borohydride in methanol, producing **4** in a modest 50% overall yield from **1**. Support for the structural assignment as the *endo* alcohol comes from NMR spectroscopy (*vide infra*) as well as the solution IR spectrum. Compound **4** shows a sharp, 3625 cm^{-1} OH absorption in dilute CCl_4, strong evidence for an intramolecular hydrogen bond to the carbonyl. In the seven-membered ring involved here, this geometric arrangement could arise only with an alcohol on the concave face of the cupped ring system. The alcohol was protected as its triisopropylsilyl (TIPS) ether (72%) by a standard protocol.[11] Other silyl or acyl groups did not survive upcoming enolate chemistry, and TIPS provided a further advantage in that it prevented the elimination of the β-diketone enolate to produce a dihydrofuran, a problem seen with other (or no) protecting groups. Construction of the flavone ring was begun by carboxylation with dimethyl carbon-

ate/sodium hydride in the presence of a catalytic amount of potassium hydride (75%), and the resulting β-ketoester **6** was aromatized with DDQ (74%). The resulting ester **7** is a protected derivative of methyl pseudosemiglabrinate, a degradation product obtained in the course of the structure determination of pseudosemiglabrin. Deprotection and comparison of spectroscopic data for our racemic material with that reported for the naturally-derived substance provided confidence that the structure and stereochemistry represented in **7** are in fact secure. The salicylate-to-flavone annulation procedure of von Strandtmann[12] was next applied. Ester **7** was treated with dimsyl anion in DMSO to form the β-ketosulfoxide **8** (85%), which on treatment with benzaldehyde and piperidine, first at 40 °C and then at reflux, delivers the tetracyclic compound **9** (80%). Presumably, Knoevenagel condensation to produce a highly-activated benzylidene β-ketosulfoxide is followed by conjugate addition of the phenolic hydroxyl and elimination of methanesulfenic acid. The TIPS group was removed with TBAF in THF to produce pseudosemiglabrinol (94%), which was acetylated with acetic anhydride to generate pseudosemiglabrin. These materials exhibited spectroscopic properties (MS, IR, NMR) consistent with their assigned structures. In particular, it was important to distinguish relative stereochemistry around the dioxabicyclo[3.3.0]octane ring system. The spectroscopic properties of this natural product class have been extensively and carefully studied by Ahmad. In Table 1 are listed the chemical shifts for the protons of this substructure in both the acetates and alcohols in $CDCl_3$. Keys to distinguishing the stereoisomers include the C-3 and C-3a signals of the alcohols, which are downfield in the *endo* diastereomers and upfield in the *exo* diastereomers. The acetate chemical shifts are also quite distinctive, appearing at ~2.2 ppm in *exo* diastereomers and ~1.5 ppm in *endo* diastereomers. The latter is presumably due to the folding of the dioxabicyclo[3.3.0]octane ring system under the aromatic nucleus, placing the acetate into a shielding region. In Table 2 are listed carbon chemical shifts for this substructure in both the acetates and alcohols. Here, the C-3 chemical shift is indicative of the relative stereochemistry.

In the optically-active series, a synthon for the terminal dimethyltetrahydrofuran ring of these metabolites was readily

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Table 2. Carbon NMR signals for the furo[2,3-*b*]furan rings of *Tephrosia* natural products[a]

	C-3	C-3a	C-8a	C-2	C-2-Me	C-2-Me'
pseudosemi-glabrin	76.86	47.97	108.94	84.65	23.15	27.61
semiglabrin	80.24	52.83	109.02	87.80	23.21	27.47
pseudosemi-glabrinol[b]	77.10	48.70	108.15	85.01	22.92	27.38
semiglabrinol[b]	80.0	54.8	108.6	88.4	23.2	27.4
multijugin	80.2	52.8	109.3	88.0	23.1	27.5
purpurin	80.37	52.39	105.04	87.65	23.09	27.46
synthetic pseudo-semiglabrin	76.86	47.97	108.94	84.65	23.15	27.61
synthetic pseudo-semiglabrinol	78.90	49.71	108.75	85.61	22.85	22.70
synthetic semi-glabrin	80.10	52.74	109.00	87.76	23.06	27.4
synthetic semi-glabrinol	80.90	54.93	109.05	88.19	22.92	27.30

[a] Spectra run in $CDCl_3$ unless otherwise indicated. [b] Run in $CDCl_3$–DMSO-d_6 (3:1).

Scheme 2
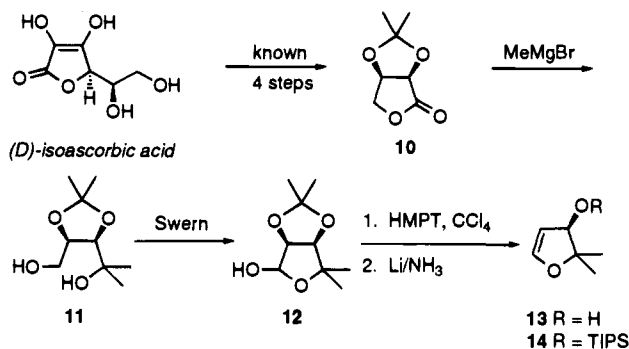
prepared from erythronolactone acetonide (**10**), itself obtained on large scale in four simple steps from isoascorbic acid in 67% yield (Scheme 2).[13] Grignard addition gives the primary–tertiary alcohol **11a** (86%) and a small (9%) but consistent amount of the monoaddition product hemiketal **11b**. The former can be selectively oxidized to the lactol **12** using the Swern modification of the Moffatt oxidation (60%). Using the methodology of Ireland,[14] the lactol was reductively eliminated to give the quite volatile dihydrofuran **13** (79%), which on silylation provided triisopropylsilyl ether **14** (80%).

The rhodium-mediated cycloaddition of **1** with **14** (2 equiv in fluorobenzene) proceeds in acceptable yield (48%) to provide a single stereoisomer (Scheme 3). The *exo* oxygen stereochemistry depicted in **15**, predicted on the assumption that cycloaddition would occur from the face of the alkene opposite the bulky TIPS group, was supported by spectroscopic data showing chemical shifts of 4.28, 3.60, and 6.32 ppm for the C-3, C-3a, and C-8a protons, respectively. The latter are coupled with a ~7 Hz coupling constant, as expected for a *cis* ring junction, but the fact that there is no coupling observed between the ethereal proton at 4.28 ppm and the bridgehead shows that they

Scheme 3
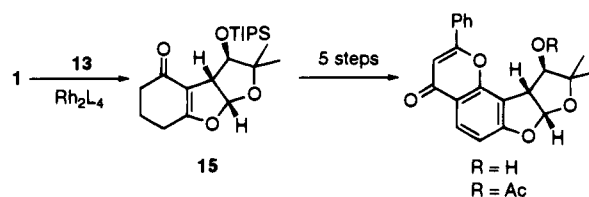
have a ~90° dihedral angle and distinguishes this structure from the pseudosemiglabrin stereochemistry. This trend, previously noted in the work of Vleggaar, was observed throughout the compounds prepared in this study, where the pseudosemiglabrin stereochemistry leads to a double doublet signal with two substantial coupling constants for the bridgehead methine. By the same route applied to its diastereomer **5**, **15** was converted to semiglabrinol and semiglabrin. Spectroscopic data for these substances also compared favorably with those published for the natural products, and direct comparison by IR and NMR proved their identity. Since these targets were obtained from a starting material of known absolute configuration, the absolute configuration of the semiglabrins could now be addressed. Circular dichroism spectra (Figures S1 and S2 in the Supplementary Material) and optical rotations obtained on both showed negative rotations, the same as that of the natural product. Therefore, the absolute configurations of semiglabrinol and semiglabrin are 3*R*,3a*R*,8*R*, opposite that depicted in the Introduction.

The diastereoselectivity (favoring the sterically-controlled pathway) of the dipolar cycloaddition with a chiral, holemic alkene in the synthesis of semiglabrin suggested the possibility to access a similar optically-active intermediate toward pseudosemiglabrin. The factors controlling the stereochemistry of this process would necessarily be attractive rather than repulsive, so the concept of a directed cycloaddition arose. In fact, carbenoid additions "directed" by neighboring hydroxyl groups are one of the oldest stereoselective reactions, the classic example being the Simmons–Smith cyclopropanation of cyclohexenol.[15] It was envisioned that preequilibrium formation of a complex (based on either hydrogen-bonding of a carbonyl to the O–H group or Lewis acid–base interaction between the carbenoid carbon and the oxygen) could deliver the carbenoid to the *syn* face of the alkene in **13**, but the presence of this hydroxyl also posed a danger that O–H insertion might occur. The fact that relative reactivity with other functional groups is not among the data available concerning the dipolar cycloaddition of cyclic diazo carbonyls provided another motivation for attempting such a reaction. In the event, the reaction of **1** with **13** mediated by rhodium acetate produces a single diastereomeric product (**16**) in 51% yield (Scheme 4). The spectroscopic properties of **16** compare favorably to **4** and are distinct from the semiglabrin (*exo*) series. Compound **16** also has the desired pseudosemiglabrin stereochemistry, as repetition of the sequence used in the racemic series provided optically-active pseudosemiglabrinol and pseudosemiglabrin. Circular dichroism spectra (Figures S3 and S4 in the Supplementary Material) and optical rotations obtained on both showed positive rotations, opposite the values for the natural products. Therefore, the absolute configuration of natural pseudosemiglabrinol and pseudosemiglabrin is 3*S*,3a*R*,8a*R*. It is worth emphasis that this sequence provides not only the second possible diastereomer at the alcohol center but the opposite *enantiomer* at the difficult-

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Scheme 4
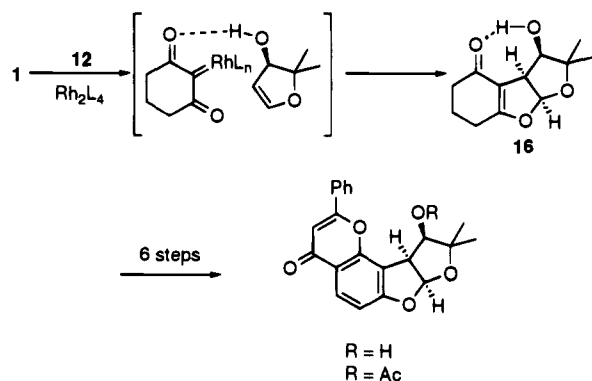
to-modify ring junction, and in principle provides access to the other enantiomer of semiglabrin by an oxidation—reduction sequence.

Conclusion

We have through three stereorational syntheses obtained four *Tephrosia* metabolites in optically-active form. The overall yield of (+)-pseudosemiglabrin from erythronolactone acetonide was 5% in 11 steps, and that of (−)-semiglabrin was 5.3% in 11 steps. These syntheses have permitted the assignment of the 3aR,8aR *absolute* configuration to all four natural products. A particular novelty of the pseudosemiglabrin synthesis is the chelation-controlled, rhodium-mediated dipolar cycloaddition.

Experimental Section

All experiments were carried out under a nitrogen or argon atmosphere. Tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were distilled from sodium/benzophenone immediately prior to use. Pyridine, methylene chloride, and dimethyl sulfoxide were distilled from calcium hydride. Merck precoated silica gel plates (Art. 5554) with fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385-9 (Merck). Melting points were determined in capillary tubes on a Haake Buchler apparatus and are corrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on GE QE-300 (300 MHz) and Varian XL-300 (300 MHz) spectrometers, using CDCl$_3$ solvent with residual protium as the internal standard (7.26 ppm). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a GE QE-300 (75 MHz) spectrometer in CDCl$_3$ using 77.0 ppm as the solvent chemical shift. IR spectra were recorded on a Bomem MB-100 Series FTIR. Low-resolution CI mass spectra were performed on a Hewlett-Packard 5988A with 1.0% NH$_3$ in methane with a source temperature of 150 °C. High-resolution mass spectra (HRMS) were obtained on a JEOL J MS-SX 102A spectrometer. Optical rotations were measured with a Perkin-Elmer 411 polarimeter. CD spectra were measured on solutions in methanol (AVIV 62DS).
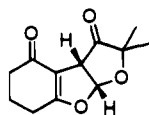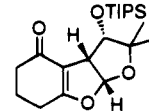

(3aS*,8aR*)-2,2-Dimethyl-2,3,3a,6,7,8a-hexahydro-5H-1,8-dioxa-cyclopent[a]indene-3,4-dione (3). To a solution of rhodium acetate (0.192 g, 0.43 mmol) in 2,2-dimethyl-3(2H)-furanone (4.871 g, 43.44 mmol) in PhF (50 mL) was added a solution of 2-diazo-1,3-cyclohexanedione (3.0 g, 21.7 mmol) in PhF (4 mL) at room temperature. The reaction mixture was stirred for 10 h. Evaporation and filtration by Celite with 25% ethyl acetate in hexane afforded a viscous oil which upon treatment with 20% ether in hexane gave 2.703 g (56%) of a gummy solid: ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.52 (d, J = 6.6 Hz, 1H), 3.95 (d, J = 6.6 Hz, 1H), 2.54—2.01 (m, 6H), 1.32 (s, 6H); IR (KBr) 2956, 1740, 1628, 1397, 1330, 1186, 1132, 1100, 915

cm^{-1}; EIMS m/z (rel intens) 222 (M$^+$, 100), 204 (14), 179 (22), 176 (13), 152 (11), 136 (10), 124 (4), 108 (4); HRMS m/z (M$^+$) for C$_{12}$H$_{14}$O$_4$, calcd 222.0892, found 222.0894. This material was relatively unstable, undergoing β-elimination, so was not subjected to combustion analysis.
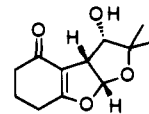
(3S*,3aR*,8aR*)-2,2-Dimethyl-3-hydroxy-2,3,3a,6,7,8a-hexahydro-5H-1,8-dioxacyclopent[a]inden-4-one (4). To a stirring solution of the diketone 3 (1.50 g, 6.75 mmol) in 40 mL of methanol at 0 °C under N$_2$ was added slowly sodium borohydride (0.765 g, 20.2 mmol). The resulting solution was stirred in the ice bath for 1 h and at room temperature for an additional 1 h. A saturated solution of NH$_4$Cl (10 mL) was added, and the reaction mixture was concentrated to give a residue that was dissolved in EtOAc, washed with brine, dried, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (elution with 50% ethyl acetate in hexane) to give 4 (1.347 g, 89%): ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.18 (d, J = 6.6 Hz, 1H), 4.20 (d, J = 8.1 Hz, 1H), 3.94 (dd, J = 8.1, 6.6 Hz, 1H), 2.50 (m, 2H), 2.43 (m, 2H), 2.09 (m, 2H), 1.32 (s, 3H), 1.18 (s, 3H); IR (neat) 3392, 2949, 1623, 1426, 1407, 1381, 1316, 1235, 1185, 1118, 1084, 1060, 1006, 906, 815 cm^{-1}; IR (CCl$_4$) 3625 cm^{-1}; EIMS m/z (rel intens) 224 (M$^+$, 30), 206 (M$^+$ − H$_2$O, 13), 191 (6), 163 (31), 153 (6), 137 (100), 128 (20), 98 (4), 72 (15), 57 (5); HRMS m/z (M$^+$) for C$_{12}$H$_{16}$O$_4$, calcd 224.1049, found 224.1055. Anal. Calcd for C$_{12}$H$_{16}$O$_4$: C, 64.27; H, 7.19 C, 64.09; H, 7.32.

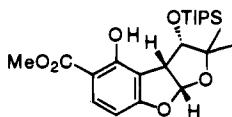**(3S*,3aR*,8aR*)-2,2-Dimethyl-3-(triisopropylsiloxy)-2,3,3a,6,7,-8a-hexahydro-5H-1,8-dioxa-cyclopent[a]inden-4-one (5).** A solution of the alcohol 4 (0.60 g, 2.7 mmol), (TIPS)Cl (0.773 g, 4.01 mmol), imidazole (0.911 g, 13.4 mmol), and DMAP (5 mg) in 20 mL of DMF was heated for 4 h at 50 °C. The reaction was quenched by the addition of a saturated NH$_4$Cl solution (30 mL). The mixture was extracted with ether (3 × 50 mL), and the combined organic layers were washed with brine, dried over MgSO$_4$, filtered, and evaporated under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel (elution with 20% ethyl acetate in hexane) to give 5 (0.733 g, 72%) as a colorless solid: mp 70—72 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.13 (d, J = 6.8 Hz, 1H), 4.34 (d, J = 8.7 Hz, 1H), 3.82 (dd, J = 8.7, 6.8 Hz), 2.43—2.26 (m, 4H), 2.01 (m, 2H), 1.31 (s, 3H), 1.19 (s, 3H), 1.18—1.15 (m, 3H), 1.09 (d, J = 12.2 Hz, 12H), 1.07 (d, J = 12.2 Hz, 6H); IR (KBr) 2944, 2867, 1662, 1632, 1462, 1405, 1229, 1144, 1096, 1007, 911, 883 cm^{-1}; EIMS m/z (rel intens) 395 (M$^+$ − iPr, 100), 369 (8), 337(6), 279 (25), 212 (2), 195 (7), 151 (4), 112 (2), 103 (3), 75 (2); HRMS m/z (M$^+$ − iPr) for C$_{18}$H$_{29}$O$_4$Si, calcd 337.1835, found 337.1834. Anal. Calcd for C$_{18}$H$_{29}$O$_4$Si: C, 66.27; H, 9.53. Found: C, 66.17; H, 9.58.
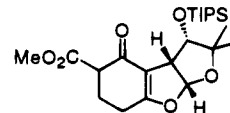
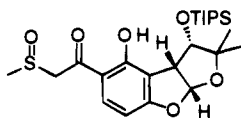**(3S*,3aR*,8aR*)-2,2-Dimethyl-3-(triisopropylsiloxy)-5-(methoxy-carbonyl)-2,3,3a,6,7,8a-hexahydro-5H-1,8-dioxacyclopent[a]inden-4-one (6).** To a stirring suspension of sodium hydride (0.220 g, 5.50 mmol, 60% dispersion in mineral oil) and potassium hydride (0.050 g, 35 wt % dispersion in mineral oil) in dry DME (25 mL) under a N$_2$ atmosphere was added a solution of triisopropylsilyl ether 5 (0.211 g, 0.55 mmol) in dry DME (3 mL) at 0 °C. The mixture was stirred for 30 min, and dimethyl carbonate (0.495 g, 5.50 mmol) was added slowly over 10 min. The ice bath was removed, and the reaction mixture was heated slowly to reflux over 30 min and maintained at reflux for a

further 30 min. After the mixture had cooled, water (10 mL) and saturated NH₄Cl solution (30 mL) were added carefully dropwise and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over MgSO₄, and evaporated under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel (elution with 20% ethyl acetate in hexane) to give a 2.3:1 mixture of the C-5-diastereomers 6 (0.182 g, 75%). Major diastereomer: white solid, mp 73−74 °C; R_f 0.40, 20% ethyl acetate in hexane; ¹H NMR (300 MHz, CDCl₃) δ 6.18 (d, J = 6.9 Hz, 1H), 4.36 (d, J = 8.9 Hz, 1H), 3.84 (dd, J = 8.9, 6.9 Hz), 3.74 (s, 3H), 3.46 (t, J = 2.0 Hz, 1H), 2.61−2.21 (m, 4H), 1.32 (s, 3H), 1.24 (s, 3H), 1.22−1.15 (m, 3H), 1.10 (d, J = 12.6 Hz, 12H), 1.07 (d, J = 12.6 Hz, 6H); IR (KBr) 2948, 2867, 1746, 1666, 1631, 1457, 1400, 1321, 1229, 1149, 1097, 1015, 912, 882 cm⁻¹; EIMS m/z (rel intens) 337 (M⁺ − iPr, 100), 309 (19), 267 (16), 253 (18), 207 (1), 185 (2), 157 (1), 137 (6), 103 (2), 75 (1), 61 (1); HRMS m/z (M⁺ − iPr) for C₂₀H₃₁O₆Si, calcd 395.1890, found, 395.1895. Minor diastereomer: R_f 0.43, 20% ethyl acetate in hexane; ¹H NMR (300 MHz, CDCl₃) δ 6.21 (d, J = 6.9 Hz, 1H), 4.37 (d, J = 8.8 Hz, 1H), 3.85 (dd, J = 8.8, 6.8 Hz), 3.75 (s, 3H), 3.50 (t, J = 2.0 Hz, 1H), 2.42−2.20 (m, 4H), 1.32 (s, 3H), 1.20 (s, 3H), 1.25−1.15 (m, 3H), 1.10 (d, J = 12.6 Hz, 12H), 1.07 (d, J = 12.6 Hz, 6H). Anal. Calcd for C₂₀H₃₁O₆Si: C, 62.98; H, 8.73. Found: C, 63.00; H, 8.63.


(3S*,3aR*,8aR*)-2,2-Dimethyl-3-(triisopropylsiloxy)-5-(methoxycarbonyl)-2,3,3a,8a-tetrahydro-1,8-dioxacyclopent[a]inden-4-ol (7). A mixture of 6 (0.205 g, 0.47 mmol) and DDQ (0.222 g, 0.93 mmol) in dry dioxane (20 mL) was heated under reflux for 5 h. The resulting mixture was cooled in an ice bath, and solids were removed by filtration through Celite. The filtrate was evaporated under reduced pressure and purified by flash column chromatography on silica gel (elution with 10% ethyl acetate in hexane) to give 7 (0.151 g, 74%) as a colorless solid: mp 75−76 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.72 (d, J = 8.7Hz, 1H), 6.33 (d, J = 8.7 Hz, 1H), 6.28 (d, J = 6.5 Hz, 1H), 4.90 (d, J = 8.7 Hz, 1H), 4.15 (dd, J = 8.7, 6.5 Hz, 1H), 3.89 (s, 3H), 1.20−1.13 (m, 3H), 1.10 (s, 3H), 1.07 (s, 3H), 1.04 (18H); IR (KBr) 3201, 2950, 2867, 1670, 1630, 1492, 1446, 1372, 1350, 1272, 1196, 1139, 1064, 996, 932, 883, 860 cm⁻¹; EIMS m/z (rel intens): 393 (M⁺ − iPr, 66), 361 (100), 359 (20), 291 (14), 282 (11), 220 (12), 201 (10), 151 (16), 131 (97), 103 (17), 75 (12), 51 (7); HRMS m/z (M⁺ − iPr) for C₂₀H₂₉O₆Si, calcd 393.1733, found 393.1745. Satisfactory combustion analysis could not be obtained for this material.

(3S*,3aR*,8aR*)-2,2-Dimethyl-3-(triisopropylsiloxy)-5-[(methylsulfinyl)acetyl]-2,3,3a,8a-tetrahydro-1,8-dioxacyclopent[a]inden-4-ol (8). A mixture of dry DMSO (1 mL) and sodium hydride (0.065 g, 2.58 mmol, 95%) in dry benzene (20 mL) was heated under reflux for N₂ for 2 h at 80 °C. The solution was cooled to 35 °C and treated dropwise with 7 (0.113 g, 0.26 mmol) in dry benzene (3 mL). The reaction mixture was then stirred for 1 h, diluted with ether (50 mL), and quenched with a saturated solution of NH₄Cl (30 mL). The organic and aqueous layers were separated, and the aqueous layer was further extracted with ether (3 × 30 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and evaporated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (elution with ethyl acetate) to give 8 (0.106 g, 85%) as a gummy solid: ¹H NMR (300 MHz, CDCl₃) δ 7.62 (d, J = 8.8Hz, 1H), 6.42 (d, J = 8.8 Hz, 1H), 6.31 (d, J = 6.5 Hz, 1H), 4.49 (d, J = 8.7 Hz, 1H), 4.37 (d, J = 13.5 Hz, 1H), 4.19 (dd, J = 8.7, 6.5 Hz, 1H), 4.16 (d, J = 13.5 Hz, 1H), 2.71 (s, 3H), 1.33 (s, 3H), 1.28−0.99 (24H); IR (neat) 3401, 2947, 2887, 1627, 1489, 1438, 1482, 1321, 1277, 1221, 1141, 1086, 1022, 922, 932, 883, 857 cm⁻¹; EIMS

m/z (rel intens) 439 (M⁺ − iPr, 66), 377 (30), 376 (100), 333 (26), 317 (6), 232 (6), 201 (6), 182 (6), 170 (5), 113 (4), 51 (5); HRMS m/z (M⁺ − iPr) for C₂₁H₃₁O₆ SiS, calcd 439.1611, found 439.1613.
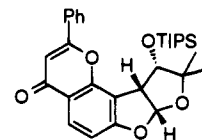
O-3-(Triisopropylsilyl)pseudosemiglabrinol (9). Benzaldehyde (0.199 g, 1.87 mmol) in 2 mL of dry toluene was slowly added to a warm solution (40 °C) of 8 (90 mg, 0.19 mmol) in dry toluene (20 mL) containing a catalytic amount of piperidine (4 drops), and the resulting mixture was allowed to reflux for 3 h. After distillation of the solvent, the residue was purified by flash column chromatography on silica gel (elution with 20% ethyl acetate in hexane) to give 9 (77 mg, 80%) as a white solid: mp 159−160 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.12 (d, J = 8.7Hz, 1H), 7.80 (m, 2H), 7.52 (m, 3H), 6.89 (d, J = 8.6 Hz, 1H), 6.66 (s, 1H), 6.48 (d, J = 6.3 Hz, 1H), 4.57 (d, J = 8.8Hz, 1H), 4.42 (dd, J = 8.8, 6.4 Hz, 1H), 1.38 (s, 3H), 1.22 (s, 3H), 0.88−0.62 (21H); IR (KBr) 2947, 2867, 1634, 1601, 1448, 1387, 1249, 1127, 1076, 917, 883, 853 cm⁻¹; EIMS m/z (rel intens) 506 (M⁺, 1), 463 (61), 435 (100), 433 (12), 394 (11), 379 (8), 275 (3), 262 (2), 220 (1), 201 (6), 185 (2), 151 (2), 141 (1), 113 (1); HRMS m/z (M⁺) for C₃₀H₃₈O₅Si, calcd 506.2488, found 506.2477, (M⁺ − iPr) for C₂₇H₃₁O₅Si, calcd 463.1941, found 463.1942. Satisfactory combustion analysis could not be obtained for this material.

(±)-Pseudosemiglabrinol. To a stirring solution of 9 (76 mg, 0.12 mmol) in THF (10 mL) at room temperature was added tetrabutylammonium fluoride (1 mL, 1.0 M in THF). The reaction mixture was stirred overnight and quenched with saturated NH₄Cl solution (30 mL). The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and evaporated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (elution with 50% ethyl acetate in hexanes) to give (±)-pseudosemiglabrinol (41 mg, 94%) as a white solid: mp 229−230 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.77−7.73 (m, 3H), 7.47−7.41 (m, 3H), 6.79 (d, J = 8.6 Hz, 1H), 6.46 (d, J = 6.1 Hz, 1H), 6.37 (s, 1H), 4.48 (m, 2H), 1.44 (s, 3H), 1.30 (s, 3H); ¹H NMR (300 MHz, CDCl₃-DMSO d₆ (3:1)): δ 8.10−7.93 (m, 3H), 7.45 (m, 3H), 6.80 (d, J = 8.5Hz, 1H), 6.61 (s, 1H), 6.36 (d, J = 6.0 Hz, 1H), 4.40 (m, 2H), 1.27 (s, 3H), 1.00 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 177.63, 165.13, 162.84, 153.88, 131.54, 131.43, 129.00, 129.00, 128.41, 126.11, 126.11, 117.93, 112.18, 111.69, 108.75, 106.86, 85.61, 78.90, 49.71, 27.76, 22.85; IR (KBr) 3432, 2978, 1632, 1633, 1593, 1492, 1449, 1394, 1321, 1124, 1119, 1102, 1080, 920 cm⁻¹.

(±)-Pseudosemiglabrin. A solution of (±)-pseudosemiglabrinol (30 mg, 0.09 mmol), acetic anhydride (0.1 mL), Et₃N (0.5 mL), and 4-(N,N-dimethylamino)pyridine (5 mg) in 2 mL of CH₂Cl₂ was stirred for 10 h at room temperature. Dilution with CH₂Cl₂ was followed by washing with saturated NH₄Cl solution and brine and drying over MgSO₄. Concentration under reduced pressure gave a viscous oil which on trituration with 20% ethyl ether in hexane afforded 31 mg (93%) of (±)-pseudosemiglabrin as a colorless solid: mp 199−200 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.17 (d, J = 8.5 Hz, 1H), 7.82 (m, 2H), 7.51 (m, 3H), 6.93 (d, J = 8.6 Hz, 1H), 6.74 (s, 1H), 6.50 (d, J = 6.5 Hz, 1H), 5.56 (d, J = 8.7 Hz, 1H), 4.61 (d, J = 6.6 Hz, 1H), 1.46 (s, 3H), 1.37 (s, 3H), 1.12 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 177.56, 169.83, 164.53, 162.65, 153.80, 131.75, 131.34, 129.12, 129.12, 128.79, 126.18, 126.18, 118.39, 111.78, 111.52, 108.97, 107.60, 84.60, 76.78, 47.92, 27.57, 23.19, 20.31; IR (KBr) 2979, 1744, 1638, 1600, 1450, 1362, 1230, 1087, 917 cm⁻¹.
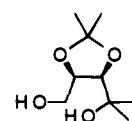
(4R,5R)-2,2-Dimethyl-4-(2-hydroxyisopropyl)-1,3-dioxane-5-methanol (11). Lactone 10 (20.0 g, 126 mmol) was dissolved in THF (400

mL), and methylmagnesium bromide (126.5 mL, 3 M in diethyl ether, 379.4 mmol) was added dropwise over 20 min at 0 °C under N$_2$. The reaction was stirred at room temperature for 5 h and quenched with saturated NH$_4$Cl solution (70 mL) at 0 °C. The organic and aqueous layers were separated, and the aqueous layer was further extracted with ether (3 × 100 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, filtered, and evaporated under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel (elution with 50% ethyl acetate in hexanes) to give **11a** (24.058 g, 86%) as a colorless oil and **11b** (1.983 g, 9%) as a white solid. **11a**: [α]$^{23}_D$ + 46.4° (c 3.31, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.16 (m, 1H), 3.90 (d, J = 5.6 Hz, 1H), 3.76 (dd, J = 12.0, 6.5 Hz, 1H), 3.64 (dd, J = 12.0, 5.4 Hz, 1H), 3.23 (br s, OH, 2H), 1.45 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H); IR (neat) 3360, 2984, 2939, 1376, 1245, 1219, 1168, 1075, 1046, 960, 936, 877 cm^{-1}; EIMS m/z (rel intens) 175 (M$^+$ − CH$_3$, 22), 159 (9), 131 (18), 117 (11), 101 (32), 99 (9), 74(13), 59 (100); HRMS m/z M$^+$ − CH$_3$) for C$_8$H$_{15}$O$_4$, calcd 175.0970, found 175.0971. Anal. Calcd for C$_8$H$_{15}$O$_4$: C, 56.82; H, 9.54. Found: C, 56.86; H, 9.57. **11b**: mp 86−87 °C; [α]$^{23}_D$ −91.4° (c 0.70, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.86 (m, 1H), 4.41 (d, J = 5.9Hz, 1H), 4.05 (dd, J = 10.3, 3.8 Hz, 1H), 3.93 (d, J = 10.3 Hz, 1H), 1.56 (s, 3H), 1.49 (s, 3H), 1.33 (s, 3H); IR (KBr) 3490, 2970, 1377, 1331, 1206, 1164, 1100, 1071, 1049, 1015, 852 cm^{-1}; CIMS m/z 157 [(M+ H − H$_2$O)$^+$], 175 [(M + H)$^+$], 192 [(M + NH$_4$)$^+$].
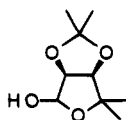

(1R,4R)-3,3,8,8-Tetramethyl-6-hydroxy-2,4,7-trioxabicyclo[3.3.0]-octane (12). To a solution of oxalyl chloride (13.211 g, 104.08 mmol) in 200 mL of CH$_2$Cl$_2$ at −78 °C was added DMSO (16.263 g, 208.16 mmol). After 5 min diol **11a** (18.0 g, 94.62 mmol) was added as a solution in 5 mL of CH$_2$Cl$_2$. After an additional 15 min triethylamine (95.74 g, 946. 17 mmol) was added. Stirring for 30 min at −78 °C was followed by stirring at 0 °C for 30 min. The reaction was quenched by the addition of water (60 mL). The organic and aqueous layers were separated, and the aqueous layer was further extracted with CH$_2$Cl$_2$ (3 × 60 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, filtered, and evaporated under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel (elution with 30% ethyl acetate in hexanes) to give the two diastereomers **12** (10.685 g, 60%). Major diastereomer: ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.34 (s, 1H), 4.69 (d, J = 5.8 Hz, 1H), 4.40 (d, J = 5.9 Hz, 1H), 3.85 (br s, OH, 1H), 1.45 (s, 3H), 1.33 (s, 3H), 1.29 (s, 3H), 1.27(s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 112.18, 102.30, 87.39, 85.82, 79.47, 28.50, 26.18, 24.83, 23.14; IR (neat) 3425, 2984, 2938, 1463, 1377, 1254, 1211, 1158, 1077, 1012, 878 cm^{-1}; CIMS m/z 171 [(M + H − H$_2$O)$^+$, 189 [(M + H)$^+$], 206 [(M + NH$_4$)$^+$]; HRMS m/z M$^+$ − CH$_3$) for C$_8$H$_{13}$O$_4$, calcd 173.0814, found 173.0822. Anal. Calcd for C$_8$H$_{13}$O$_4$: C, 57.43; H, 8.57. Found: C, 57.47; H, 8.45. Minor diastereomer: ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.14 (d, J = 5.9 Hz, 1H), 4.59 (dd, J = 6.0, 5.9 Hz, 1H), 4.32 (d, J = 6.0 Hz, 1H), 3.85 (br s, OH, 1H), 1.52 (s, 3H), 1.34 (s, 3H), 1.27 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 112.99, 95.12, 85.56, 84.79, 78.37, 28.46, 25.82, 24.67, 22.26.


(3R)-2,2-Dimethyl-2,3-dihydro-2H-furan-3-ol (13). To a stirring solution of lactol **12** (6.510 g, 34.59 mmol) and CCl$_4$ (5.20 mL, 53.89 mmol) in 100 mL of dry THF at −78 °C under an argon atmosphere was added HMPT (7.02 mL, 38.6 mmol). After 30 min the mixture was warmed in an ice bath. After 3 min at 0 °C, the entire reaction mixture was taken up in an argon-flushed syringe and added rapidly to a cold (−78 °C), stirring solution of lithium (3.01 g, 434 mmol) in 400 mL of anhydrous NH$_3$. The cooling bath was removed, and after 2 h of ammonia reflux, solid NH$_4$Cl (31.20 g, 583.3 mmol) was added

to the blue reaction mixture. The resulting colorless mixture was diluted with ether (400 mL) as the ammonia was allowed to evaporate, and anhydrous MgSO$_4$ (20 g) was added. The ethereal suspension was filtered, and the solids were washed with ether (2 × 30 mL). The combined filtrates were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (elution with 30% ether in pentane) to give **13** (3.119 g, 79%) as a colorless oil: [α]$^{23}_D$ −62.7° (c 12.40, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.48 (d, J = 2.7Hz, 1H), 5.07 (dd, J = 2.7, 2.6 Hz, 1H), 4.32 (d, J = 2.6 Hz, 1H), 1.38 (s, 3H), 1.25 (s, 3H); IR (neat) 3416, 2982, 2937, 1612, 1461, 1376, 1212, 1185, 1126, 1077, 918, 875 cm^{-1}; HRMS m/z M$^+$ − CH$_3$) for C$_5$H$_7$O$_2$, calcd 99.0446, found 99.0447.
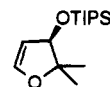
(3R)-2,2-Dimethyl-3-(triisopropylsiloxy)-2,3-dihydro-2H-furan (14). A solution of the alcohol **13** (1.740 g, 15.24 mmol), (TIPS)Cl (4.409 g, 22.86 mmol), imidazole (5.189 g, 76.22 mmol), and DMAP (5 mg) in 20 mL of DMF was heated for 4 h at 50 °C. The reaction was quenched by the addition of a saturated NH$_4$Cl solution (30 mL) and the mixture was extracted with ether (3 × 50 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, filtered, and evaporated under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel (elution with 5% ether in pentane) to give **14** (3.30 g, 80%) as a colorless oil: [α]$^{23}_D$ −112.7° (c 4.85, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.41 (d, J = 2.8 Hz, 1H), 4.96 (dd, J = 2.8, 2.4 Hz, 1H), 4.54 (d, J = 2.4 Hz, 1H), 1.37 (s, 3H), 1.25 (s, 3H), 1.08−1.17 (m, 3H), 1.04 (d, J = 4.7 Hz, 18H); IR (neat) 2946, 2868, 1613, 1463, 1383, 1369, 1256, 1127, 1094, 1054, 999, 888 cm^{-1}; HRMS m/z (M$^+$ − CH$_3$) for C$_{12}$H$_{23}$O$_2$Si, calcd 227.1467, found 227.1471.
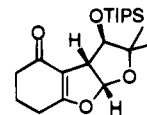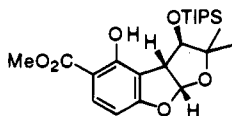

(3R,3aR,8aR)-2,2-Dimethyl-3-(triisopropylsiloxy)-2,3,3a,6,7,8a-hexahydro-5H-1,8-dioxacyclopent[a]inden-4-one (15). To a solution of rhodium acetate (52 mg, 0.12 mmol) and triisopropylsilyl ether **14** (3.20 g, 11.8 mmol) in PhF (30 mL) was added a solution of 2-diazo-1,3-cyclohexanedione (0.817 g, 5.92 mmol) in PhF (5 mL) at room temperature under N$_2$, and the reaction mixture was stirred for 10 h. Evaporation and purification by flash column chromatography on silica gel (elution with 20% ethyl acetate in hexane) gave **15** (0.552 g, 48%) as a colorless oil: [α]$^{22}_D$ −86.3° (c 1.10, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.32 (d, J = 6.6 Hz, 1H), 4.28 (s, 1H), 3.60 (d, J = 6.6 Hz, 1H), 2.41(m, 2H), 2.33 (m, 2H), 2.02 (m, 2H), 1.34 (s, 3H), 1.31−1.15 (m, 3H), 1.13 (s, 3H), 1.09 (d, J = 6.9Hz, 18H); IR (neat): 2945, 2868, 1657, 1632, 1462, 1424, 1404, 1369, 1242, 1105, 997, 925, 883 cm^{-1}; EIMS m/z (rel intens) 337 M$^+$ − CH$_3$, 100), 309 (32), 266 (74), 251(30), 223 (60), 196 (19), 181 (11), 137 (12), 131 (5), 71 (7), 61 (2); HRMS m/z M$^+$ − CH$_3$) for C$_{18}$H$_{29}$O$_4$Si, calcd 337.1835, found 337.1833. Anal. Calcd for C$_{18}$H$_{29}$O$_4$Si: C, 66.27; H, 9.53. Found: C, 66.54; H, 9.50.
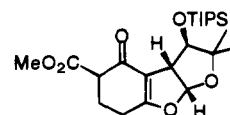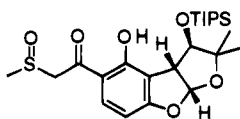

(3R,3aR,8aR)-2,2-Dimethyl-3-(triisopropylsiloxy)-5-(methoxycarbonyl)-2,3,3a,6,7,8a-hexahydro-5H-1,8-dioxacyclopent[a]inden-4-one. Applying the procedure for the preparation of **6** to triisopropylsilyl ether **15** on a 1.31 mmol scale gave a 1.85:1 mixture of the C-5-diastereomers (0.455 g, 79 %) as a colorless oil. Major isomer: ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.36 (d, J = 6.7 Hz, 1H), 4.29 (s, 1H), 3.72 (s, 3H), 3.60 (d, J = 6.7 Hz, 1H), 3.55 (t, J = 2.4 Hz, 1H), 2.51−2.24 (m, 4H), 1.35 (s, 3H), 1.31−1.21 (m, 3H), 1.20 (s, 3H), 1.09 (18H); IR (neat) 2946, 2867, 1743, 1660, 1636, 1461, 1401, 1242, 1101, 883

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cm⁻¹; EIMS *m/z* (rel intens) 395 M⁺ − CH₃, 100), 369 (11), 337 (5), 279 (5), 266 (93), 223 (67), 195 (211), 181 (10), 167 (7), 129 (3), 75(2), 51 (2); HRMS *m/z* M⁺ − CH₃) for C₁₈H₂₉O₄Si, calcd 337.1835, found 337.1833. Minor isomer: ¹H NMR (300 MHz, CDCl₃) δ 6.37 (d, *J* = 6.5 Hz, 1H), 4.27 (s, 1H), 3.77 (s, 3H), 3.65 (d, *J* = 6.5 Hz, 1H), 3.47 (t, *J* = 2.3 Hz, 1H), 2.51−2.24 (m, 4H), 1.35 (s, 3H), 1.31−1.21 (m, 3H), 1.20 (s, 3H), 1.09 (18H).

(3R,3aR,8aR)-2,2-Dimethyl-3-(triisopropylsiloxy)-5-(methoxycarbonyl)-2,3,3a,8a-tetrahydro-1,8-dioxacyclopent[a]inden-4-ol. Applying the procedure for the preparation of **7** to the preceding substance on a 0.65 mmol scale gave the title compound (0.202 g, 71%) as a colorless solid: mp 87−89 °C; [α]²⁴_D −57.1° (*c* 0.74, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 11.05 (s, OH, 1H), 7.73 (d, *J* = 8.9 Hz, 1H), 6.46 (d, *J* = 6.4 Hz, 1H), 6.37 (d, *J* = 8.6 Hz, 1H), 4.47 (s, 1H), 3.97 (d, *J* = 6.4 Hz, 1H), 3.90 (s, 3H), 1.36 (s, 3H), 1.27−1.11 (m, 3H), 1.10−1.04 (18H), 0.91 (s, 3H); IR (KBr) 3420, 2930, 2859, 1671, 1633, 1560, 1463, 1437, 1306, 1194, 1137, 1109, 992, 924, 881 cm⁻¹; HRMS *m/z* (M⁺ − iPr) for C₂₀H₂₉O₆Si, calcd 393.1733, found: 393.1729.

(3R,3aR,8aR)-2,2-Dimethyl-3-(triisopropylsiloxy)-5-[(methylsulfinyl)acetyl]-2,3,3a,8a-tetrahydro-1,8-dioxacyclopent[a]inden-4-ol. Applying the procedure for the preparation of **8** to the preceding substance on a 0.23 mmol scale gave 91 mg (82%) of the β-ketosulfoxide as a pale yellow solid: mp 128 °C; [α]²⁴_D −70.9° (*c* 1.16, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.63 (d, *J* = 8.7Hz, 1H), 6.51(d, *J* = 6.4 Hz, 1H), 6.45 (d, *J* = 8.7Hz, 1H), 4.45 (s, 1H), 4.30 (d, *J* = 14.7 Hz, 1H), 4.23 (d, *J* = 14.7 Hz, 1H), 3.96 (d, 1H, *J* = 6.3 Hz), 2.77 (s, 3H), 1.37 (s, 3H), 1.31−1.21 (m, 3H), 1.19−1.09 (18H), 0.93 (s, 3H); IR (KBr) 3398, 2944, 2867, 1629, 1607, 1489, 1408, 1369, 1314, 1282, 1095, 1031, 924, 882 cm⁻¹; EIMS *m/z* (rel intens) 395 (M⁺ − iPr, 100), 423 (53), 376 (65), 369 (20), 317 (13), 220 (8), 166 (9), 165 (8), 113 (6), 70 (4); HRMS *m/z* (M⁺ − iPr) for C₂₁H₃₁O₆Si S, calcd 439.1611, found 439.1613.
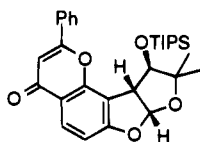

(−)-O-3-(Triisopropylsilyl)semiglabrinol. Applying the procedure for the preparation of **9** to the preceding substance on a 0.19 mmol scale gave 81 mg (84%) of the title compound as a pale yellow solid: mp 120−121 °C; [α]²⁴_D −151.0° (*c* 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.16 (d, *J* = 8.6 Hz, 1H), 7.74 (m, 2H), 7.51 (m, 3H), 6.95 (d, *J* = 8.6 Hz, 1H), 6.60 (s, 1H), 6.55 (d, *J* = 6.0 Hz, 1H), 4.59 (s, 1H), 4.23 (d, *J* = 5.9 Hz, 1H), 1.39 (s, 3H), 1.16−1.09 (m, 3H), 1.05−1.00 (18H), 0.90 (s, 3H); IR (KBr) 2945, 2866, 1650, 1604, 1450, 1378, 1341, 1243, 1205, 1116, 1069, 997, 951, 922 cm⁻¹; EIMS *m/z* (rel intens) 506 (M⁺, 10), 463 (100), 446 (30), 435 (28), 393 (15), 369 (15), 317 (10), 201 (81), 185 (8), 151 (7), 120 (3), 51 (3); HRMS *m/z* (M⁺) for C₃₀H₃₈O₅Si, calcd 506.2488, found: 506.2481, (M⁺ − iPr) for C₂₇H₃₁O₅Si, calcd 463.1941, found 463.1927.

(−)-Semiglabrinol. Applying the procedure used for pseudosemiglabrinol on a 0.15 mmol scale gave the natural product (50 mg, 95%) as a white solid: mp 241 °C (lit.⁴ᵈ mp 245−247 °C, lit.⁴ᵇ mp 245−246 °C); [α]²⁴_D −271.1° (*c* 0.90, CHCl₃) (lit.⁴ᵈ [α]²⁹_D −270 °, lit.⁴ᵇ [α]²⁸_D −267°); ¹H NMR (300 MHz, CDCl₃) δ 8.12 (d, *J* = 8.7 Hz, 1H), 7.92 (m, 2H), 7.55−7.53 (m, 3H), 6.91 (d, *J* = 8.6 Hz, 1H), 6.80 (s, 1H), 6.63 (d, *J* = 6, 5 Hz, 1H), 4.36 (s, 1H), 4.29 (d, *J* = 6.5 Hz, 1H), 1.41 (s, 3H), 1.05 (s, 3H); ¹H NMR (300 MHz, CDCl₃−DMSO-

d₆ (3:1)) δ 8.06−8.01 (m, 3H), 7.62−7.55 (m, 3H), 6.90 (d, *J* = 8.6 Hz, 1H), 6.79 (s, 1H), 6.59 (d, *J* = 6.6 Hz, 1H), 4.29 (d, *J* = 6.6 Hz, 1H), 4.29 (s, 1H), 1.38 (s, 3H), 1.00 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 177.68, 163.68, 162.40, 153.13, 131.73, 131.51, 129.40, 129.08, 128.29, 125.96, 125.81, 118.42, 113.70, 112.60, 109.05, 107.37, 88.19, 80.90, 54.93, 27.39, 22.92; IR (KBr) 3360, 2975, 1633, 1598, 1449, 1389, 1348, 1137, 1322, 1257, 1076, 1030, 911 cm⁻¹.

(−)-Semiglabrin. Applying the procedure used for the acetylation of racemic pseudosemiglabrinol to semiglabrinol on a 0.10 mmol scale gave the natural product (36 mg, 92%) as a colorless solid: mp 242−243 °C (lit.⁴ᶠ mp 253−256 °C, lit.⁴ᵈ mp 254−255 °C, lit.³ mp 248−250 °C, lit.⁴ᵇ mp 244−248 °C); [α]²⁴_D −272.0° (*c* 1.0, CHCl₃) (lit.⁴ᵇ [α]²⁵_D −265° (*c* 0.08, CHCl₃), lit.⁴ᶠ [α]²⁵_D −293° (*c* 0.42, CHCl₃), lit.³ [α]²⁵_D −273°, lit.⁴ᵈ [α]²⁵_D −263°); ¹H NMR (300 MHz, CDCl₃) δ 8.17-(d, *J* = 8.6 Hz, 1H), 7.92−7.87 (m, 2H), 7.53−7.50 (m, 3H), 6.93 (d, *J* = 8.6 Hz, 1H), 6.78 (s, 1H), 6.63 (d, *J* = 6,5 Hz, 1H), 5.64 (s, 1H), 4.29 (d, *J* = 6.4 Hz, 1H), 2.23 (s, 3H), 1.32 (s, 3H), 1.09 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 177.38, 169.56, 163.63, 162.77, 153.16, 131.44 131.44, 129.05, 128.91, 128.80 126.33, 126.23, 118.63, 113.70, 112.34, 112.34, 109.00, 107.68, 87.76, 80.10, 52.74, 27.40, 23.06, 20.78; IR (neat) 2931, 1739, 1641, 1603, 1448, 1437, 1380, 1234, 1074, 1034, 911 cm⁻¹.
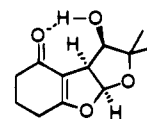

(3R,3aS,8aS)-2,2-Dimethyl-3-hydroxy-2,3,3a,6,7,8a-hexahydro-5H-1,8-dioxacyclopent[a]inden-4-one (16). To a solution of rhodium acetate (0.128 mg, 0.29 mmol) and the alcohol **13** (3.305 g, 23.93 mmol) in PhF (40 mL) was added a solution of 2-diazo-1,3-cyclohexanedione (2.0 g, 14 mmol) in PhF (5 mL) at room temperature under N₂. The reaction mixture was stirred for 10 h. Evaporation and purification by flash column chromatography on silica gel (elution with 50% ethyl acetate in hexanes) gave **16** (1.656 g, 51%) as a colorless oil: [α]²²_D +247.2° (*c* 2.14, CHCl₃). The spectroscopic data are consistent with those obtained earlier for **4**, the racemic modification.
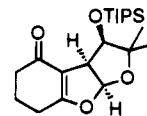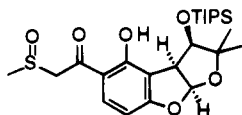

(3R,3aS,8aS)-2,2-Dimethyl-3-(triisopropylsiloxy)-2,3,3a,6,7,8a-hexahydro-5H-1,8-dioxacyclopent[a]inden-4-one. Applying the same procedure used earlier for **4** on a 3.43 mmol scale, alcohol **16** was converted to the title compound (0.941 g, 72%), obtained as a colorless solid: mp 102−103 °C; [α]²²_D +85.9° (*c* 6.01, CHCl₃).
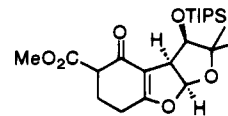

(3R,3aS,8aS)-2,2-Dimethyl-3-(triisopropylsiloxy)-5-(methoxycarbonyl)-2,3,3a,6,7,8a-hexahydro-5H-1,8-dioxacyclopent[a]inden-4-one. Applying the procedure used earlier for **5** to the preceding substance on a 0.66 mmol scale gave a 2.3:1 mixture of the C-5-diastereomers of the title compound (0.216 g, 75%) as a viscous oil. Spectroscopic data were as earlier reported.
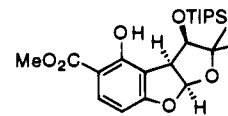
(3R,3aS,8aS)-2,2-Dimethyl-3-(triisopropylsiloxy)-5-(methoxycarbonyl)-2,3,3a,8a-tetrahydro-1,8-dioxacyclopent[a]inden-4-ol. Applying the procedure used for **6** to the preceding substance on a 0.43 mmol scale gave the title compound (0.140 g, 74%) as a colorless solid: mp 79−81 °C; [α]²²_D +75.0° (*c* 1.60, CHCl₃).

(3*R*,3a*S*,8a*S*)-2,2-Dimethyl-3-(triisopropylsiloxy)-5-[(methylsulfi-nyl)acetyl]-2,3,3a,8a-tetrahydro-1,8-dioxacyclopent[*a*]inden-4-ol. Applying the procedure used for **7** to the preceding substance on a 0.23 mmol scale gave the title compound (0.094 g, 85%) as a gummy solid: [α]^{22}$_D$ +102.2° (*c* 1.51, CHCl$_3$).
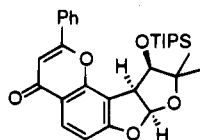
(+)-*O*-3-(Triisopropylsilyl)pseudosemiglabrinol. Applying the procedure used for **8** to the preceding substance on a 0.17 mmol scale gave the title compound (0.068 g, 80%) as a white solid: mp 162–163 °C; [α]^{22}$_D$ +198.3° (*c* 3.01, CHCl$_3$).

(+)-Pseudosemiglabrinol. Applying the procedure used for **9** to the preceding substance on a 0.10 mmol scale gave (+)-pseudosemi-glabrinol (34 mg, 94%) as a white solid: mp 268–270 °C, (lit.[4b] mp 270–272 °C); [α]^{22}$_D$ +320.0° (*c* 1.20, CHCl$_3$) (lit.[4b] [α]^{28}$_D$ −293°).

(+)-Pseudosemiglabrin. Applying the procedure used in the racemic series on a 0.60 mmol scale gave (+)-pseudosemiglabrin (21 mg, 93%) as a white solid: mp 169–171 °C, (lit.[4f] mp 181–183 °C, lit.[3] mp 173–175 °C, lit.[4b] mp 171–174 °C); [α]^{22}$_D$ +383.3° (*c* 0.61, CHCl$_3$) (lit.[4b] [α]^{25}$_D$ −328° (*c* 0.23, CHCl$_3$), lit.[4f] [α]^{25}$_D$ −384° (*c* 0.49, CHCl$_3$), lit.[3] [α]^{25}$_D$ −318°.[3]

Supplementary Material Available: Figures showing CD spectra for (+)-pseudosemiglabrinol, (+)-pseudosemiglabrin, (−)-semiglabrinol, and (−)-semiglabrin (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.