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Total Syntheses of (±)-Rhodonoids A and B and C12-*epi*-Rhodonoid B

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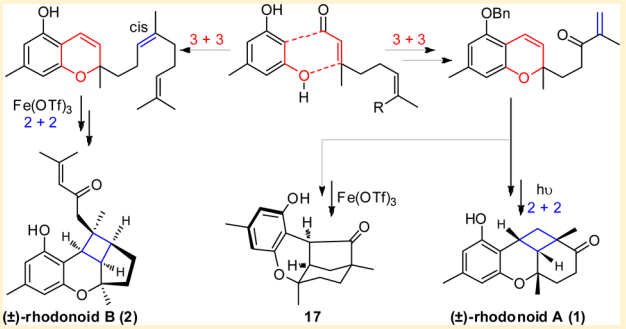
Supporting Information

ABSTRACT: Total syntheses of (±)-rhodonoids A and B and C12-*epi*-rhodonoid B are described here. A unified strategy employed in these syntheses is an intramolecular *oxa*-[3 + 3] annulation for accessing the chromene unit. A $Fe(OTf)_3$-promoted diastereoselective cationic [2 + 2] cycloaddition and a photochemical [2 + 2] cycloaddition were featured to construct the cyclobutane core of (±)-rhodonoids A and B and C12-*epi*-rhodonoid B, respectively. $Fe(OTf)_3$ also leads to an interesting bridged tetracycle, which was unambiguously confirmed by single crystal X-ray analysis.



INTRODUCTION

Isolated from various medicinal plants, chromanes and their derivatives are widely distributed in nature and are useful in the treatment of diverse ailments.[1] Within this family, cyclobutane-containing natural products fused with a chromane nucleus display a wide spectrum of biological activity, including cytotoxic, anti-HIV, antihistamine, anti-inflammatory, antiemetic, analgesic, and psychotropic effects.[2] Recently, (±)-rhodonoids A (**1**) and B (**2**) (Figure 1) were isolated from *Rhododendron capitatum* Maxim, a small deciduous shrub in the Qinghai province of China.[3] Preliminary biological data reported by the isolation chemists showed (+)-rhodonoid B and (−)-rhodonoid B to have moderate inhibitory effects on protein tyrosine phosphatase 1B (43.56 ± 8.53 and 30.38 ± 13.41 μM, respectively), which has been identified as a promising target against type 2 diabetes for decades.[4] Although (±)-rhodonoid A are inactive, they are the first examples of meromono-terpenes featuring a unique 6/6/6/4 ring system.

Our long-standing interests in developing a [3 + 3] annulation (or formal cycloaddition)[5,6] and thermal-cationic [2 + 2][7] cycloaddition reactions easily led us to chromene-containing natural products bearing a cyclobutane ring (Figure 1).[8] While these cyclobutane natural products, structurally similar to (±)- rhodonoid B, were achieved through intramolecular acid-promoted Gassman's cationic [2 + 2] cycloaddition, all of them differ from (±)-rhodonoid B at the C12 stereocenter.[1e,8a,d] Photochemical [2 + 2] cycloadditions have also been utilized for the preparation of the polycyclic

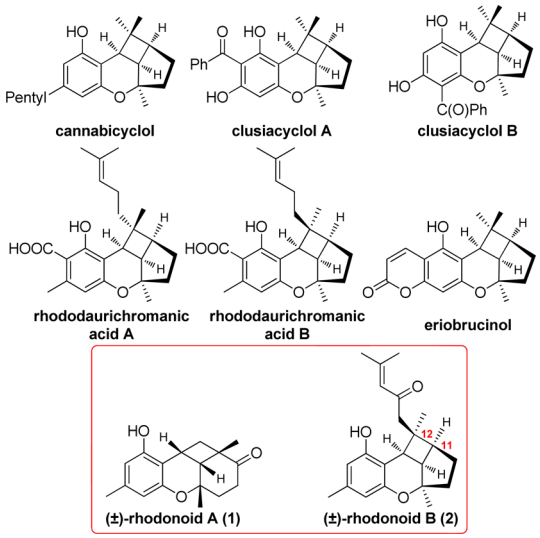


Figure 1. (±)-Rhodonoids A and B and related natural products.

nucleus.[8a,9] However, the reported photochemical intramolecular [2 + 2] cycloadditions sometimes provide cyclobutane products as mixtures of diastereomers. Herein, we wish to report the first total syntheses of (±)-rhodonoids A and B and C12-*epi*-rhodonoid B featuring an intramolecular *oxa*-[3 +

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3] annulation and a highly stereoselective [2 + 2] cycloaddition strategy.

RESULTS AND DISCUSSION

As outlined in Figure 2, we envisioned that the diastereoselectivity of C12 could be derived from isomerization of the

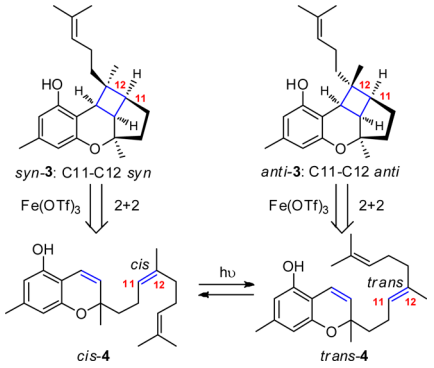
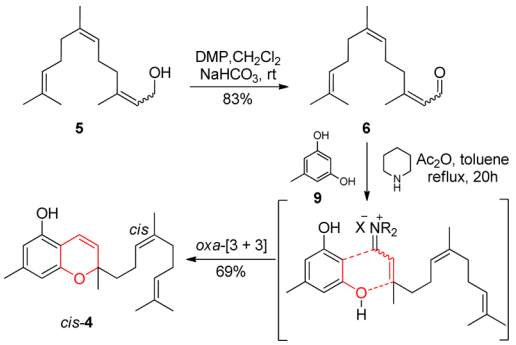


Figure 2. Bioinspired diastereoselective [2 + 2] cycloaddition.

C11−C12 olefin in a biogenetically relevant fashion.[2d] Based on our prior work with total synthesis of (±)-rhododaurichromanic acid A,[8d] we anticipated a highly diastereoselective event through a $Fe(OTf)_3$ promoted cationic [2 + 2] cycloaddition.

To confirm our strategy for the key intermediate *syn*-**3**, the synthesis of *cis*-**4** is outlined in Scheme 1. Dess−Martin

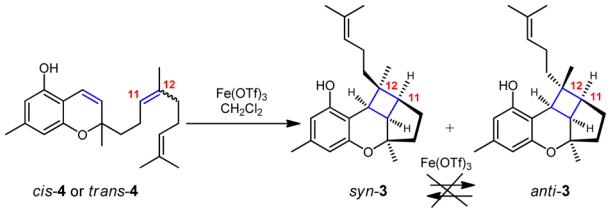
Scheme 1. An *oxa*-[3 + 3] Annulation Approach to *cis*-4



oxidation of (6*Z*)-farnesol **5**[10] led to the corresponding enal **6** as a 1:4 *cis*/*trans* isomeric mixture. The *oxa*-[3 + 3] annulation of **9** proceeded smoothly with the iminium salt generated from enal **6** using our piperidine and acetic anhydride conditions, providing *cis*-**4** in 57% yield.[8c]

With *cis*-**4** in hand, we then turned to a study of the critical cationic [2 + 2] cyclization reaction. An initial, unsuccessful attempt was highlighted in Table 1 (entry 1), which involved competing pathways. Diastereoisomer *anti*-**3** was found as the major product. However, treating *cis*-**4** with $Fe(OTf)_3$ at low temperature changed the outcome, especially when it was carried out under −20 °C (entries 2, 3), as the dr was raised to an acceptable 11:1 ratio. In an effort to further confirm the diastereoselectivity of the intramolecular [2 + 2] cycloaddition, we repeated the reaction (entries 4, 5) reported in our lab that was believed to provide a single product, *anti*-**3**.[8d] Although ignored before, we could indeed observe *syn*-**3** with $Fe(OTf)_3$ providing high diastereoselectivities (>10:1) at both ambient and low temperature.

Table 1. Diastereoselective Cationic [2 + 2] Cycloaddition

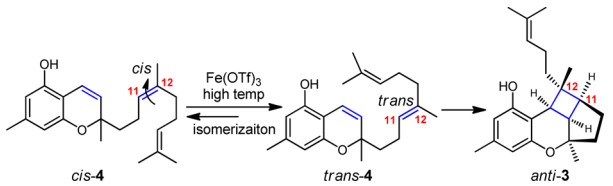


				yields(%) of:[a]		
entry	chromene	time (h)	temp (°C)	*syn*-3	*anti*-3	dr[b]
1	*cis*-4	12	rt	19	35	1:2
2	*cis*-4	12	−20	60	7	9:1
3	*cis*-4	12	−40	57	5	11:1
4	*trans*-4	4	rt	5	50	1:10
5	*trans*-4	4	−40	5	70	1:14

[a]Isolation yield. [b]Diastereomeric ratios (dr) were determined by ^1H NMR.

Mechanistically, the formation of *anti*-**3** via a reaction with *cis*-**4** may be the result of a Lewis acid-promoted *cis*/*trans* alkene isomerization rather than a stepwise cycloaddition reaction (Scheme 2).[11] Because of the thermodynamic nature,

Scheme 2. *Anti*-3 from Isomerization of *cis*-4



at higher temperature, the rate of *cis*/*trans* isomerization is even faster, and thus, the *cis*-isomer could start to scramble before any cycloaddition takes place. However, at low temperature, the rate of cationic [2 + 2] cycloaddition is faster than the isomerization. Thus, [2 + 2] cycloadditions of *cis*- and *trans*-alkene isomers would favor the opposite epimeric cycloadduct.

With *syn*-**3** in hand, the necessary allylic oxidation was installed through a nine-step procedure (Scheme 3). Electrophilic addition of benzenesulphenyl chloride was carried out by treating Ac-protected **3** with a mixture of thiophenol and *N*-chlorosuccinimide in dichloromethane at 0 °C.[12] Without further purification, the crude adduct was treated with sodium acetate in acetic acid glacial at ambient temperature for 1.5 h to provide the tertiary acetoxy sulfide **7**. Compound **7** was converted into the *trans*-allylic acetate **8** in 58% overall yield by oxidation with hydrogen peroxide (30%) in acetic acid glacial, followed by thermal elimination of the intermediary sulfoxide in toluene under reflux in the presence of sodium bicarbonate.[13] Deacetylation of **7** and a subsequent acetylation of the phenolic hydroxyl afforded the tertiary allylic alcohol **9**. To complete the total synthesis, tertiary allylic alcohol **9** was subjected to $TEMPO^+BF4^-$ oxidative conditions[14] to give α,β-unsaturated carbonyl **10** in 35% yield. Unfortunately, we could not improve the yield via other oxidative rearrangement conditions, such as $TEMPO/NaIO_4{\cdot}SiO_2$,[15] $TEMPO/CuCl_2$,[16] PCC, and PDC. Nevertheless, (±)-rhodonoid B could be synthesized from **10** through standard manipulations in 81% yield.

While this concludes our total synthesis effort of (±)-rhodonoid B (**2**), we were still intrigued by *anti*-**3**, which could provide an analogue of (±)-rhodonoid B different only at

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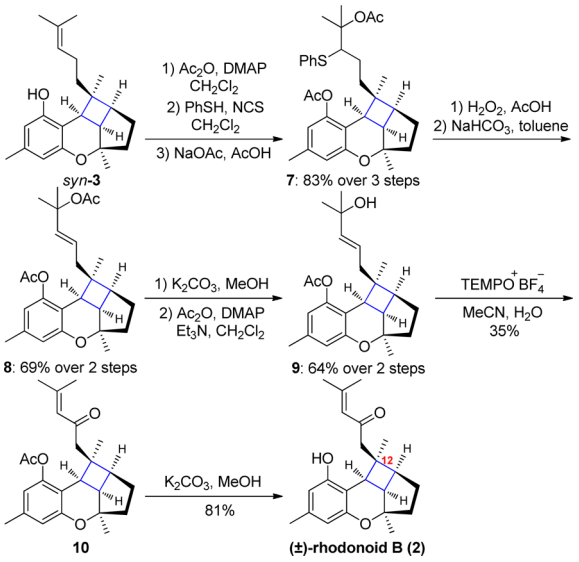
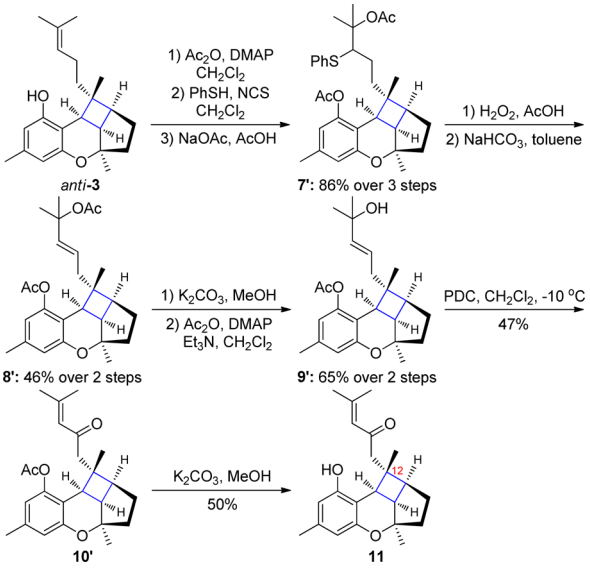
Scheme 3. Total Synthesis of (±)-Rhodonoid B



the C12 stereocenter. Tertiary allylic alcohol **9**, the precursor for preparing the analogue, was obtained from *anti*- **3** following a similar strategy (Scheme 4). Although the alcohols **9′** and **9**

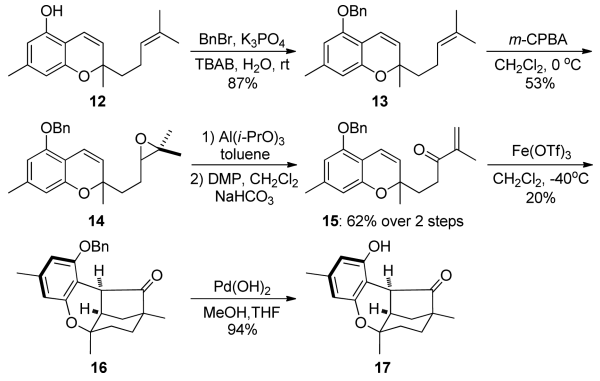
Scheme 4. Synthesis of (±)-C12-*epi*-Rhodonoid B (11)



differ only at the C12 stereocenter, the $TEMPO^{+}BF_4^{-}$ oxidation that worked for the oxidation of **9** was not applicable for **9′**. However, an alternative approach using PDC successfully generated the desired **10′** from **9′**. Subsequent removal of the Ac group afforded compound **11**, which is (±)-C12-*epi*-rhodonoid B.

Our total synthesis of (±)-rhodonoid A commenced with chromene **12**, which was readily prepared from citral via an *oxa*-[3 + 3] annulation of **9**[8d] (Scheme 5). Benzylation of the phenol within **12** generated **13** in a robust and scalable fashion. Benzyl-protected **13** reacted with *m*-CPBA under standard conditions (dichloromethane, 0 °C) to give epoxide **14** as a mixture of two diastereomers in 53% yield. Refluxing **14** in toluene with aluminum iso-propoxide followed with DMP oxidation afforded the enone **15**. However, exposure of **15** to

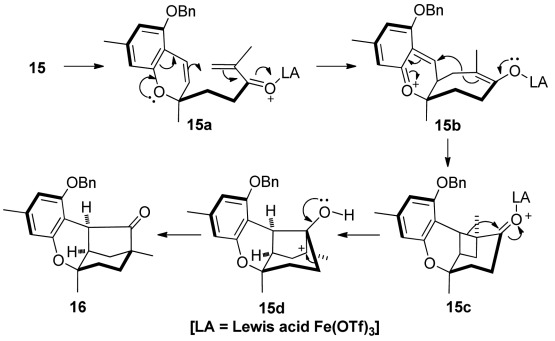
Scheme 5. An Unexpected Formation of Tetracycle 17



$Fe(OTf)_3$ provided an unexpected ketone **16** in 20% yield instead of the desired head-to-head cycloadduct **18**. Subsequent removal of the benzyl group by hydrogenolysis [5% palladium hydroxide, methanol-tetrahydrofuran (v/v = 1:1)] gave an analogue (**17**). The structural integrity of **17** could be unambiguously confirmed using single crystal X-ray analysis.

Mechanistically, the formation of **16** likely proceeds through the sequence shown in Scheme 6. It commences with a classic

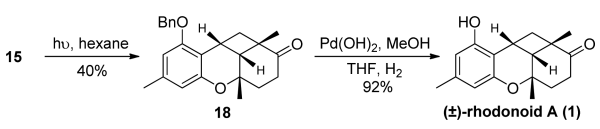
Scheme 6. Possible Pathway to Ketone 16



Gassman's cationic [2 + 2] cycloaddition. The activation of the enone motif in **15** by Lewis acid $Fe(OTf)_3$ would give vinyl oxocarbenium ion **15a**. The ensuing trapping of the resulting cation in **15b** could afford the cyclobutane **15c**. While the formation of tetracyle **16** is very interesting as well as potentially useful, its formation via the initial [2 + 2] cycloadduct **15c** should not have come as a complete surprise. Regiochemically, the formation of **15c** could have been predicted based on matching the respective bond polarizations between the enone motif and chromene olefin. A subsequent ring opening of **15c** gives the intermediate **15d**,[17] and the sequence concludes with a pinacol type rearrangement to give ketone **16**.

To complete the total synthesis of (±)-rhodonoid A, we examined the photochemical [2 + 2] cycloaddition of enone **15**.[18] As shown in Scheme 7, irradiation of **15** in hexane (concentration =0.15 mM) using a high-pressure mercury lamp

Scheme 7. Synthesis of (±)-Rhodonoid A



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afforded the desired cycloadducts **18** as a single diastereomer in 40% yield. It is also noteworthy that the formation of **18** regiochemically is in complete agreement with the theory of reversed polarization in photochemical transformations. The polarity of the enone is now reversed in the excited state from that of its respective ground state. Our results also suggest that biosynthetically some of these chromane-fused cyclobutane natural products such as (±)-rhodonoid A could simply be a result of photochemical [2 + 2] cycloadditions and not of a cationic pathway. A successful debenzylation with 5% palladium hydroxide afforded (±)-rhodonoid A (**1**) in 92% yield. Both (±)-rhodonoids A and B matched the spectroscopic data in literature.[3]

We have described here the total syntheses of (±)-rhodonoids A and B as well as C12-*epi*-rhodonoid B. A unified theme in approaching the chromene core involves a formal [3 + 3] annulation. A diastereoselective Gassman's type cationic [2 + 2] annulation and a photochemical [2 + 2] cycloaddition were employed to construct the cyclobutane core, leading to efficient access to (±)-rhodonoids A and B as well as a structural variant C12-*epi*-rhodonoid B that could be useful for further biological studies. Investigations pertaining to these biological studies are currently underway.

EXPERIMENTAL SECTION

General Information. Unless otherwise indicated, all reactions were performed in flame-dried glassware under a N_2 atmosphere. Solvents were distilled prior to use. All chemical and reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. Chromatographic separations were performed using 48−75 Å SiO_2. All NMR spectra were run at 500 MHz (^{1}H NMR) or 125 MHz (^{13}C NMR) in $CDCl_3$ solution. ^{1}H NMR and ^{13}C NMR spectra were internally referenced to TMS or residual solvent as standard unless otherwise noted. Melting points were determined using a melting point apparatus and are uncorrected/calibrated. TLC analysis was performed using glass-backed plates (60 Å, 250 μm) and visualized using UV and phosphomolybdic acid stains. High-resolution mass spectra were obtained using a UHPLC-Q-TOF MS in the ESI mode. All spectral data obtained for new compounds are reported here.

Enone 6. To a solution of alcohol 5 (1 g, 4.5 mmol) in CH_2Cl_2 was added Dess−Martin reagent (2.3 g, 5.4 mmol). After the reaction was complete, the solid was filtered off using a bed of Celite and washed with CH_2Cl_2. The filtrate was concentrated *in vacuo* and was then purified by silica gel flash column chromatography (5% EtOAc in petroleum ether) to yield enone **6** (800 mg, 83%) as a colorless oil.

6. R_f = 0.5 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61 (s, 3H), 1.69 (s, 6H), 2.01−2.09 (m, 4H), 2.17 (s, 3H), 2.19−2.27 (m, 4H), 5.07−5.13 (m, 2H), 5.88 (d, 1H, J = 8 Hz), 9.99 (d, 0.25H, J = 8 Hz), 10.01 (d, 0.83H, J = 8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) (trans) δ 17.6, 17.6, 23.3, 25.5, 25.7, 26.5, 32.0, 40.9, 123.0, 124.0, 127.4, 131.8, 136.7, 163.8, 191.3; (cis) 23.3, 25.1, 25.5, 26.5, 26.9, 31.9, 32.9, 40.9, 123.0, 124.0, 128.6, 131.8, 137.3, 163.8, 190.8; MS (ESI): m/z (%) = 243.2 (100) $(M + Na)^+$. HRMS (ESI): m/z $(M + Na)^+$ calcd for $C_{15}H_{24}NaO^+$: 243.1725; found: 243.1717.

Chromene *Cis*-4. To a solution of enone **6** (800 mg, 3.6 mmol) and piperidine (0.78 mL, 7.9 mmol) in toluene (5 mL) was added Ac_2O (0.68 mL, 7.2 mmol) dropwise at 0 °C under N_2. After addition, the flask was sealed, and the reaction mixture was heated in a 110 °C oil bath for 1 h. This iminium salt solution was then added to a solution of resorcinol **9** (446 mg, 3.6 mmol) in toluene (3 mL) dropwise via cannula at room temperature under N_2. The resulting mixture was stirred at 110 °C for 18 h before it was cooled to room temperature and concentrated under reduced pressure. The crude residue was purified using silica gel flash column chromatography (gradient eluent: 5% EtOAc in petroleum ether) to give *cis*-**4** (811 mg, 69%) as a colorless oil.

Cis-4. R_f = 0.5 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.60 (s, 3H), 1.61−1.65 (m, 1H), 1.66 (s, 3H), 1.68 (s, 3H), 1.69−1.75 (m, 2H), 2.01 (s, 3H), 2.07−2.14 (m, 2H), 2.19 (s, 3H), 4.82 (s, 1H), 5.07−5.13 (m, 2H), 5.47 (d, 1H, J = 10 Hz), 6.10 (s, 1H), 6.23 (s, 1H), 6.60 (d, 1H, J = 10 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 21.5, 22.5, 23.4, 25.7, 26.2, 26.6, 31.9, 41.3, 78.2, 106.8, 108.3, 109.8, 116.8, 124.3, 124.9, 127.2, 131.5, 135.4, 139.5, 151.0, 154.1; MS (ESI): m/z (%) = 349.1 (100) $(M + Na)^+$. HRMS (ESI): m/z $(M + Na)^+$ calcd for $C_{22}H_{30}NaO_2^+$: 349.2143; found: 349.2135.

Syn-3. To a solution of *cis*-**4** (881 mg, 2.5 mmol) in CH_2Cl_2 (25 mL) was added $Fe(OTf)_3$ (375 mg, 0.75 mmol) at −40 °C under a blanket of N_2. After stirring for overnight, the reaction mixture was quenched with sat aq $NaHCO_3$ (5 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (2% EtOAc in petroleum ether) to provide the *syn*-**3** (628 mg, 75%) as a light yellow oil. R_f = 0.5 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11−1.26 (m, 2H), 1.33 (s, 3H), 1.39 (s, 3H), 1.50 (s, 3H), 1.60 (s, 3H), 1.61−1.87 (m, 5H), 2.02−2.10 (m, 1H), 2.22 (s, 3H), 2.42 (dt, 1H, J = 3.5, 8.5 Hz), 2.57 (t, 1H, J = 8.5 Hz), 3.11 (d, 1H, J = 10 Hz), 4.44 (br s, 1H), 4.93 (t, 1H, J = 7 Hz), 6.18 (s, 1H), 6.33 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.5, 21.2, 23.3, 25.7, 25.9, 26.2, 30.4, 31.1, 36.0, 38.4, 40.0, 42.2, 46.1, 83.5, 108.1, 108.6, 111.4, 125.2, 130.5, 137.3, 153.7, 154.5; MS (ESI): m/z (%) = 349.0 (100) $(M + Na)^+$. HRMS (ESI): m/z $(M + Na)^+$ calcd for $C_{22}H_{30}NaO_2^+$: 349.2143; found: 349.2142.

Alkene 8. The preliminary intermediate 7 was prepared as follows: Ac_2O (0.37 mL, 3.85 mmol) was progressively added to a solution of the *syn*-**3** (628 mg, 1.92 mmol) and DMAP (353 mg, 2.89 mmol) in CH_2Cl_2 (10 mL). The resulting mixture was stirred at rt overnight and then diluted with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the organic phases were washed with brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (2% EtOAc in petroleum ether) to provide the Ac-protected chromenol 702 mg as a colorless oil.

To a CH_2Cl_2 (15 mL) solution of NCS (636 mg, 4.76 mmol) was added PhSH (0.43 mL, 4.2 mmol) at 0 °C. After the mixture was stirred for 1 h, a solution of the Ac-protected chromenol (702 mg, 1.9 mmol) was added dropwise in CH_2Cl_2 (5 mL) at 0 °C. After being stirred for further 0.5 h, the mixture was concentrated under reduced pressure to give the crude adduct that was used in the next step without further purification.

The PhSCl-adduct, prepared as above from Ac-protected chromenol, was stirred with AcONa (469 mg, 5.72 mmol) in AcOH (10 mL) at room temperature for 1 h. The solvents were removed then washed with saturated aqueous $NaHCO_3$ (10 mL). The aqueous washes were extracted with EtOAc (2 × 5 mL), and the combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (gradient eluent: 2−5% EtOAc in petroleum ether) to provide the diastereoisomeric mixture 7 (861 mg, 83% overall three steps) as a colorless oil.

To a solution of β-acetoxysulfide 7 (861 mg, 1.6 mmol) in AcOH (5 mL) was added H_2O_2 (30%, 0.25 mL, 2.41 mmol). The reaction was allowed to stir at room temperature for 20 h before saturated aqueous $Na_2S_2O_3$ (5 mL) was added. The solvents were removed then washed with saturated aqueous $NaHCO_3$ (10 mL). The aqueous washes were extracted with EtOAc (2 × 5 mL), and the combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give the oily diastereoisomeric mixture that was used in the next step without further purification.

To a solution of crude sulfoxide (prepared above 864 mg) in toluene (10 mL) was added $NaHCO_3$ (605 mg, 7.2 mmol). The resulting solution was heated in a 90 °C oil bath for overnight before it was cooled to room temperature and concentrated under reduced pressure. The crude residue was purified using silica gel flash column

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chromatography (5% EtOAc in petroleum ether) to give alkene **8** (470 mg, 69% over two steps) as a light yellow oil.

8. R_f = 0.5 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.29 (s, 3H), 1.43 (s, 6H), 1.58−1.63 (m, 2H), 1.65−1.72 (m, 2H), 1.93 (s, 3H), 2.00−2.07 (m, 1H), 2.27 (s, 3H), 2.28 (s, 3H), 2.43 (dt, 1H J = 4, 8.5 Hz), 2.53 (t, 1H, J = 9 Hz), 3.02 (d, 1H, J = 10 Hz), 5.29−5.36 (m, 1H), 5.58 (d, 1H, J = 16 Hz), 6.46 (s, 1H), 6.61 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 21.2, 22.3, 25.6, 26.0, 26.8, 26.9, 30.9, 34.8, 36.1, 39.0, 40.6, 42.0, 46.1, 80.5, 84.0, 114.4, 115.0, 116.8, 125.9, 136.3, 137.5, 148.9, 154.6, 169.1, 169.9; MS (ESI): m/z (%) = 449.1 (100) $(M + Na)^+$. HRMS (ESI): m/z $(M + Na)^+$ calcd for $C_{26}H_{34}NaO_5^+$: 449.2304; found: 449.2299.

Chromenol 9. In a 10 mL round-bottom flask equipped with magnetic stirbar, alkene **8** (260 mg, 0.61 mmol) was taken up in MeOH (3 mL), and K_2CO_3 (338 mg, 2.44 mmol) was added in one portion. The solution was stirred at ambient temperature for 1 h, as TLC analysis indicated complete consumption of the starting material. The reaction mixture was quenched with H_2O (3 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic phase was separated, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (20% EtOAc in petroleum ether) to provide corresponding allelic alcohol 148 mg as a colorless oil.

Ac_2O (46 μL, 0.48 mmol) was added to a solution of the allelic alcohol (148 mg, 0.44 mmol), Et_3N (184 μL, 1.32 mmol), and DMAP (81 mg, 0.66 mmol) in CH_2Cl_2 (5 mL). The resulting mixture was stirred at rt for 2.5 h and then diluted with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL), and the organic phases were washed with brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (20% EtOAc in petroleum ether) to provide the Ac-protected chromenol 9 (152 mg, 64% over two steps) as a yellow oil.

9. R_f = 0.4 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (s, 3H), 1.23 (s, 3H), 1.28 (s, 3H), 1.29 (s, 3H), 1.59−1.64 (m, 1H), 1.70−1.76 (m, 2H), 1.85−1.91 (m, 1H), 1.97−2.08 (m, 2H), 2.28 (s, 3H), 2.29 (s, 3H), 2.44 (dt, 1H, J = 4.5, 8.5 Hz), 2.54 (t, 1H, J = 9.5 Hz), 3.05 (d, 1H, J = 9.5 Hz), 5.31−5.38 (m, 1H), 5.42−5.46 (d, J = 16 Hz), 6.48 (s, 1H), 6.63 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 21.2, 25.5, 25.8, 29.8, 29.8, 30.9, 34.7, 35.9, 39.2, 40.7, 42.1, 46.3, 70.6, 84.1, 114.7, 115.1, 116.8, 123.5, 137.5, 140.0, 148.8, 154.7, 169.1; MS (ESI): m/z (%) = 407.1 (100) $(M + Na)^+$. HRMS (ESI): m/z $(M + Na)^+$ calcd for $C_{24}H_{32}NaO_4^+$: 407.2198; found: 407.2189.

Ketone 10. To a solution of **9** (40 mg, 0.1 mmol) in MeCN (1 mL) and H_2O (1 mL) was added $TEMPO^+BF_4^{-1}$ (101 mg, 0.42 mmol) at 70 °C. The reaction mixture was stirred for 6 h and then diluted with H_2O. The aqueous layer was extracted with EtOAc (3 × 3 mL). The solution was concentrated *in vacuo*, and the residue was purified by flash column chromatography (20% EtOAc in petroleum ether) to give ketone **10** (14 mg, 37%) as a colorless oil.

10. R_f = 0.3 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.48 (s, 3H), 1.51−1.54 (m, 1H), 1.57−1.61 (m, 1H), 1.73−1.77 (m, 1H), 1.79 (s, 3H), 1.89−1.95 (m, 1H), 2.05 (s, 3H), 2.16 (d, 1H, J = 18.5 Hz), 2.29 (s, 3H), 2.30 (s, 3H), 2.42 (d, 1H, J = 18.5 Hz), 2.55 (t, 1H, J = 9 Hz), 2.66 (dt, 1H, J = 3.5, 8 Hz), 2.99 (d, 1H, J = 9.5 Hz), 5.90 (s, 1H), 6.49 (s, 1H), 6.63 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5, 21.2, 21.3, 25.7, 27.4, 27.5, 30.7, 36.7, 39.3, 39.9, 41.9, 45.4, 46.4, 84.3, 114.3, 115.2, 116.9, 124.8, 137.7, 148.9, 153.6, 154.6, 169.2, 200.3; MS (ESI): m/z (%) = 405.0 (100) $(M + Na)^+$. HRMS (ESI): m/z $(M + Na)^+$ calcd for $C_{24}H_{30}NaO_4^+$: 405.2042; found: 405.2033.

(±) Rhodonoid B (2). In a 10 mL round-bottom flask equipped with magnetic stirbar, ketone **10** (11 mg, 0.029 mmol) was taken up in MeOH (2 mL), and K_2CO_3 (8 mg, 0.058 mmol) was added in one portion. The solution was stirred at ambient temperature for 1 h, as TLC analysis indicated complete consumption of the starting material. The reaction mixture was quenched with H_2O (3 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic phase was separated, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (20% EtOAc in petroleum ether) to provide (±) rhodonoid B (**2**) (8 mg, 81%) as a white solid.

(±) Rhodonoid B. R_f = 0.2 (20% EtOAc in hexanes); mp 151−153 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.54 (s, 3H), 1.60−1.76 (m, 3H), 1.78 (s, 3H), 1.91−1.97 (m, 1H), 2.04 (s, 3H), 2.22 (s, 3H), 2.38 (d, 1H, J = 18.5 Hz), 2.47 (d, 1H, J = 18.5 Hz), 2.57−2.62 (m, 1H), 3.17 (d, 1H, J = 9.5), 5.26 (br s, 1H), 5.88 (s, 1H), 6.25 (s, 1H), 6.33 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.7, 21.4, 26.3, 26.9, 27.7, 30.5, 36.5, 39.1, 39.5, 41.7, 45.6, 47.0, 83.9, 109.7, 109.7, 112.0, 125.0, 137.8, 154.1, 154.4, 154.6, 201.6; MS (ESI): m/z (%) = 363.1 (100) $(M + Na)^+$. HRMS (ESI): m/z $(M + Na)^+$ calcd for $C_{22}H_{28}NaO_3^+$: 363.1936; found: 363.1928.

Alkene 8′. The preliminary intermediate **7′** was prepared as **7** from *anti*-**3** in 86% yield over three steps. Employing the same procedure for converting **7** to **8**, **8′** can be obtained from **7′** in 46% yield over two steps.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.68 (s, 3H), 1.26−1.31 (m, 2H), 1.33 (s, 3H), 1.51 (s, 3H), 1.52 (s, 3H), 1.60−1.64 (m 3H), 1.97 (s, 3H), 2.27 (s, 3H), 2.30 (s, 3H), 2.33−2.38 (m, 1H), 2.44−2.49 (m, 1H), 2.54 (br, 1H), 3.00 (d, J = 9.5 Hz), 5.62−5.69 (m, 1H), 5.83 (d, 1H, J = 15.5 Hz), 6.48 (s, 1H), 6.60 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.3, 21.2, 21.5, 22.4, 25.4, 26.8, 27.1, 27.2, 35.1, 39.0, 39.1, 42.6, 42.9, 48.5, 80.3, 83.8, 114.0, 114.9, 116.6, 125.0, 137.4, 137.8, 149.1, 154.5, 169.0, 170.0; MS (ESI): m/z (%) = 449.1 (100) $(M + Na)^+$. HRMS (ESI): m/z $(M + Na)^+$ calcd for $C_{26}H_{34}NaO_5^+$: 449.2304; found: 449.2299.

Chromenol 9′. Employing the same procedure for converting **8** to **9**, **9′** can be obtained from **8′** in 65% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.68 (s, 3H), 1.23−1.29 (m, 2H), 1.33 (s, 9H), 1.58−1.66 (m, 3H), 2.27 (s, 3H), 2.30 (s, 3H), 2.33−2.38 (m, 1H), 2.45−2.50 (m, 1H), 2.52−2.57 (m, 1H), 3.01 (d, 1H, J = 9.5 Hz), 5.68−5.70 (m, 2H), 6.48 (s, 1H), 6.60 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.3, 21.2, 21.4, 25.4, 26.8, 30.0, 30.0, 35.0, 39.0, 39.0, 42.6, 43.0, 48.5, 70.7, 83.7, 114.0, 114.9, 116.6, 122.8, 137.4, 141.4, 149.0, 154.5, 168.9; MS (ESI): m/z (%) = 407.1 (100) $(M + Na)^+$. HRMS (ESI): m/z $(M + Na)^+$ calcd for $C_{24}H_{32}NaO_4^+$: 407.2198; found: 407.2193.

Ketone 10′. To a solution of **9′** (20 mg, 0.052 mmol) in CH_2Cl_2 (2 mL) were added PDC (30 mg, 0.078 mmol) and 4 Å MS (40 mg) at 10 °C. After 6 h stirring at this temperature, the resulting mixture was filtrated on a pad of Celite. The solids were washed with CH_2Cl_2 (6 × 3 mL), and the pooled organic extracts were concentrated under reduced pressure. The residue was purified by flash chromatograph on silica gel (20% EtOAc in petroleum ether) to afford **10′** 14 mg (47%) as a colorless oil.

R_f = 0.3 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (s, 3H), 1.32 (s, 3H), 1.60−1.73 (m, 3H), 1.77−1.82 (m, 1H), 1.89 (s, 3H), 1.94−2.00 (m, 1H), 2.14 (s, 3H), 2.27 (s, 3H), 2.32 (s, 3H), 2.54 (t, 1H, J = 9 Hz), 2.67 (d, 1H, J = 15 Hz), 2.81 (d, 1H, J = 15 Hz), 3.09 (d, 1H, J = 10 Hz), 6.05 (s, 1H), 6.49 (s, 1H), 6.60 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.2, 20.7, 21.2, 21.4, 25.5, 26.7, 27.7, 35.7, 39.2, 39.5, 41.9, 44.3, 58.6, 83.9, 113.6, 114.9, 116.7, 124.9, 137.6, 149.0, 154.6, 155.0, 169.0, 199.8; MS (ESI): m/z (%) = 405.0 (100) $(M + Na)^+$. HRMS (ESI): m/z $(M + Na)^+$ calcd for $C_{24}H_{30}NaO_4^+$: 405.2042; found: 405.2035.

C12-*epi*-Rhodonoid B (11). Employing the same procedure for converting **10** to **2**, **11** can be obtained from **10′** in 50% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (s, 3H), 1.32 (s, 3H), 1.52−1.55 (m, 1H), 1.61−1.67 (m, 1H), 1.74−1.81 (m, 1H), 1.94 (s, 3H), 2.03−2.08 (m, 1H), 2.21 (s, 3H), 2.24 (s, 3H), 2.30−2.34 (m, 1H), 2.67 (t, 1H, J = 9 Hz), 2.78 (d, 1H, J = 17.5 Hz), 2.96 (d, 1H, J = 17.5 Hz), 3.38 (d, 1H, J = 9.5 Hz), 6.12 (s, 1H), 6.28 (s, 1H), 6.40 (s, 1H), 9.24 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.3, 21.2, 21.4, 24.7, 26.1, 28.1, 29.7, 34.1, 38.4, 40.5, 41.6, 46.8, 82.9, 107.9, 110.2, 110.6, 124.0, 138.1, 154.5, 156.0, 159.4, 203.0; MS (ESI): m/z (%) = 341.2 (100) $(M + H)^+$. HRMS (ESI): m/z $(M + H)^+$ calcd for $C_{22}H_{29}O_3^+$: 341.2117; found: 341.2109.

Chromene 13. **12** (2.26g, 8.8 mmol), benzyl bromide (1.84 mL, 26.3 mmol equiv), TBAB (2.9 g, 8.8 mmol), $K_3PO_4{\cdot}7H_2O$ (9g, 26.4 mmol), and water (15 mL) were added to a reaction vessel. The

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mixture was stirred at room temperature for overnight under air. After the reaction was completed, the mixture was diluted with water and extracted with CH_2Cl_2 (15 mL × 3). The combined organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether) to give the pure product **13** (2.665g, 87%) as a light yellow oil.

13. R_f = 0.5 (petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.58 (s, 3H), 1.60−1.64 (m, 1H), 1.66 (s, 3H), 1.69−1.76 (m, 1H), 2.05−2.15 (m, 2H), 2.25 (s, 3H), 5.03 (s, 2H), 5.08 (t, 1H, J = 10 Hz), 5.43 (1H, d, J = 10 Hz), 6.29 (s, 2H), 6.72 (d, J = 10 Hz), 7.29−7.45 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 22.0, 22.8, 25.7, 26.3, 41.2, 70.2, 78.1, 105.2, 108.3, 110.2, 117.5, 124.3, 126.8, 127.3, 127.8, 128.5, 131.6, 137.3, 139.4, 153.9, 154.3; MS (ESI): m/z (%) = 371.1 (100) $(M + Na)^+$. HRMS (ESI): m/z $(M + H)^+$ calcd for $C_{24}H_{29}O_2^+$: 349.2168; found: 349.2162.

Epoxychromene 14. To a solution of chromene **13** (2.465g, 7.06 mmol) in CH_2Cl_2 (40 mL) was added *m*-CPBA (85%, 1.72g, 8.47 mmol) at 0 °C. The reaction was stirred at this temperature for 1.5 h before a saturated $NaHCO_3$ solution was added. The resulting mixture was allowed to warm up to rt and was stirred for another 2 h. Aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. Solvents were removed under reduced pressure, and the crude residue was purified using silica gel flash column chromatography (5% EtOAc in petroleum ether) to afford epoxychromene **14** (1.365g, 53%) as a diastereoisomeric mixture.

14. R_f = 0.3 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24, 1.24 (s, each 3/2H), 1.28, 1.30 (s, each 3/2), 1.39 (s, 3H), 1.66−1.78 (m, 2H), 1.80−1.93 (m, 2H), 2.27 (s, 3H), 2.70−2.77 (m, 1H), 5.05 (s, 2H), 5.42 (t, 1H, J = 10 Hz), 6.29 (s, 1H), 6.31 (s, 1H), 6.75 (d, 1H, J = 10 Hz), 7.31−7.46 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.6, 18.7, 22.0, 23.7, 24.0, 24.9, 26.2, 26.7, 37.6, 37.9, 58.4, 58.6, 64.3, 64.5, 70.2, 77.6, 78.0, 105.3, 105.3, 108.0, 108.1, 110.1, 110.2, 117.8, 118.0, 127.3, 127.3, 127.8, 128.5, 137.2, 139.5, 153.63, 153.7, 154.3, 154.3; MS (ESI): m/z (%) = 387.1 (100) $(M + Na)^+$. HRMS (ESI): m/z $(M + Na)^+$ calcd for $C_{24}H_{28}NaO_3^+$: 387.1936; found: 387.1928.

Enone 15. In a 250 mL round-bottom flask equipped with a water-cooled condenser, epoxychromene **14** was taken up in toluene (20 mL), and aluminum isopropoxide was added in one portion. The solution was refluxed for 24h with stirring. After cooling to rt, the resulting mixture was slowly added to a stirred mixture of ether (10 mL) and saturated potassium sodium tartrate solution (50 mL). After 1 h stirring, the aqueous layer was extracted with ether (3 × 50 mL), and the organic layers were washed with brine (20 mL) and dried over Na_2SO_4. Solvents were removed *in vacuo* to give an alcohol that was used in the next step without further purification.

To a solution of crude alcohol (made from **14**) in CH_2Cl_2 was added Dess−Martin reagent (1.6 g, 3.91 mmol). After the reaction was deemed complete, the solid was filtered off using a bed of Celite and washed with CH_2Cl_2. The filtrate was concentrated *in vacuo* and was then purified by silica gel flash column chromatography (5% EtOAc in petroleum ether) to yield enone **15** (729 mg, 62%) as a colorless oil.

15. R_f = 0.2 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.85 (s, 3H), 1.94−2.06 (m, 2H), 2.25 (s, 3H), 2.75−2.94 (m, 2H), 5.03 (s, 2H), 5.39 (d, 1H, J = 10 Hz), 5.70 (s, H), 5.92 (s, 1H), 6.27 (s, 1H), 6.30 (s, 1H), 6.74 (d,1H, J = 10 Hz), 7.30−7.44 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.8, 22.1, 26.7, 32.7, 35.8, 70.4, 78.0, 105.5, 108.1, 110.2, 118.3, 124.7, 126.2, 127.4, 128.0, 128.6, 137.3, 139.7, 144.5, 153.8, 154.5, 201.9; MS (ESI): m/z (%) = 385.1 (100) $(M + Na)^+$. HRMS (ESI): m/z $(M + Na)^+$ calcd for $C_{24}H_{26}NaO_3^+$: 385.1780; found: 385.1774.

Ketone 16. To a solution of enone **15** (120 mg, 0.33 mmol) in CH_2Cl_2 (2 mL) was added $Fe(OTf)_3$ (50.0 mg, 0.1 mmol) at −10 °C under a blanket of N_2. After stirring for overnight, the reaction mixture was quenched with sat aq $NaHCO_3$ (2 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (2 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (20% EtOAc in petroleum ether) to provide the ketone **16** (25 mg, 20%) as a colorless oil.

16. R_f = 0.5 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.46−1.54 (m, 2H), 1.59 (s, 3H), 1.60−1.62 (m, 1H), 1.70−1.74 (m, 1H), 2.00 (br s, 2H), 2.26 (s, 3H), 2.36−2.38 (m, 1H), 3.63 (d, 1H, J = 6 Hz), 5.08 (d, 1H, J = 12 Hz), 5.21 (d, 1H, J = 12 Hz), 6.31 (s, 1H), 6.38 (s, 1H), 7.29−7.58 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.1, 21.7, 25.9, 30.2, 35.9, 38.7, 39.2, 46.0, 47.1, 70.4, 75.7, 105.3, 105.7,110.5, 127.3, 127.6, 128.5, 137.7, 138.6, 152.7, 157.7, 217.7; MS (ESI): m/z (%) = 385.0(100) $(M + Na)^+$. HRMS (ESI): m/z $(M + Na)^+$ calcd for $C_{24}H_{26}NaO_3^+$: 385.1780; found: 385.1775.

Tetracycle 17. Under an H_2 atmosphere, $Pd(OH)_2/C$ (20%, 10 mg) was added to a solution of **16** (14 mg, 0.039 mmol) in a sovent mixture of THF/MeOH (1:1 v/v, 2 mL). The resulting reaction mixture was stirred at rt under H_2 for 6 h, until TLC showed that the reaction was completed. The reaction mixture was filtered to remove the catalyst. The filtrate was evaporated, and the residue was rapidly purified by flash chromatograph on silica gel (5% EtOAc in petroleum ether) to afford **17** (10 mg 94%) as a white solid.

17. R_f = 0.3 (5% EtOAc in hexanes); mp 167−169 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.53−1.56 (m, 1H), 1.57−1.59 (m, 2H), 1.60 (s, 3H), 1.72−1.79 (m, 1H), 2.05 (br s, 2H), 2.24 (s, 3H), 2.41−2.45 (m, 1H), 3.51 (d, 1H, J = 6.5 Hz), 6.28 (s, 1H), 6.44 (s, 1H), 7.97 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.4, 21.4, 25.5, 28.9, 35.0, 38.7, 39.8, 46.6, 47.8, 75.3, 105.1, 110.3, 110.6, 139.7, 152.4, 155.5, 225.6; MS (ESI): m/z (%) = 295.0(100) $(M + Na)^+$. HRMS (ESI): m/z $(M + Na)^+$ calcd for $C_{17}H_{20}NaO_3^+$: 295.1310; found: 295.1306.

Cycloadduct 18. Enone **15** (160 mg, 0.44 mmol) was transferred into a 10 mL size round-bottom flask and dissolved in hexanes (3 mL). The reaction mixture was irritated with a high-pressure mercury lamp for 36 h at room temperature, while the lamp was placed 5 cm away from the flask. The crude product was purified by silica gel flash column chromatography (5% EtOAc in petroleum ether) to give **18** (64 mg 40%) as a colorless oil.

18. R_f = 0.3 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (s, 3H), 1.42 (s, 3H), 1.98−2.05 (m, 1H), 2.15−2.20 (m, 1H), 2.27 (s, 3H), 2.31−2.37 (m, 2H), 2.39−2.45 (m, 1H), 2.55 (d, 1H, J = 9.5 Hz), 2.71−2.79 (m, 1H), 3.79−3.86 (td, 1H, J = 7.5, 9.5 Hz), 4.98 (d, 1 H, J = 11.5 Hz), 5.02 (d, 1 H, J = 11.5 Hz), 6.37(s, 1H), 6.38(s, 1H), 7.30−7.40 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 22.0, 24.9, 25.5, 33.7, 33.9, 39.0, 44.0, 50.8, 70.1, 73.4, 106.1, 112.3, 114.3, 127.2, 127.8, 128.5, 137.3, 137.4, 153.7, 155.8, 215.4; MS (ESI): m/z (%) = 385.1(100) $(M + Na)^+$. HRMS (ESI): m/z $(M + Na)^+$ calcd for $C_{24}H_{26}NaO_3^+$: 385.1780; found: 385.1776.

(±) Rhodonoid A (1). Under an H_2 atmosphere, $Pd(OH)_2/C$ (20%, 10 mg) was added to a solution of **18** (54 mg, 0.15 mmol) in a sovent mixture of THF/MeOH (1:1 v/v, 2 mL). The resulting reaction mixture was stirred at rt under H_2 for 6 h, until TLC showed that the reaction was completed. The reaction mixture was filtered to remove the catalyst. The filtrate was evaporated, and the residue was rapidly purified by flash chromatograph on silica gel (20% EtOAc in petroleum ether) to afford (±) rhodonoids A (1) 38 mg (92%) as a white solid.

1. R_f = 0.2 (20% EtOAc in hexanes); mp 180−181 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (s, 3H), 1.43 (s, 3H), 1.98−2.07 (m, 1H), 2.14−2.18 (m, 1H), 2.20 (s, 3H), 2.29−2.38 (m, 2H), 2.39−2.44 (m, 1H), 2.58 (d, 1H, J = 9.5 Hz), 2.74−2.84 (m, 1H), 3.71−3.80 (m, 1H), 5.29 (br s, 1H), 6.21(s, 1H), 6.32 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 21.8, 24.9, 25.4, 33.6, 34.1, 38.9, 43.8, 51.1, 73.5, 109.3, 112.0, 112.5, 137.4, 152.7, 154.1, 216.2; MS (ESI): m/z (%) = 295.0 (100) $(M + Na)^+$. HRMS (ESI): m/z $(M + Na)^+$ calcd for $C_{17}H_{20}NaO_3^+$: 295.1310; found: 295.1305.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02739.

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Copies of NMR spectra for all substrates and products (PDF)
X-ray structural file of compound **17** (CIF)

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The authors declare no competing financial interest.

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