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Enantioselective Total Synthesis of Cerorubenic Acid-III via Type II [5+2] Cycloaddition Reaction

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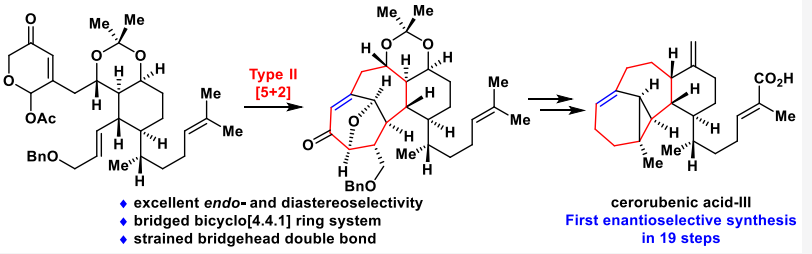

ABSTRACT: The first enantioselective total synthesis of cerorubenic acid-III is described in detail. Different strategies and attempts, based on a type II [5+2] cycloaddition reaction, leading to the bicyclo[4.4.1] ring system with a strained bridgehead double bond, are depicted. Furthermore, sodium naphthalenide was found to be efficient in the chemoselective reduction of 8-oxabicyclo[3.2.1]octene, with three transformations completed in one operation. An unusual S_N1 transannular cyclization reaction was applied to construct the synthetically challenging vinylcyclopropane moiety. This strategy enabled the total synthesis of cerorubenic acid-III in 19 steps.

INTRODUCTION

Natural products from the sesterterpenoid family[1] usually present highly attractive targets for total synthesis owing to their unusual structural features and interesting bioactivity.[2] Cerorubenic acid-III (**1**, Figure 1), along with its four analogues (**3**−**6**), were isolated from the secretion of *Ceropiastes rubens* (Coccidae, a scale insect) by Naya and co-workers in 1983.[3] These unusual sesterterpenoids were found to act as kairomones,[4] responsible for controlling the ovipositional behavior of parasitic wasp *Anicetus beneficus*. Owing to the scarcity of these isolated natural samples, no further biological activity of these compounds has been determined other than their reported role in insect communication. Structurally, cerorubenic acid-III (**1**), the most complex compound in this family, possesses a unique 6/3/7/6 tetracyclic skeleton, featuring a bridged bicyclo[4.4.1]undecene ring system (highlighted in red), and a highly strained vinylcyclopropane moiety with the double bond at the bridgehead position.[5] Furthermore, seven contiguous stereocenters with an all-carbon quaternary stereocenter (C3) make this molecule a formidable synthetic challenge that has attracted much attention from the chemical community.[6] After a ten-year journey, Paquette and co-workers finished their elegant total synthesis of cerorubenic acid-III methyl ester (**2**) in 1998, comprising 30 steps with an overall yield of 0.3%.[6g] However, the synthesis of **1** from **2** was still unknown at the time. For the total synthesis of **1**, the development of an efficient method to construct the complex ring system with high stereoselectivity, regioselectivity, and enantioselectivity is a critical challenge. As part of our ongoing endeavor toward the total synthesis of bioactive natural products with a seven-membered ring,[7] we reported herein an efficient

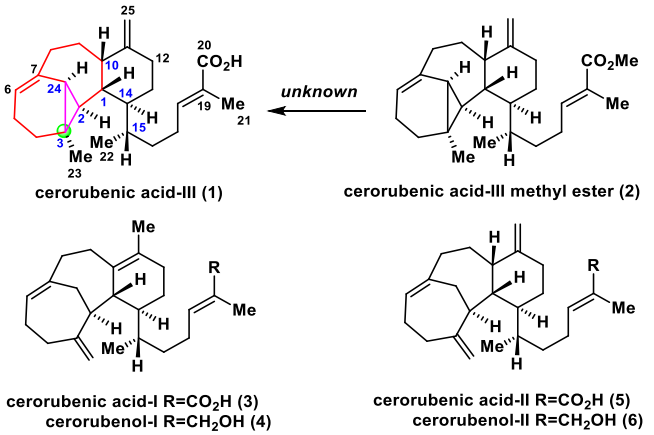

Figure 1. Structures of cerorubenic acid-III and its analogues.

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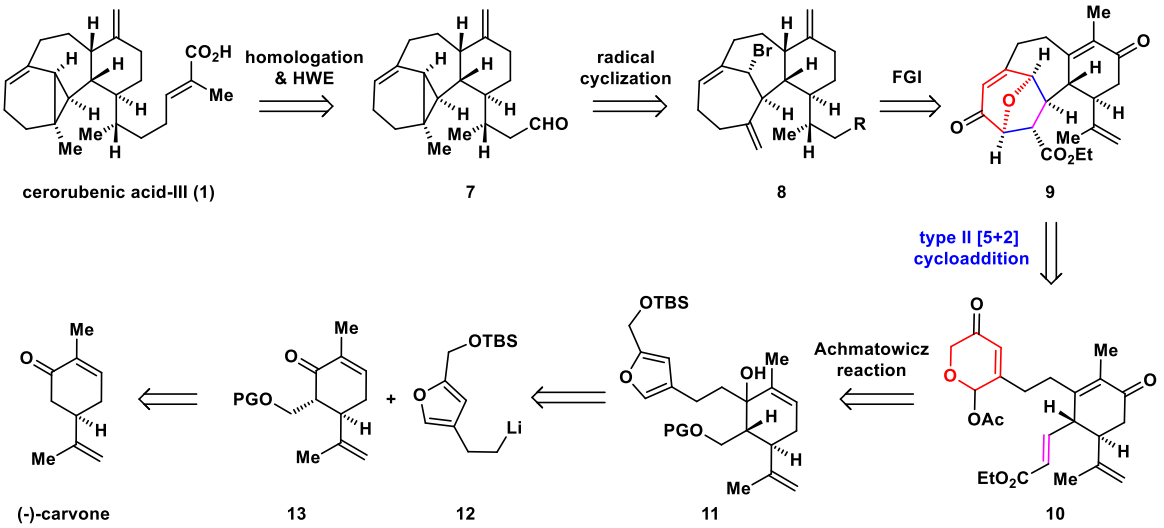


Figure 2. Retrosynthetic analysis of cerorubenic acid-III (**1**).

Scheme 1. Preparation of Diol 19

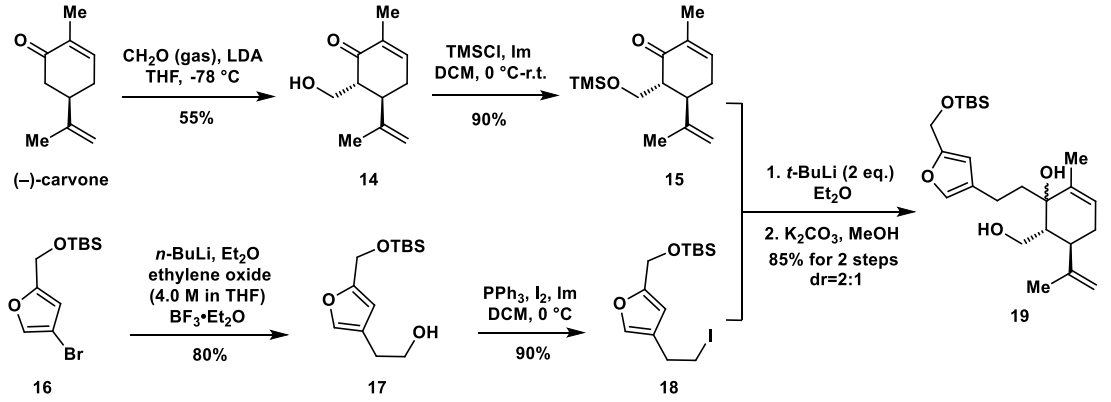
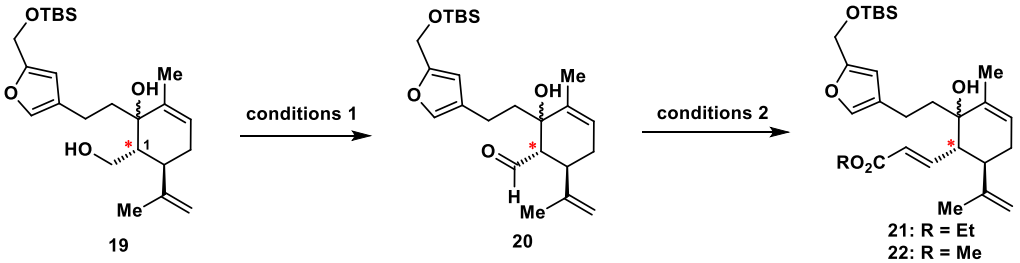


Table 1. Optimization of Conditions for Oxidation and Olefination Reactions



conditions 1					conditions 2					
entry	reagent	solvent	temp.	yield	entry	reagent	solvent	temp.	yield	dr
1	DMP	DCM	r.t.	about 20%	1	$(EtO)_2P(O)CH_2CO_2Et$, *n*-BuLi	THF	-78 °C	59%	1.5:1
2	TPAP/NMO	DCM/CH_3CN	r.t.	67%, 15% of 19	2	$Ph_3P=CHCO_2Me$	$PhCH_3$	80 °C	85%	10:1
3	$(COCl)_2$/TEA	DMSO	-78 °C	75%	3		$PhCH_3$	100 °C	85%	5:1
4	IBX	DMSO	r.t	88%	4		DCE	80 °C	90%	≥ 20:1
5	PCC	DCM	0 °C to r.t.	about 40%						

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strategy for the enantioselective total synthesis of cerorubenic acid-III,[8] which was enabled by a type II [5+2] cycloaddition reaction.

RESULT AND DISCUSSION

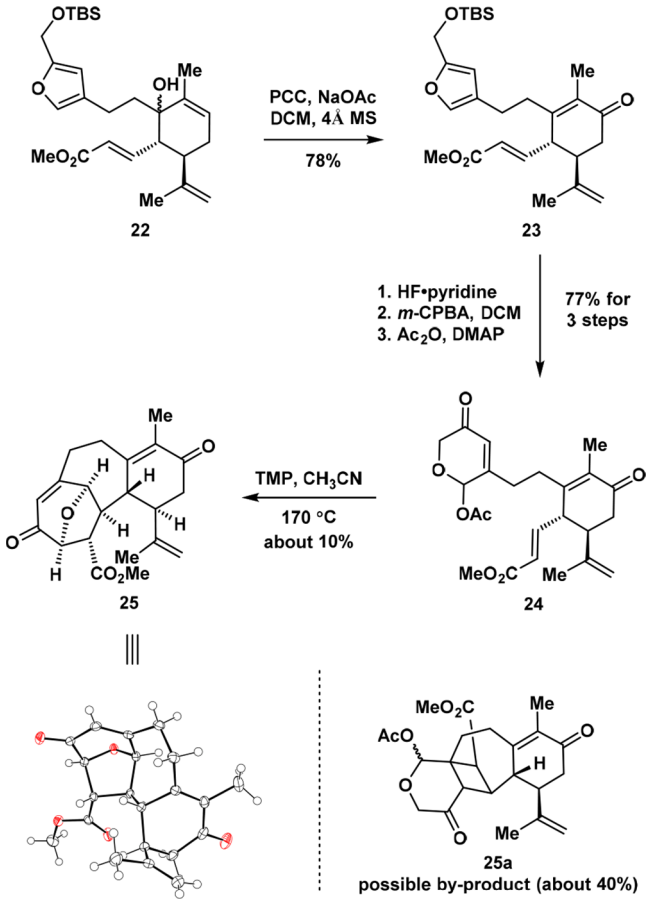
Retrosynthetic Analysis of Cerorubenic Acid-III (1). Figure 2 shows our retrosynthetic analysis of cerorubenic acid-III (**1**). We planned to install the tiglic acid side chain via the homologation of aldehyde **7**, followed by a Horner−Wadsworth−Emmons (HWE) reaction.[9] The challenging vinylcyclopropane fragment was designed to be formed by a radical-initiated cyclization[10] from advanced intermediate **8**. Tricyclic core **8** could be achieved through a series of functional group interconversions (FGIs) of **9**. Bridged skeleton **9** was proposed to be prepared by the type II [5+2] cycloaddition reaction[11] of **10**. Acetoxypyranone **10** could be synthesized from furan **11** using an Achmatowicz reaction[12] after installing the unsaturated ester. Finally, furan **11** could be readily prepared by coupling lithium reagent **12** with enone **13**, which would be accessed from (−)-carvone.

Our synthetic work started with the synthesis of compound **19** (Scheme 1). The reported Tollens condensation reaction of (−)-carvone was used to yield **14** with high stereoselectivity.[13] Subsequent protection of the primary alcohol with trimethylsilyl chloride (TMSCl) gave **15** in a moderate yield over two steps and could be conducted on a 10 g scale. 2,4-Disubstituted furan iodide **18** was prepared efficiently from known furan bromide compound **16**[11b] in two steps. Subsequent coupling of the two fragments was realized using a 1,2-addition reaction, followed by a mild deprotection of the TMS group to furnish diol compound **19** in 85% yield over two steps with 2:1 dr.

With diol **19** in hand, we focused on the installation of the olefin moiety for the type II [5+2] cycloaddition while avoiding the racemization at the C1 position and the elimination of tertiary alcohol. The first challenge was to oxidize the primary alcohol to aldehyde **20**. Selective conditions (conditions 1) are shown in Table 1. IBX and DMSO were finally found to be the best conditions, resulting in an 88% yield and no racemization. For the olefination reaction, different HWE and Wittig reaction conditions were screened (conditions 2, Table 1), with the condition shown in entry 4 giving ester **22** in high yield (90%) with limited racemization.

Having secured a method for the synthesis of compound **22**, we proceeded to prepare acetoxypyranone **24**, a precursor for the type II [5+2] cycloaddition reaction (Scheme 2). The tertiary alcohol was expected to be a good nucleophile in the presence of the acetoxypyranone. Therefore, PCC-mediated Babler oxidation of **22** provided the corresponding cyclohexenone (**23**) in a good yield. Subsequent deprotection of the TBS group using Olah's reagent released furan alcohol (not shown) smoothly. Achmatowicz rearrangement of the furan alcohol initiated by *m*-CPBA, followed by acetylation, gave the desired precursor **24** for the type II [5+2] cycloaddition in a high yield. Fortunately, the key reaction furnished desired tricyclic compound **25** successfully, with the structure confirmed by X-ray crystallography. However, the yield was as low as about 10%, with several attempts (different base and solvent) at improved yields failing. After careful analysis of the byproducts, we found that a possible four-membered ring structure related to the unsaturated ester might contribute to the low cyclization yield. Therefore, a modification of precursor **24** was proposed, replacing the unsaturated ester with an allylic alcohol.

Scheme 2. First Attempt at Type II [5+2] Cycloaddition Reaction[a]



[a]ORTEP drawing of **25** showing thermal ellipsoids at the 50% probability level.

Starting from ester **22**, reduction with DIBAL-H, protection of the corresponding allylic alcohol with acetic anhydride followed by Babler oxidation gave enone **26** in 63% overall yield for three steps (Scheme 3). Another three-step transformation from **26** gave modified precursor **28** efficiently. Subjecting **28** to the standard conditions, the type II [5+2] cycloaddition of **28** afforded desired product **29** as a single diastereomer in an improved yield of 71%, its structure was later confirmed by X-ray crystallography.

With compound **29** in hand, the main skeleton of our target natural product had been prepared, allowing us to proceed to the next phase of our synthesis (Scheme 4). As the radical-initiated reductive cleavage of C−O bonds (Li, $MeNH_2$) in 8-oxabicyclo[3.2.1]octene has been well studied by our group,[11c] we initially planned to prepare triolefin **30** by directly reducing the two enones in **29**. After screening many different conditions, treating **29** with $NaBH_3CN$ in the presence of $BF_3{\cdot}Et_2O$,[14] was found to reduce the enones smoothly, giving alcohol **30** as a single diastereomer in moderate yield. Next, a two-step Barton−McCombie deoxygenation of **30** yielded a mixture of target compound **32** and side-product **31** with the migration of the bridgehead olefin. Selective cleavage of the C−O bond was completed by treating this mixture with Li/$MeNH_2$ to give diol **33**, which was then protected to afford **34** in good yield. As the subsequent installation of the cyclopropane moiety and a side chain to create a chiral center at C15 from **34** proved to be

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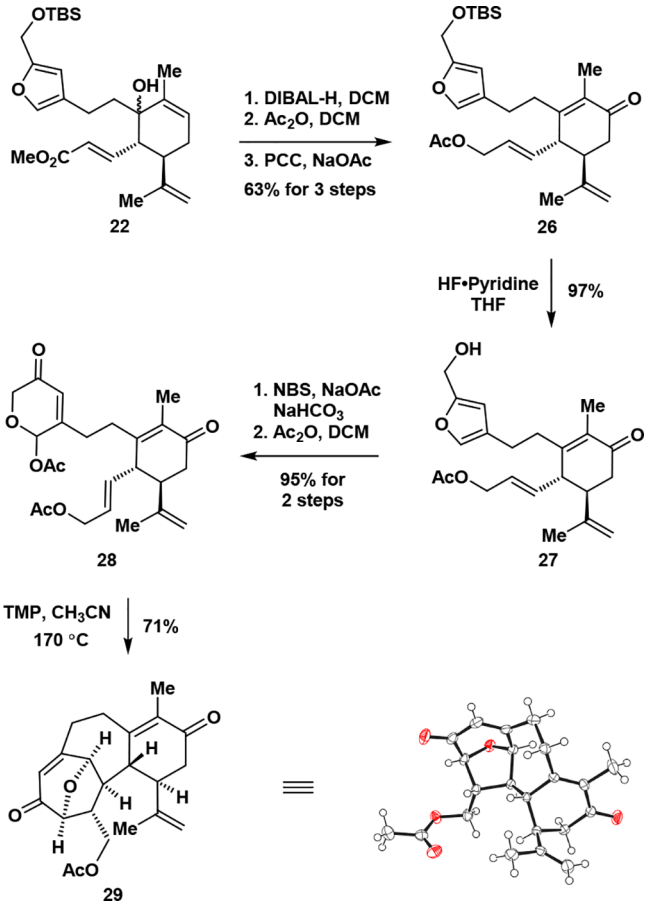
Scheme 3. Second Attempt at Type II [5+2] Cycloaddition Reaction[a]



[a]ORTEP drawing of **29** showing thermal ellipsoids at the 50% probability level.

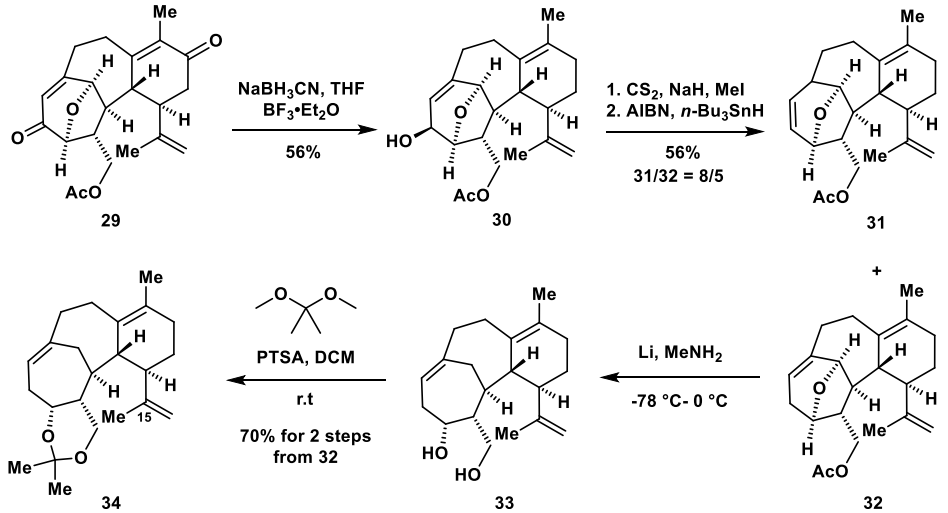
difficult, we turned to another approach to accomplish the synthesis of cerorubenic acid-III.

Retrosynthetic Analysis of Cerorubenic Acid-III (1): Second Generation. A modified retrosynthetic analysis of cerorubenic acid-III (**1**) is shown in Figure 3. We envisaged that cerorubenic acid-III could be generated from advanced intermediate **35** through a selective cross-metathesis (CM) reaction with methacrylic acid.[15] The challenging cyclopropane moiety[16] in **35** could be prepared from tricyclic intermediate **36** through a key transannular cyclization reaction followed by a series of FGIs. Aldehyde **36** was proposed to be obtained from **37** via a selective C−O bond cleavage.[17] The well-studied type II [5+2] cycloaddition of **38** would then yield tricyclic skeleton **37** stereoselectively according to our results above. Key reaction precursor **38** would be accessed from **39** through an Achmatowicz reaction. Finally, ketone **39** would be combined in a one-step process via a cascade 1,4-addition−aldol reaction[18] from enone **42**, which could be prepared from commercially available (*S*)-citronellal and methyl vinyl ketone (MVK).

This new approach started from the asymmetric synthesis of enone **42** (Scheme 5). In contrast to reported work,[19] we employed more readily available proline-derived catalyst **44**,[20] prepared from (*S*)-(+)-α,α-diphenyl-2-pyrrolidinemethanol (**43**) in one step, in the asymmetric Michael addition reaction to afford **45** in 79% yield with 95% de from commercially available (−)-citronellal. The subsequent aldol condensation and dehydration provided enone **42** on a 20 g scale with 93% de. Meanwhile, furan aldehyde **41** was synthesized on a gram scale from alcohol **17** by oxidation using IBX, and the tin reagent **47** was prepared in two steps from propargyl alcohol (**46**) according to the reported procedure.[21]

With the building blocks **41**, **42**, and **47** in hand, we attempted the three-component coupling reaction (Scheme 6). Copper-catalyzed conjugate addition of the organolithium reagent, prepared from **47** via tin−lithium exchange, to enone **42** yielded silyl enol ether **48** smoothly after quenching the enolate with TMSCl. Treatment of **48** with *n*-BuLi, followed by trapping of the lithium enolate with aldehyde **41** in the presence of $ZnBr_2$, furnished β-hydroxyketone **49**. Compound **49** was found to be acid-sensitive and partially cyclized to give **50** during the workup and purification. The β-hydroxyketone moiety in **49** was also sensitive to base owing to a possible retro-aldol reaction. Careful acetyl-protection of the hydroxy group and TBS group deprotection then gave **51** in moderate yield. However, the subsequent Achmatowicz reaction to prepare **52** gave undesired products (such as **53** and **54**) under different conditions. As the ketone group in **49** was the main issue during synthesis, in situ

Scheme 4. Synthesis of Core Skeleton of Cerorubenic Acid



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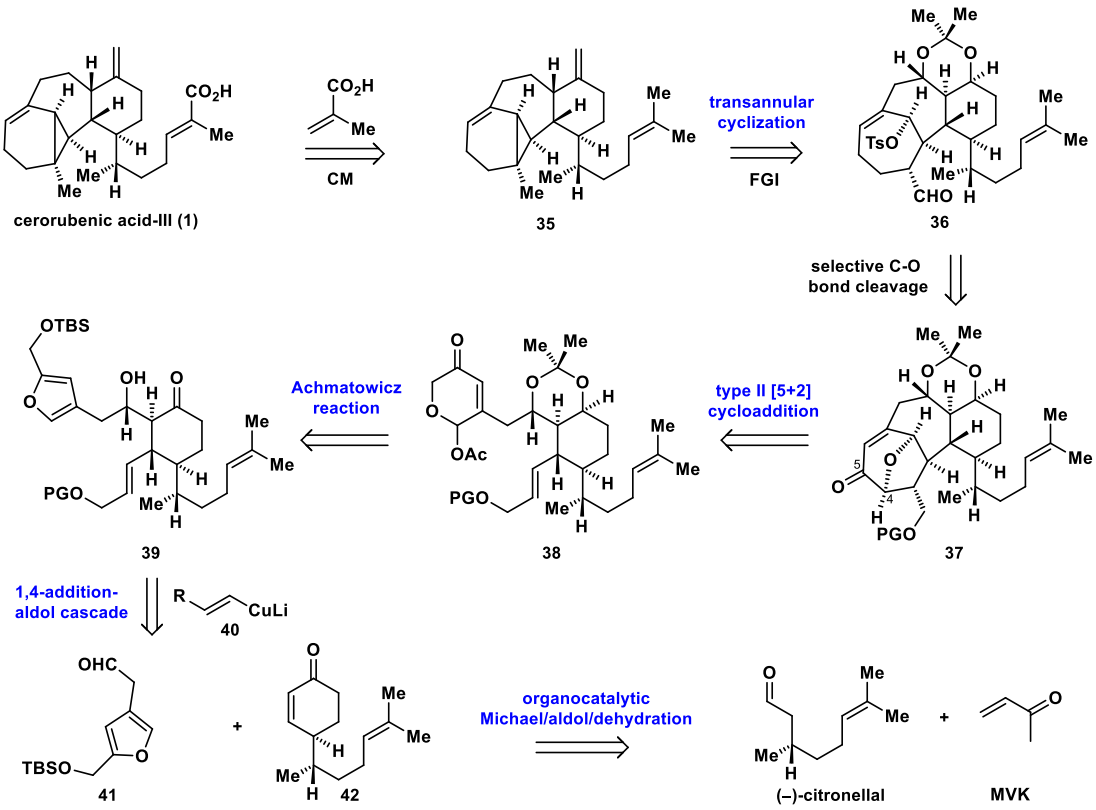
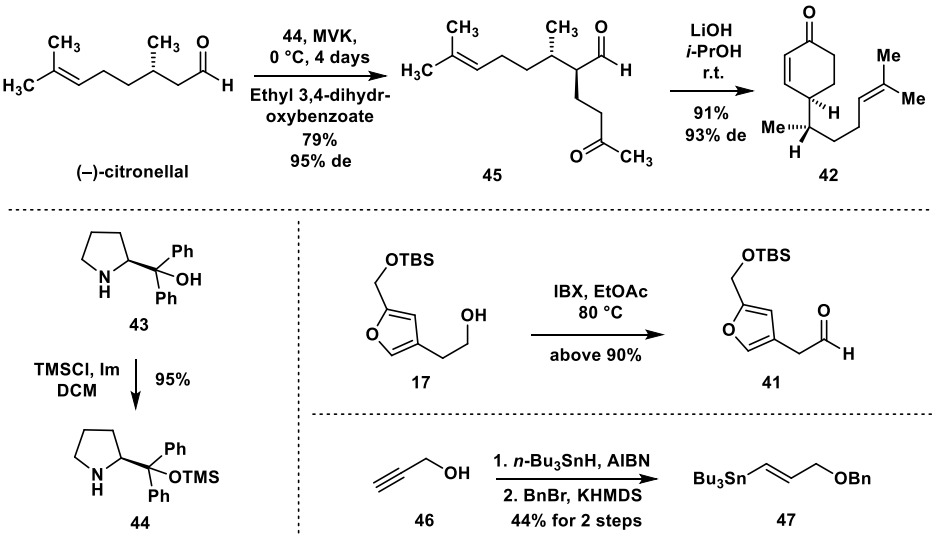


Figure 3. Retrosynthetic analysis of cerorubenic acid-III.

Scheme 5. Gram-Scale Synthesis of Building Blocks 42, 41, and 47



reduction of the β-hydroxyketone using DIBAL-H after the aldol reaction gave stable diol **55** efficiently with 50% overall yield over two steps from **42**.

After successful installation of the furan and olefin, we proceeded to the type II [5+2] cycloaddition (Scheme 7). Acetalization of diol **55** with acetone by TsOH, followed by removal of TBS protecting group with TBAF, afforded **56** in good yield. $VO(acac)_2$ and TBHP were found to be the best reagents for the oxidative rearrangement of **56**. Protection of the anomeric hydroxyl group with Ac_2O in one pot afforded precursor **57** in 71% yield. The type II intramolecular [5+2] cycloaddition of **57** gave target product **58** in 72% yield with excellent *endo* selectivity and diastereoselectivity. The structure was confirmed by X-ray crystallographic analysis of its derivative (**60**, Scheme 7), obtained from **58** in two steps, namely, a reduction to give **59** and subsequent esterification. A suitable quantity (20 g) of **59** was successfully prepared using this facile synthetic route.

We next investigated the selective cleavage of the C−O bond in the bridged ring system (Scheme 8). Our initial attempt aimed to achieve direct cleavage of the C−O bond at the C4 position in enone **58** (Scheme 7). However, the treatment of enone **58** with SmI_2 in various solvents failed to give the desired product. Accordingly, bromide **61**, prepared from alcohol **59** in

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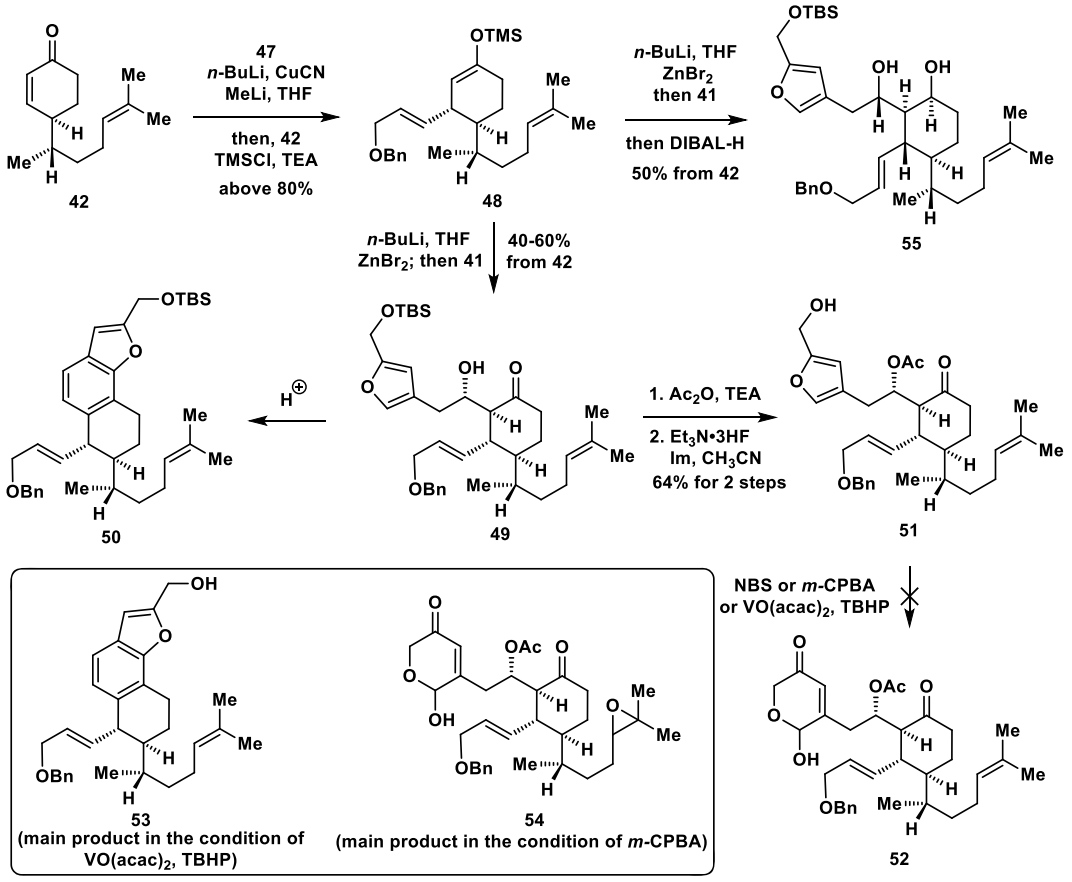
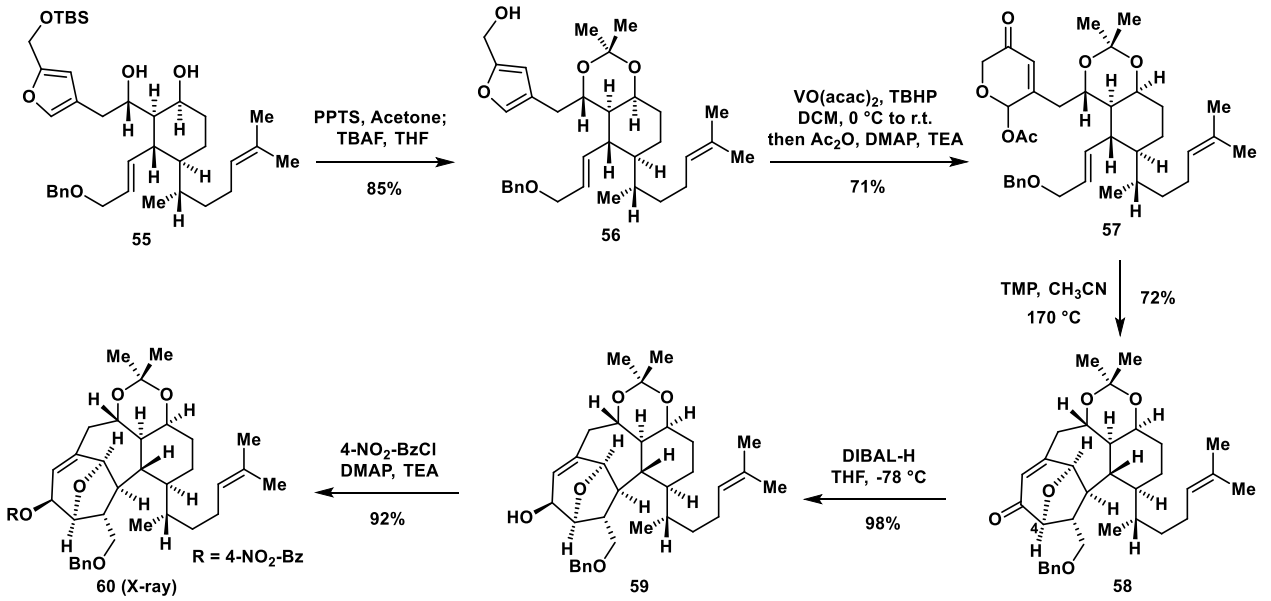
Scheme 6. Attempts at a Three-Component Coupling Reaction



Scheme 7. Construction of the Tricycle Skeleton via Type II [5+2] Cycloaddition



one step, was treated with SmI_2 or *t*-BuLi to give diene **62** with cleavage of the oxygen bridge. However, the yield was relatively low and difficult to repeat (21%−35%). Subsequently, we switched to treatment of **61** with Na-naphthalenide in THF−H_2O, which smoothly afforded diol **64** in 78% yield. Notably, when the reaction was conducted in anhydrous THF solution (gram scale), diene compound **63** was obtained as a major product. The diene intermediate could also be converted to **64** by subjecting to the Na-naphthalenide conditions again, but the yield was lower than that of the one-pot process. Therefore, this remarkable reaction successfully cleaved the C4−O bond, removed the benzyl group, and reduced the less hindered C4−C5 double bond of the diene intermediate. The structure of diol **64** was finally confirmed by 2D-NMR.

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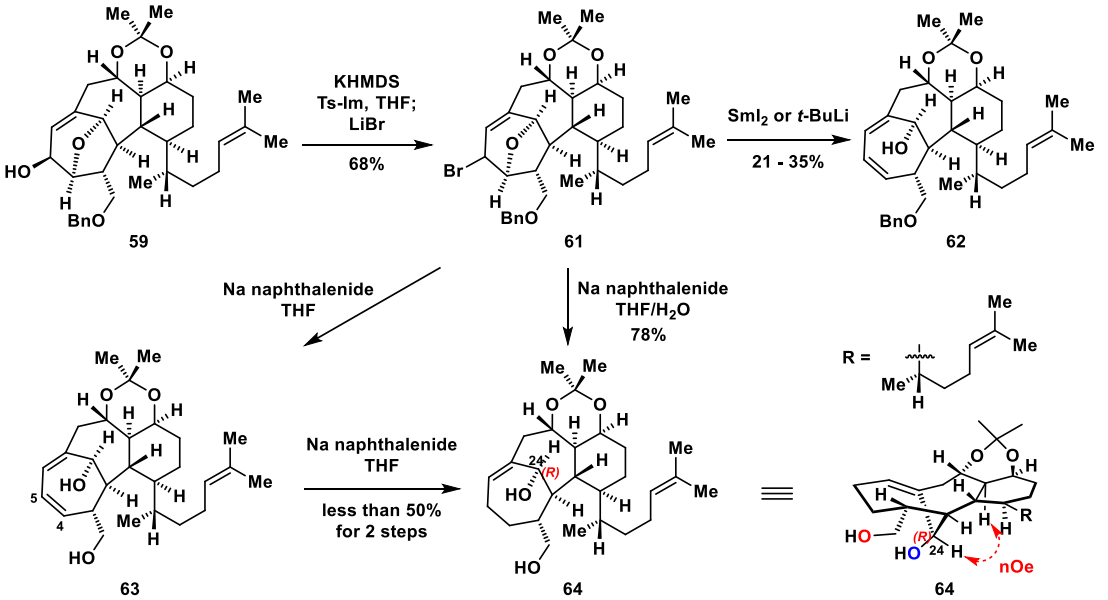
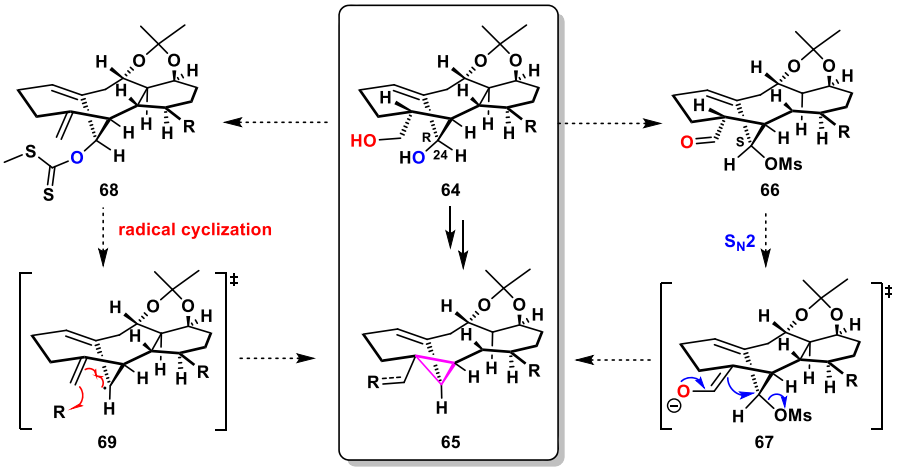
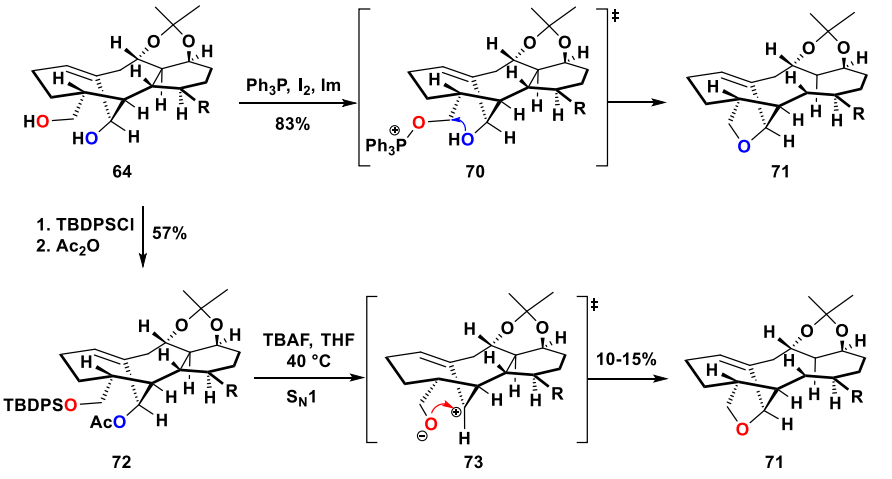
Scheme 8. Selective C−O Bond Cleavage



Scheme 9. Proposed S_N2 and Radical Cyclization Pathways for Cyclopropanation



Scheme 10. Discovery of an Unusual S_N1 Cyclization



As shown in Scheme 9, two cyclopropanation pathways (S_N2 and radical cyclization) were proposed for accessing compound **65** from **64**. In the S_N2 pathway, the stereocenter at C24 needed to be inverted from *R* (**64**) to *S* (**66**), then cyclized to give **65** via intermediate **67**. In the radical cyclization pathway, the external olefin in **68** needed to be installed first, with subsequent radical-

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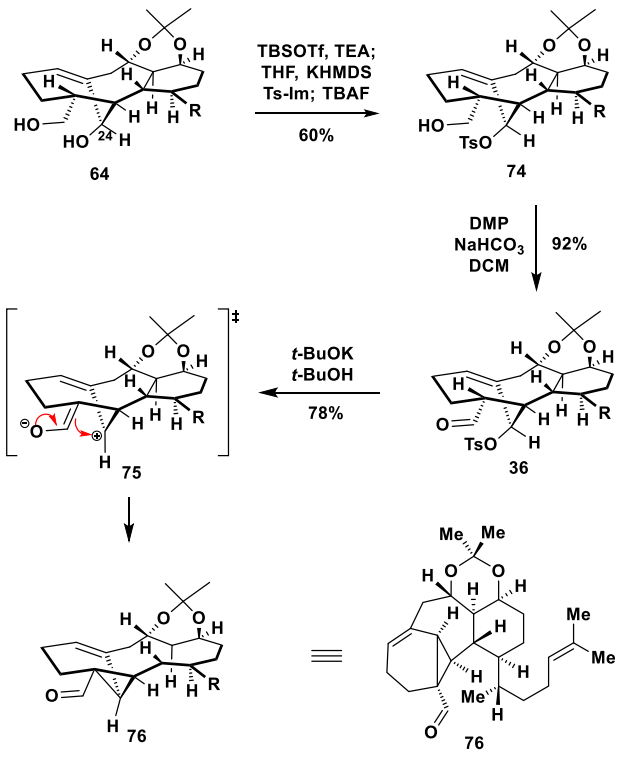
initiated cyclization[9b] affording compound **65** via intermediate **69**.

The radical cyclization pathway was studied first. We attempted to install the terminal alkene at C3 through selective iodination of the primary alcohol in **64**, which seemed theoretically feasible, followed by elimination of the hydrogen halide under basic conditions. To our surprise, subjecting diol **64** to Ph_3P/I_2/imidazole conditions afforded ring closure product **71**, containing a tetrahydrofuran moiety, in 83% yield (Scheme 10). We reasoned that the activated primary alcohol in **64** was attacked by the hydroxyl group (blue) at C24. Therefore, the secondary alcohol needed to be protected in advance. Two-step protection of the two hydroxyl groups furnished **72** in 57% yield, followed by deprotection of the TBDPS group. Surprisingly, when **72** was treated with TBAF, byproduct **71** was obtained in 10%−15% yield, along with the target product in 45% yield. Regarding the mechanism, this reaction proceeded via an S_N1 pathway through cation intermediate **73**, with the oxygen in the tetrahydrofuran moiety originating from the primary alcohol (red).

Inspired by this observation, a more direct and feasible method for cyclopropanation via a cationic intermediate was proposed. Aldehyde **36** was prepared from **64** in moderate yield over two steps (Scheme 11). As expected, the cyclization

Scheme 11. Cyclopropanation via an S_N1 Pathway



proceeded smoothly under basic conditions to afford **76** diastereoselectively in 78% yield. Regarding the mechanism, cationic intermediate **75**, stabilized by the adjacent vinyl group, was proposed to be generated when treated with *t*-BuOK, which was then attacked by the enolate to yield the desired vinylcyclopropane.

Our total synthesis of cerorubenic acid-III now entered the final stages. First, a one-pot Wolff−Kishner reduction[22] (Scheme 12) and deprotection using acetic acid was conducted to afford diol **77** in a high yield. Subsequently, the less sterically hindered hydroxyl group (left) in **77** was selectively protected by low-temperature acetylation. The remaining alcohol was oxidized by DMP in one pot to give the corresponding ketone in a high yield. Base-mediated elimination was conducted carefully with KHMDS to give target enone **78** in 80% yield over two steps. The next task was the crucial 1,4-reduction of enone **78** to complete the final chiral center. Fortunately, **78** was reduced by $NaBH_4$ and $NiCl_2$ to afford the corresponding ketone efficiently.[23] Subsequent olefination of the carbonyl group afforded triene **35**. The endgame and completion of the total synthesis were realized by cross-metathesis (CM) to install the side chain. The designed CM reaction of **35** with methacrylic acid catalyzed by Grubbs II reagent failed to give the natural product. However, an alternative CM reaction with methacrylaldehyde using Grubbs II catalyst proceeded well, with subsequent oxidation by in situ generated Ag_2O giving **1** in 27% overall yield from **78**. To confirm this result, treatment of **1** with $TMSCHN_2$ afforded cerorubenic acid-III methyl ester (**2**) in 95% yield.[24] Therefore, the enantioselective total synthesis of cerorubenic acid-III was completed.

CONCLUSIONS

In summary, we have accomplished the first enantioselective total synthesis of cerorubenic acid-III in 19 steps after two different synthetic strategies were studied. This work features a powerful type II [5+2] cycloaddition reaction. The synthetically challenging bicyclo[4.4.1] ring system with a strained bridgehead double bond was constructed efficiently. Besides, a chemoselective cascade cleavage of 8-oxabicyclo[3.2.1]octene was realized using sodium naphthalenide condition. This reaction largely improved the synthetic efficiency as three transformations occurred in one operation. Finally, the vinylcyclopropane moiety was installed using an unusual transannular cyclization reaction with retention of the desired stereochemistry. The detailed efficient and diastereoselective approach described above can also be extended to the asymmetric synthesis of other cerorubenic acids, cerorubenols, and their derivatives and provide materials for further biological research.

EXPERIMENTAL SECTION

General Experimental Information. Unless otherwise mentioned, all reactions were carried out under a nitrogen atmosphere under anhydrous conditions, and all reagents were purchased from commercial suppliers without further purification. Solvent purification was conducted according to Purification of Laboratory Chemicals (Perrin, D. D.; Armarego, W. L. and Perrins, D. R., Pergamon Press: Oxford, 1980). Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography on plates (GF254) supplied by Yantai Chemicals (China) using UV light as a visualizing agent, an ethanolic solution of phosphomolybdic acid, or basic aqueous potassium permanganate ($KMnO_4$), and heat as developing agents. If not specially mentioned, flash column chromatography uses silica gel (200−300 mesh) supplied by Tsingtao Haiyang Chemicals (China). NMR spectra were recorded on Bruker AV-500 and calibrated using a residual undeuterated solvent as an internal reference ($CHCl_3$, δ 7.26 ppm ^{1}H NMR, δ 77.16 ^{13}C NMR; CH_2Cl_2, δ 5.32 ppm ^{1}H NMR, δ 54.00 ^{13}C NMR; C_6D_6, δ 7.15 ppm ^{1}H NMR, δ 128.00 ^{13}C NMR). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, b = broad, m = multiplet, td = triplet of doublets, dt = doublet of triplets. High-resolution mass spectrometric (HRMS) data were recorded on a Brüker Apex IV RTMS instrument using a quadrupole analyzer or on a Thermo Scientific Q Exactive using an orbitrap analyzer. X-ray

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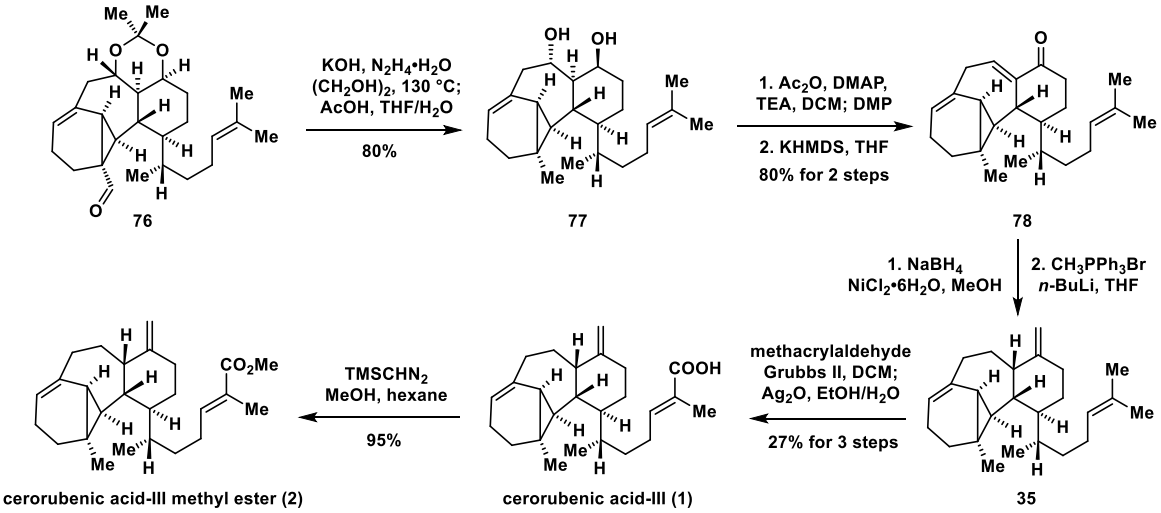
Scheme 12. Total Synthesis of Cerorubenic Acid-III



diffraction data were collected at 100 K on a Bruker-D8 venture microsource diffractometer.

Procedures and characterization data for compounds **16**, **17**, **35**, **42**, **45**, **55**, **56**, **57**, **58**, **59**, **61**, **64**, **76**, and **78** were reported previously.[8]

(5*R*,6*R*)-2-Methyl-5-(prop-1-en-2-yl)-6-(((trimethylsilyl)oxy)-methyl)cyclohex-2-en-1-one (15). To a solution of **14** (5.0 g, 27.78 mmol) in anhydrous DCM (60 mL) was added imidazole (2.8 g, 41.67 mmol) at 0 °C. After the mixture was stirred at the same temperature for 5 min, chlorotrimethylsilane (3.6 g, 33.34 mmol) was added to the reaction slowly. The mixture was warmed to 25 °C and stirred for 2 h. The reaction was quenched by the addition of saturated NH_4Cl (50 mL). Then the aqueous layer was extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4. The dried solution was filtered and concentrated. The residue obtained was purified by flash column chromatography on silica gel (hexane/EtOAc = 30:1) to afford **15** (6.3 g, 90%) as a colorless oil: R_f = 0.65 (hexane/EtOAc = 10:1); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{25}O_2Si$ 253.1618, found 253.1615; ^1H NMR (500 MHz, $CDCl_3$) δ 6.66 (ddt, J = 5.6, 3.0, 1.4 Hz, 1H), 4.83−4.76 (m, 2H), 4.07 (dd, J = 9.7, 3.4 Hz, 1H), 3.58 (dd, J = 9.7, 3.5 Hz, 1H), 2.97−2.89 (m, 1H), 2.33 (ddt, J = 18.5, 11.6, 3.0 Hz, 3H), 1.79−1.73 (m, 3H), 1.70 (d, J = 1.2 Hz, 3H), 0.03 (d, J = 1.2 Hz, 9H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 199.1, 145.6, 143.8, 135.6, 112.9, 59.0, 51.6, 43.7, 30.4, 19.6, 16.2, −0.5.

***tert*-Butyl((4-(2-iodoethyl)furan-2-yl)methoxy)-dimethylsilane (18).** I_2 (3.0 g, 12 mmol), triphenylphosphine (3.1 g, 12 mmol), and imidazole (1.0 g, 15 mmol) were dissolved in anhydrous DCM (50 mL), and the mixture was stirred at room temperature for 5 min. A solution of compound **17** (2.6 g, 10.0 mmol) in anhydrous DCM (5 mL) was added dropwise to the mixture. The reaction was stirred at rt for 3 h. The mixture was quenched with saturated $Na_2S_2O_3$ solution (50 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (15 mL). After drying over Na_2SO_4, the solution was concentrated in vacuo and purified by flash chromatography on silica gel quickly (hexane/EtOAc = 80:1) to afford **18** (3.3 g, 90%) as a colorless oil: R_f = 0.3 (hexane/EtOAc = 50:1); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{23}IO_2Si$ 367.0585, found 367.0588; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 1.0 Hz, 1H), 6.14 (d, J = 0.9 Hz, 1H), 4.60 (d, J = 0.7 Hz, 2H), 3.27 (t, J = 7.5 Hz, 2H), 2.97 (td, J = 7.6, 0.8 Hz, 2H), 0.91 (s, 9H), 0.08 (s, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 154.7, 138.7, 124.4, 107.9, 58.2, 29.7, 25.9, 18.4, 4.8, −5.3.

(5*R*,6*R*)-1-(2-(5-(((*tert*-Butyldimethylsilyl)oxy)methyl)furan-3-yl)ethyl)-6-(hydroxymethyl)-2-methyl-5-(prop-1-en-2-yl)-cyclohex-2-en-1-ol (19). To a solution of **18** (2.01 g, 5.5 mmol) in anhydrous Et_2O (30 mL) under an argon atmosphere was added dropwise *t*BuLi (8.5 mL, 11.0 mmol, 1.3 M solution in pentane) at −78 °C. After stirring at −78 °C for 1 h, a solution of **15** (1.26 g, 5.0 mmol) in anhydrous Et_2O (10 mL) was added dropwise. The reaction mixture was left to stir at −78 °C until completion (30 min), and it was quenched by saturated NH_4Cl and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a crude product. The crude product was redissolved in the MeOH (50 mL), and a catalytic amount of K_2CO_3 (138 mg, 1.0 mmol) was added to the solution at room temperature; the mixture was stirred for 1 h at the same temperature. The reaction was quenched by saturated NH_4Cl. Then, MeOH was removed under reduced pressure, and the aqueous was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by flash chromatography on silica gel (hexane/EtOAc = 20:1) to afford **19** (1.79 g, 85%, dr = 2:1, partly separable) as a colorless oil. Note that to be accurate and for convenience, two diastereisomers of **19** were characterized by NMR spectroscopy and mass spectrometry independently (named **19a** and **19b**), but their relative configuration has not been determined. The same situation obtains compounds **20**, **21**, and **22**: HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{24}H_{40}NaO_4Si$ 443.2588, found 443.2588. Compound **19a**: R_f = 0.30 (hexane/EtOAc = 5:1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, J = 1.1 Hz, 1H), 6.18−6.12 (m, 1H), 5.54 (dt, J = 3.1, 1.5 Hz, 1H), 4.80−4.69 (m, 2H), 4.58 (s, 2H), 3.81−3.69 (m, 2H), 3.31 (s, 1H), 2.90 (d, J = 4.6 Hz, 1H), 2.52−2.35 (m, 3H), 2.14−1.88 (m, 5H), 1.77 (d, J = 1.9 Hz, 3H), 1.68 (d, J = 1.1 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 6H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 154.6, 146.6, 138.1, 137.4, 126.1, 124.3, 112.9, 108.7, 77.0, 63.7, 58.4, 47.5, 42.8, 36.9, 30.4, 26.1, 21.4, 18.6, 17.8, 17.5, −5.1. Compound **19b**: R_f = 0.28 (hexane/EtOAc = 5:1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, J = 1.1 Hz, 1H), 6.10 (d, J = 0.9 Hz, 1H), 5.69 (dq, J = 5.7, 1.7 Hz, 1H), 4.99−4.80 (m, 2H), 4.64−4.51 (m, 2H), 4.04 (dd, J = 11.9, 2.2 Hz, 1H), 3.73 (dd, J = 12.0, 3.3 Hz, 1H), 2.96 (d, J = 0.0 Hz, 2H), 2.71 (ddd, J = 12.0, 10.8, 5.7 Hz, 1H), 2.25−2.12 (m, 2H), 2.11−1.97 (m, 4H), 1.72 (t, J = 1.9 Hz, 6H), 1.65 (dtd, J = 12.2, 3.4, 2.2, 0.0 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 6H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 154.7, 147.5, 138.0, 135.7, 127.2, 125.3, 113.0, 108.5, 76.7, 61.1, 58.4, 42.9, 40.0, 36.7, 31.2, 26.0, 20.6, 19.1, 18.5, 17.9, −5.1.

(1*S*,6*R*)-2-(2-(5-(((*tert*-Butyldimethylsilyl)oxy)methyl)furan-3-yl)ethyl)-2-hydroxy-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1-carbaldehyde (20). To a solution of **19** (1.68 g, 4.0 mmol) in DMSO (40 mL) was added IBX (2.8 g, 10.0 mmol) at room temperature, and the mixture was stirred for 1 h. The reaction was quenched by saturated Na_2SO_3. The mixture was diluted with water (200 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with water (100 mL) again and then washed with brine (50 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by flash chromatography on silica gel (hexane/EtOAc = 15:1) to afford **20** (1.47 g, 88%) as a colorless oil: HRMS (ESI) m/z

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calcd for $[M + NH_4]^+$ $C_{24}H_{42}NO_4Si$ 436.2878, found 436.2878. Compound **20a**: R_f = 0.55 (hexane/EtOAc = 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (d, J = 3.4 Hz, 1H), 7.13 (d, J = 1.1 Hz, 1H), 6.09 (s, 1H), 5.54−5.45 (m, 1H), 4.90−4.80 (m, 2H), 4.57 (s, 2H), 2.91 (ddd, J = 11.8, 9.1, 6.7 Hz, 1H), 2.69−2.61 (m, 2H), 2.54−2.35 (m, 2H), 2.31−2.21 (m, 1H), 2.12−2.04 (m, 1H), 1.97 (ddd, J = 14.1, 12.2, 5.5 Hz, 1H), 1.86 (ddd, J = 14.1, 12.6, 4.5 Hz, 1H), 1.78 (d, J = 1.8 Hz, 3H), 1.74−1.70 (m, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 206.3, 154.7, 146.4, 138.2, 137.6, 125.5, 123.7, 113.1, 108.5, 75.5, 59.1, 58.4, 40.5, 38.4, 30.1, 26.0, 20.8, 19.9, 18.6, 17.9, −5.1. Compound **20b**: R_f = 0.55 (hexane/EtOAc = 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.61 (d, J = 4.6 Hz, 1H), 7.15 (d, J = 1.0 Hz, 1H), 6.12 (d, J = 0.9 Hz, 1H), 5.74 (dt, J = 5.8, 1.7 Hz, 1H), 4.85 (dt, J = 5.6, 1.6 Hz, 2H), 4.62−4.50 (m, 2H), 2.94 (dt, J = 11.9, 5.9 Hz, 1H), 2.44 (ddd, J = 17.8, 9.4, 4.8 Hz, 2H), 2.20−2.12 (m, 1H), 2.07−1.99 (m, 3H), 1.94 (ddd, J = 9.6, 6.0, 2.6 Hz, 2H), 1.76−1.73 (m, 3H), 1.69 (d, J = 1.2 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 206.2, 154.7, 145.4, 138.2, 135.3, 127.6, 125.0, 113.8, 108.6, 75.0, 58.4, 55.3, 39.6, 37.4, 30.9, 26.1, 20.3, 19.6, 18.6, 17.4, −5.1.

Ethyl (*E*)-3-((1*S*,6*R*)-2-(2-(5-(((*tert*-Butyldimethylsilyl)oxy)-methyl)furan-3-yl)ethyl)-2-hydroxy-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-en-1-yl)acrylate (21). *n*-BuLi (1.1 mL, 2.2 mmol, 2.0 M solution in pentane) was slowly added to a solution of triethylphosphonoacetate **20** (449 mg, 2.0 mmol) in THF (20 mL) at −78 °C. After 5 min, aldehyde (418 mg, 1.0 mmol) was slowly added, and the resulting mixture was stirred at −78 °C for 10 min and then at room temperature for 1 h. The reaction was quenched with the addition of brine (5 mL), and the mixture was diluted with ether (10 mL), washed with brine (3 × 10 mL), and dried with anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and purified by flash chromatography on silica gel (hexane/EtOAc = 10:1) to afford **21** (288 mg, 59%; dr = 1.5:1) as a colorless oil. Note that data of two target (major) diastereisomers were shown. Compound **21a**: R_f = 0.5 (hexane/EtOAc = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19−7.14 (m, 1H), 6.93−6.84 (m, 1H), 6.12 (s, 1H), 5.97 (d, J = 15.6 Hz, 1H), 5.60 (d, J = 1.8 Hz, 1H), 4.86−4.76 (m, 2H), 4.59 (s, 2H), 4.21 (qd, J = 7.1, 0.7 Hz, 2H), 2.68−2.58 (m, 2H), 2.52−2.40 (m, 2H), 2.15 (dq, J = 6.4, 2.5 Hz, 2H), 1.92 (ddd, J = 13.8, 12.2, 5.7 Hz, 2H), 1.84 (s, 1H), 1.80 (q, J = 1.9 Hz, 3H), 1.78−1.69 (m, 2H), 1.67 (d, J = 1.4 Hz, 1H), 1.30 (dd, J = 7.2, 0.8 Hz, 3H), 0.92 (d, J = 0.8 Hz, 9H), 0.10 (d, J = 0.8 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.9, 154.5, 147.8, 146.5, 138.1, 136.7, 125.6, 124.3, 123.9, 113.1, 108.5, 75.2, 60.4, 58.3, 52.1, 44.6, 38.0, 29.3, 25.9, 20.5, 18.5, 18.4, 18.3, 14.3, −5.2. Compound **21b**: R_f = 0.5 (hexane/EtOAc = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 1.1 Hz, 1H), 6.94 (dd, J = 15.9, 10.4 Hz, 1H), 6.11 (d, J = 1.0 Hz, 1H), 5.81 (d, J = 15.9 Hz, 1H), 5.79−5.70 (m, 1H), 4.86−4.69 (m, 2H), 4.60 (s, 2H), 4.20 (qd, J = 7.1, 1.3 Hz, 2H), 2.62 (td, J = 11.3, 5.5 Hz, 1H), 2.41 (dd, J = 11.8, 10.4 Hz, 1H), 2.33 (ddd, J = 10.8, 8.5, 5.7 Hz, 1H), 2.17−1.96 (m, 4H), 1.94−1.80 (m, 3H), 1.77 (dt, J = 2.5, 1.5 Hz, 3H), 1.75 (s, 1H), 1.64 (s, 1H), 1.31 (t, J = 7.2 Hz, 3H), 0.92 (s, 9H), 0.10 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.1, 154.6, 148.2, 145.9, 137.9, 135.2, 127.6, 124.9, 123.1, 113.2, 108.5, 74.4, 60.3, 58.3, 48.0, 42.6, 36.6, 30.7, 25.9, 20.1, 18.7, 18.5, 18.1, 14.3, −5.2.

Methyl (*E*)-3-((1*S*,6*R*)-2-(2-(5-(((*tert*-Butyldimethylsilyl)oxy)-methyl)furan-3-yl)ethyl)-2-hydroxy-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-en-1-yl)acrylate (22). To a solution of **20** (1.25 g, 3.0 mmol) in DCE (50 mL) was added phosphorus ylide (5.0 g, 15 mmol) at rt. Then, the mixture was warmed to 80 °C and stirred at the same temperature overnight. After the reaction finished, the mixture was concentrated in vacuo and purified by flash chromatography on silica gel (hexane/EtOAc = 10:1) to afford **22** (1.28 g, 90%; dr ≥ 20:1) as a colorless oil: HRMS (ESI) m/z $[M + NH_4]^+$ calcd for $C_{27}H_{46}NO_5Si$ 492.3140, found 492.3140. Compound **22a**: R_f = 0.5 (hexane/EtOAc = 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, J = 1.0 Hz, 1H), 6.86 (dd, J = 15.6, 9.9 Hz, 1H), 6.10 (s, 1H), 5.95 (d, J = 15.7 Hz, 1H), 5.58 (td, J = 3.8, 1.7 Hz, 1H), 4.78 (dt, J = 3.8, 1.5 Hz, 2H), 4.57 (s, 2H), 3.73 (s, 3H), 2.68−2.55 (m, 2H), 2.52−2.33 (m, 2H), 2.15−2.09 (m, 2H), 1.89 (ddd, J = 14.0, 12.3, 5.6 Hz, 1H), 1.78 (q, J = 2.0 Hz, 4H), 1.73−1.67 (m, 1H), 1.61 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 166.5, 154.6, 148.2, 146.6, 138.2, 136.9, 125.7, 124.5, 123.6, 113.3, 108.7, 75.4, 58.4, 52.3, 51.7, 44.7, 38.1, 29.5, 26.1, 20.6, 18.6, 18.5, 18.4, −5.1. Compound **22b**: R_f = 0.5 (hexane/EtOAc = 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, J = 1.1 Hz, 1H), 6.93 (dd, J = 15.9, 10.4 Hz, 1H), 6.08 (d, J = 0.9 Hz, 1H), 5.80 (d, J = 15.9 Hz, 1H), 5.75−5.65 (m, 1H), 4.84−4.68 (m, 2H), 4.57 (s, 2H), 3.72 (s, 3H), 3.67−3.63 (m, 1H), 2.59 (td, J = 11.3, 5.3 Hz, 1H), 2.39 (dd, J = 11.8, 10.3 Hz, 1H), 2.34−2.24 (m, 1H), 2.09−2.00 (m, 3H), 1.89−1.79 (m, 2H), 1.77−1.74 (m, 3H), 1.57 (t, J = 1.0 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 166.6, 154.7, 148.6, 146.0, 138.1, 135.3, 127.8, 125.0, 122.9, 113.4, 108.6, 74.5, 58.4, 51.6, 48.1, 42.7, 36.7, 30.8, 26.1, 20.2, 18.8, 18.6, 18.2, −5.1.

Methyl (*E*)-3-((1*S*,6*R*)-2-(2-(5-(((*tert*-Butyldimethylsilyl)oxy)-methyl)furan-3-yl)ethyl)-3-methyl-4-oxo-6-(prop-1-en-2-yl)-cyclohex-2-en-1-yl)acrylate (23). To a slurry solution of pyridinium chlorochromate (1.5 g, 7.0 mmol) and 4 Å MS in dichloromethane (50 mL) was added a solution of alcohol **22** (1.66 g, 3.5 mmol) in dichloromethane (10 mL) at rt, and the resulting dark red mixture was stirred at the same temperature for 2 h. The reaction was worked up by the addition of ether (20 mL), and the formed solution was first filtered through a silica gel pad and washed with ether (3 × 30 mL). The combined organic phases were sequentially washed with an aqueous solution of NaOH (5%, 50 mL), an aqueous solution of HCl (5%, 50 mL), and a saturated aqueous solution of $NaHCO_3$ (2 × 40 mL), and finally dried over anhydrous Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by a flash chromatography on silica gel (hexane/EtOAc = 15:1) to afford **23** (1.28 g, 78%) as a colorless oil: R_f = 0.6 (hexane/EtOAc = 5:1); HRMS (ESI) m/z $[M + NH_4]^+$ calcd for $C_{27}H_{44}NO_5Si$ 490.2983, found 490.2982; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.11 (s, 1H), 6.89 (dd, J = 15.6, 8.5 Hz, 1H), 6.09 (s, 1H), 5.92−5.79 (m, 1H), 4.83 (s, 1H), 4.66 (s, 1H), 4.57 (s, 2H), 3.75 (s, 3H), 3.25 (t, J = 6.8 Hz, 1H), 2.65 (q, J = 5.6 Hz, 1H), 2.61−2.54 (m, 2H), 2.47 (ddt, J = 28.0, 15.4, 5.1 Hz, 3H), 2.25 (ddd, J = 12.4, 9.8, 5.8 Hz, 1H), 1.80 (d, J = 1.5 Hz, 3H), 1.69 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 197.8, 166.4, 155.0, 153.3, 148.1, 144.5, 138.5, 133.4, 124.4, 123.4, 113.5, 108.4, 58.3, 51.9, 46.4, 45.5, 39.2, 34.2, 26.0, 22.9, 21.0, 18.6, 11.1, −5.1.

Methyl (*E*)-3-((1*S*,6*R*)-2-(2-(2-Acetoxy-5-oxo-5,6-dihydro-2*H*-pyran-3-yl)ethyl)-3-methyl-4-oxo-6-(prop-1-en-2-yl)cyclohex-2-en-1-yl)acrylate (24). To a solution of **23** (944 mg, 2.0 mmol) in THF (20 mL) was added pyridine hydrofluoride (1.29 mL, 10 mmol, aq 70% HF) at 0 °C. Then, the mixture was warmed to rt and stirred at the same temperature stirred for 1 h. After the reaction finished, the mixture was cooled to 0 °C and quenched slowly with saturated $NaHCO_3$ (50 mL) until the pH was 7. The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by flash chromatography on silica gel (hexane/EtOAc = 5:1) to give the corresponding free alcohol (651 mg, 91%).

To a solution of the alcohol prepared above (537 mg, 1.5 mmol) in DCM (10 mL) was added 3-chloroperoxybenzoic acid (*m*-CPBA, 75% purity, 414 mg, 1.8 mmol) at rt. Then, the mixture was warmed to 38 °C and stirred at the same temperature for 1.5 h. After the reaction finished, the mixture was quenched with saturated Na_2SO_3 (50 mL). The result mixture was extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a crude product, which was used in the next step without further purification. The crude product was dissolved in anhydrous DCM (10 mL) and cooled to 0 °C. Et_3N (0.32 mL, 2.3 mmol), 4-dimethylaminopyridine (DMAP, 92 mg, 0.75 mmol), and acetic anhydride (Ac_2O, 0.22 mL, 2.3 mmol) were added to the reaction in sequence. Then mixture was stirred at the same temperature until the end of reaction. The reaction was quenched by saturated NH_4Cl (10 mL), and the mixture was extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The dried solution was filtered and concentrated and purified by flash chromatography on silica gel (hexane/EtOAc = 8:1) to afford **24** (530 mg, 85% for two steps; totally 77% for three steps from **23**, dr ≈ 1:1) as a colorless oil: R_f = 0.52 (hexane/EtOAc = 2:1); HRMS (ESI) m/z $[M + NH_4]^+$ calcd for $C_{23}H_{32}NO_7$ 434.2173, found 434.2172; ^{1}H NMR (500 MHz, $CDCl_3$) δ

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6.86 (dt, J = 15.7, 8.6 Hz, 1H), 6.43 (d, J = 2.7 Hz, 1H), 6.05 (d, J = 5.8 Hz, 1H), 5.89 (ddd, J = 15.6, 8.0, 0.9 Hz, 1H), 4.85 (d, J = 1.5 Hz, 1H), 4.71−4.61 (m, 1H), 4.41 (dd, J = 17.0, 1.2 Hz, 1H), 4.17 (d, J = 17.0 Hz, 1H), 3.76 (d, J = 0.7 Hz, 3H), 3.23 (q, J = 7.1 Hz, 1H), 2.67 (ddd, J = 7.6, 5.1, 2.4 Hz, 1H), 2.62−2.46 (m, 3H), 2.30−2.20 (m, 3H), 2.16 (d, J = 4.2 Hz, 3H), 1.82 (dd, J = 5.2, 1.5 Hz, 3H), 1.73−1.70 (m, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 197.4, 197.3, 193.2, 193.2, 169.9, 169.8, 166.2, 166.2, 156.3, 156.3, 151.3, 151.2, 147.3, 144.1, 144.1, 134.0, 125.4, 125.3, 123.8, 123.8, 113.9, 113.8, 88.4, 88.3, 66.5, 66.5, 52.0, 46.7, 46.5, 45.8, 45.6, 39.4, 39.3, 30.9, 30.6, 30.2, 30.1, 21.0, 21.0, 20.9, 20.8, 11.2.

Methyl (2*S*,10*R*,10a*R*,11*S*,11a*R*,12*S*)-7-Methyl-3,8-dioxo-10-(prop-1-en-2-yl)-2,3,5,6,8,9,10,10a,11,11a-decahydro-2,11-methanobenzo[5,6]cyclohepta[1,2-*b*]pyran-12-carboxylate (25). To a dried sealed tube with anhydrous acetonitrile (CH_3CN, 50 mL) were added **24** (208 mg, 0.5 mmol) and 2,2,6,6-tetramethylpiperidine (TMP, 0.12 mL, 0.75 mmol). Then the mixture was heated at 170 °C for 20 h. The reaction was worked up by transferring the solution to a round-bottomed flask; the solvents were removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 10:1) to afford **25** (17.8 mg, about 10%) as a white solid. Crystals suitable for X-ray analysis were obtained from dissolving **25** in CH_2Cl_2 followed by the addition of hexane and then allowing the solvent to evaporate slowly: R_f = 0.55 (hexane/EtOAc = 2:1); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{25}O_5$ 357.1697, found 357.1694; ^1H NMR (500 MHz, $CDCl_3$) δ 6.86 (dt, J = 15.7, 8.6 Hz, 1H), 6.43 (d, J = 2.7 Hz, 1H), 6.05 (d, J = 5.8 Hz, 1H), 5.89 (ddd, J = 15.6, 8.0, 0.9 Hz, 1H), 4.85 (d, J = 1.5 Hz, 1H), 4.71−4.61 (m, 1H), 4.41 (dd, J = 17.0, 1.2 Hz, 1H), 4.17 (d, J = 17.0 Hz, 1H), 3.76 (d, J = 0.7 Hz, 3H), 3.23 (q, J = 7.1 Hz, 1H), 2.67 (ddd, J = 7.6, 5.1, 2.4 Hz, 1H), 2.62−2.46 (m, 3H), 2.30−2.20 (m, 3H), 2.16 (d, J = 4.2 Hz, 3H), 1.82 (dd, J = 5.2, 1.5 Hz, 3H), 1.73−1.70 (m, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 197.0, 194.5, 172.7, 165.9, 152.9, 145.3, 132.9, 123.1, 112.7, 84.4, 81.0, 53.3, 51.9, 48.5, 48.0, 43.1, 36.7, 35.5, 33.1, 29.5, 22.5.

(*E*)-3-((1*S*,6*R*)-2-(2-(5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-furan-3-yl)ethyl)-3-methyl-4-oxo-6-(prop-1-en-2-yl)cyclohex-2-en-1-yl)allyl Acetate (26). To a solution of **22** (2.8 g, 6.0 mmol) in anhydrous DCM (50 mL) was added DIBAL-H (1.5 M in toluene, 10.0 mL, 15.0 mmol) dropwise at −78 °C. After the mixture was stirred at the same temperature for 15 min, the reaction was quenched by the addition of potassium sodium tartrate saturated solution (100 mL). The mixture was warmed to 25 °C and stirred for 3 h. Then it was transferred to a separatory funnel, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo to give a crude product, which was used in the next step without further purification. The crude product was dissolved in anhydrous DCM (50 mL) and cooled to 0 °C. Et_3N (1.25 mL, 9.0 mmol), 4-dimethylaminopyridine (DMAP, 73.6 mg, 0.75 mmol), and acetic anhydride (Ac_2O, 0.86 mL, 9.0 mmol) were added to the reaction in sequence. The mixture was stirred at the same temperature until the end of the reaction. The reaction was quenched by saturated NH_4Cl (30 mL), and the mixture was extracted with DCM (3 × 30 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. The dried solution was filtered, concentrated, and purified by flash chromatography on silica gel (hexane/EtOAc = 20:1) to afford the acetate (2.49 g, 85%) as a colorless oil.

To a slurry solution of pyridinium chlorochromate (1.6 g, 7.5 mmol) and 4 Å MS in dichloromethane (50 mL) was added a solution of acetate prepared above (2.44 g, 5.0 mmol) in dichloromethane (10 mL) at rt, and the resulting dark red mixture was stirred at the same temperature for 2 h. The reaction was worked up by the addition of ether (20 mL), and the formed solution was first filtrated through a silica gel pad and washed with ether (3 × 30 mL). The combined organic phases were sequentially washed with an aqueous solution of NaOH (5%, 50 mL), an aqueous solution of HCl (5%, 50 mL), and a saturated aqueous solution of $NaHCO_3$ (2 × 40 mL) and finally dried over anhydrous Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by a flash chromatography on silica gel (hexane/EtOAc = 20:1) to afford **26** (1.79 g, 74%; totally 63% for three steps from **22**) as a colorless oil: R_f = 0.7 (hexane/EtOAc = 5:1); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{28}H_{42}NaO_5Si$ 509.2694, found 509.2698; ^1H NMR (500 MHz, $CDCl_3$) δ 7.14 (s, 1H), 6.11 (s, 1H), 5.74−5.59 (m, 2H), 4.80 (t, J = 1.5 Hz, 1H), 4.64 (s, 1H), 4.56 (d, J = 7.8 Hz, 4H), 3.11 (t, J = 5.9 Hz, 1H), 2.62−2.52 (m, 3H), 2.52−2.37 (m, 3H), 2.31 (td, J = 10.9, 10.5, 5.2 Hz, 1H), 2.05 (s, 3H), 1.78 (d, J = 1.3 Hz, 3H), 1.69 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 198.4, 170.9, 155.3, 154.8, 145.1, 138.5, 135.1, 132.5, 127.0, 124.7, 113.0, 108.5, 64.5, 58.4, 46.7, 46.2, 39.3, 34.1, 26.0, 22.9, 21.1, 21.0, 18.6, 11.1, −5.1.

(*E*)-3-((1*S*,6*R*)-2-(2-(5-(Hydroxymethyl)furan-3-yl)ethyl)-3-methyl-4-oxo-6-(prop-1-en-2-yl)cyclohex-2-en-1-yl)allyl Acetate (27). To a solution of **26** (1.46 g, 3.0 mmol) in THF (30 mL) was added pyridine hydrofluoride (1.94 mL, 10 mmol, aq 70% HF) at 0 °C. Then, the mixture was warmed to rt and stirred at the same temperature for 2 h. After the reaction finished, the mixture was cooled to 0 °C and quenched slowly with saturated $NaHCO_3$ until the pH was 7. The result mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by flash chromatography on silica gel (hexane/EtOAc = 4:1) to afford **27** (1.08 g, 97%) as a colorless oil: R_f = 0.15 (hexane/EtOAc = 5:1); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{22}H_{28}NaO_5$ 395.1829, found 395.1827; ^1H NMR (500 MHz, $CDCl_3$) δ 7.17 (s, 1H), 6.18 (s, 1H), 5.73−5.56 (m, 2H), 4.80 (d, J = 1.9 Hz, 1H), 4.64 (s, 1H), 4.55 (s, 4H), 3.11 (t, J = 6.1 Hz, 1H), 2.57 (tq, J = 15.5, 5.1 Hz, 3H), 2.52−2.39 (m, 3H), 2.32 (td, J = 10.8, 10.3, 5.0 Hz, 1H), 2.05 (s, 4H), 1.78 (d, J = 1.4 Hz, 3H), 1.69 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 198.4, 170.9, 155.2, 154.6, 145.1, 139.0, 135.0, 132.5, 127.1, 124.9, 113.0, 109.0, 64.5, 57.7, 46.7, 46.2, 39.4, 34.1, 22.8, 21.1, 21.0, 11.1.

(*E*)-3-((1*S*,6*R*)-2-(2-(2-Acetoxy-5-oxo-5,6-dihydro-2*H*-pyran-3-yl)ethyl)-3-methyl-4-oxo-6-(prop-1-en-2-yl)cyclohex-2-en-1-yl)allyl Acetate (28). To a solution of compound **27** (744 mg, 2.0 mmol) in THF (21.0 mL) and H_2O (7.0 mL) were added $NaHCO_3$ (336 mg, 4.0 mmol), NaOAc (164 mg, 2.0 mmol), and NBS (374 mg, 2.1 mmol) sequentially at 0 °C, and the mixture was stirred at the same temperature for 30 min. The reaction was worked up by the addition of water (8.0 mL), followed by extraction with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a crude product, which was used in the next step without further purification. The crude product was dissolved in anhydrous DCM (15 mL) and cooled to 0 °C. Et_3N (0.42 mL, 3.0 mmol), 4-dimethylaminopyridine (DMAP, 120 mg, 1.0 mmol), and acetic anhydride (Ac_2O, 0.29 mL, 3.0 mmol) were added to the reaction in sequence. Then mixture was stirred at the same temperature until the end of reaction. The reaction was quenched by saturated NH_4Cl (10 mL), and the mixture was extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvents were removed under a vacuum, and the residue was purified by a flash column chromatography on silica gel (hexane/EtOAc = 15:1) to afford **28** (817 mg, 95% for two steps, dr ≈ 1:1) as a colorless oil: R_f = 0.55 (hexane/EtOAc = 2:1); HRMS (ESI)) m/z $[M + H]^+$ calcd for $C_{24}H_{31}O_7$ 431.2064, found 431.2061; ^1H NMR (500 MHz, $CDCl_3$) δ 6.45 (d, J = 2.5 Hz, 1H), 6.07 (s, 1H), 5.69−5.63 (m, 2H), 4.81 (s, 1H), 4.63 (s, 1H), 4.55 (ddt, J = 17.9, 13.2, 5.8 Hz, 2H), 4.41 (d, J = 17.0 Hz, 1H), 4.16 (d, J = 17.0 Hz, 1H), 3.07 (d, J = 6.5 Hz, 1H), 2.60−2.55 (m, 2H), 2.54−2.44 (m, 2H), 2.38−2.23 (m, 3H), 2.16 (3H), 2.06 (3H), 1.79 (s, 3H), 1.69 (3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 197.9, 193.3, 193.3, 170.9, 169.9, 169.8, 156.8, 156.7, 153.1, 153.1, 144.8, 144.7, 134.4, 134.4, 133.2, 133.1, 127.7, 127.6, 125.2, 125.1, 113.3, 88.5, 88.4, 66.5, 64.3, 47.0, 46.7, 46.4, 46.3, 39.5, 39.5, 30.6, 30.2, 30.1, 21.1, 21.0, 20.9, 20.8, 11.2.

((2*S*,10*R*,10a*R*,11*S*,11a*R*,12*R*)-7-Methyl-3,8-dioxo-10-(prop-1-en-2-yl)-2,3,5,6,8,9,10,10a,11,11a-decahydro-2,11-methanobenzo[5,6]cyclohepta[1,2-*b*]pyran-12-yl)methyl Acetate (29). To a dried sealed tube with anhydrous acetonitrile (CH_3CN, 50 mL) were added **28** (430 mg, 1.0 mmol) and 2,2,6,6-tetramethylpiperidine (TMP, 0.24 mL, 1.5 mmol). Then the mixture was heated at 170 °C for 20 h. The reaction was worked up by transferring the solution to a round-bottomed flask, the solvents were

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removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 8:1) to afford **29** (262 mg, 71%) as a white solid. Crystals suitable for X-ray analysis were obtained from dissolving **29** in CH_2Cl_2, followed by the addition of hexane, and then allowing the solvent to evaporate slowly: R_f = 0.50 (hexane/EtOAc = 2:1); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{22}H_{27}O_5$ 371.1853, found 371.1851; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 (s, 1H), 4.79 (s, 1H), 4.50−4.44 (m, 2H), 4.34 (s, 1H), 4.25 (dd, J = 11.0, 6.5 Hz, 1H), 4.10 (dd, J = 10.9, 8.7 Hz, 1H), 3.10 (ddd, J = 12.8, 6.5, 2.4 Hz, 1H), 2.85 (d, J = 17.2 Hz, 2H), 2.77 (ddd, J = 12.0, 6.6, 2.3 Hz, 1H), 2.63 (d, J = 17.1 Hz, 1H), 2.49 (ddd, J = 11.0, 7.1, 4.2 Hz, 1H), 2.45−2.38 (m, 1H), 2.15 (d, J = 10.5 Hz, 1H), 2.09 (s, 3H), 2.08−2.03 (m, 1H), 1.87 (td, J = 12.6, 6.6 Hz, 1H), 1.80 (s, 3H), 1.67 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 196.7, 195.3, 170.9, 165.9, 153.6, 145.3, 132.6, 123.4, 112.7, 84.1, 80.8, 66.1, 48.3, 47.5, 46.6, 42.9, 36.6, 35.6, 33.1, 22.5, 21.0, 10.8.

((2*S*,3*S*,10*R*,10a*R*,11*S*,11a*R*,12*R*)-3-Hydroxy-7-methyl-10-(prop-1-en-2-yl)-2,3,5,6,8,9,10,10a,11,11a-decahydro-2,11-methanobenzo[5,6]cyclohepta[1,2-*b*]pyran-12-yl)methyl Acetate (30). To a solution of compound **29** (185 mg, 0.5 mmol) in anhydrous THF (10.0 mL) was added boron trifluoride etherate (1.1 mL, 9.0 mmol) at rt, and the mixture was stirred at the same temperature for 5 min. Then, sodium cyanoborohydride ($NaBH_3CN$, 471 mg, 7.5 mmol) was added, and the mixture was stirred at rt overnight. The reaction was quenched by added saturated $NaHCO_3$ (5 mL), and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvents were removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to afford **30** (100 mg, 56%) as a foam: R_f = 0.60 (hexane/EtOAc = 1:1); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{22}H_{31}O_4$ 359.2217, found 359.2214; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.31 (d, J = 1.9 Hz, 1H), 4.76−4.70 (m, 2H), 4.48 (dq, J = 1.8, 0.9 Hz, 1H), 4.24 (dd, J = 10.8, 5.2 Hz, 1H), 4.20−4.15 (m, 1H), 4.11 (d, J = 6.2 Hz, 1H), 4.00 (dd, J = 10.8, 9.3 Hz, 1H), 2.86 (ddd, J = 13.1, 5.5, 2.7 Hz, 1H), 2.54−2.47 (m, 1H), 2.33−2.24 (m, 2H), 2.14 (d, J = 9.0 Hz, 1H), 2.11−2.07 (m, 1H), 2.06 (s, 3H), 2.04−1.98 (m, 1H), 1.91 (dd, J = 7.0, 5.6 Hz, 1H), 1.87−1.83 (m, 2H), 1.78−1.74 (m, 1H), 1.73−1.71 (m, 3H), 1.55 (d, J = 1.1 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.3, 146.9, 144.8, 128.8, 128.4, 120.6, 110.1, 81.7, 80.4, 68.1, 67.7, 53.0, 45.3, 44.6, 43.3, 34.7, 33.7, 28.3, 22.7, 21.1, 21.0, 19.3.

((2*R*,10*R*,10a*R*,11*S*,11a*R*,12*R*)-7-Methyl-10-(prop-1-en-2-yl)-2,3,5,6,8,9,10,10a,11,11a-decahydro-2,11-methanobenzo-[5,6]cyclohepta[1,2-*b*]pyran-12-yl)methyl Acetate (32). NaH (20.8 mg, 0.52 mmol, 60% suspension in mineral oil) was washed twice with hexanes and added slowly to a well-stirred and precooled (0 °C) solution of alcohol **30** (71.6 mg, 0.2 mmol) in anhydrous THF (10 mL). Immediately thereafter, CS_2 (36 μL, 0.6 mmol) was added, and the red-orange solution was allowed to warm at 25 °C, at which temperature it was stirred over a period of 3 h. The reaction mixture was then recooled at 0 °C and treated with methyl iodide (64 μL, 1.1 mmol). After the mixture was stirred at 25 °C for an additional 30 min, the colorless solution was quenched with ice−water (5 mL) and extracted with ethyl ether (3 × 10 mL). The combined ethereal layers were washed with aqueous saturated sodium bicarbonate (10 mL) and brine (10 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was subjected to chromatography (0−20% ether in hexanes) to afford the corresponding xanthate as a light-yellow liquid. This liquid was dissolved in dry benzene (10 mL) and treated with Bu_3SnH (0.41 mL, 1.5 mmol). The reaction mixture was preheated at 80 °C and treated with AIBN (3.28 mg, 0.02 mmol) added in four portions over a period of 2 h. After the end of the reaction, the solvent was removed under reduced pressure and the crude residue was purified through flash chromatography on silica gel (hexane/EtOAc = 30:1) to afford a mixture of **31** and **32** (38 mg, 56%, **31**/**32** = 1.6:1, detected by crude NMR) as a foam: R_f = 0.2 (hexane/EtOAc = 20:1); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{22}H_{31}O_3$ 343.2268, found 343.2270; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (ddd, J = 9.8, 4.1, 2.8 Hz, 1H), 5.65 (dt, J = 9.8, 1.9 Hz, 1H), 5.37−5.33 (m, 1H), 4.76−4.71 (m, 2H), 4.53−4.47 (m, 2H), 4.34 (ddd, J = 7.6, 4.5, 1.6 Hz, 1H), 4.25 (d, J = 5.4 Hz, 1H), 4.19−4.14 (m, 2H), 4.08 (d, J = 5.9 Hz, 1H), 4.01−3.95 (m, 2H), 3.26−3.17 (m, 1H), 2.85 (ddd, J = 13.0, 5.6, 2.5 Hz, 1H), 2.70 (ddd, J = 17.4, 5.4, 2.6 Hz, 1H), 2.55−2.48 (m, 1H), 2.37 (d, J = 11.4 Hz, 1H), 2.31 (ddd, J = 12.4, 5.7, 2.5 Hz, 1H), 2.28−2.23 (m, 2H), 2.23−2.16 (m, 2H), 2.14−2.09 (m, 2H), 2.06 (s, 6H), 1.95 (dtd, J = 13.8, 7.1, 6.6, 4.8 Hz, 4H), 1.89−1.81 (m, 6H), 1.79 (d, J = 4.3 Hz, 1H), 1.74 (s, 3H), 1.72 (s, 3H), 1.69−1.67 (m, 1H), 1.64 (td, J = 7.6, 2.6 Hz, 4H), 1.56 (s, 3H), 1.52 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.1, 171.0, 147.2, 147.2, 142.3, 142.3, 130.2, 129.8, 129.4, 129.3, 128.0, 126.6, 115.7, 109.8, 109.8, 81.4, 80.0, 77.7, 75.1, 68.0, 67.0, 55.9, 53.8, 52.5, 51.5, 45.7, 44.4, 43.0, 42.2, 40.6, 35.1, 34.4, 33.4, 30.2, 29.7, 28.9, 28.2, 28.2, 27.9, 26.9, 22.6, 22.6, 21.0, 21.0, 20.3, 19.2, 18.9, 17.5, 13.6.

(4a*R*,13*R*,13a*S*,14*S*,14a*R*)-3,3,10-Trimethyl-13-(prop-1-en-2-yl)-4a,5,8,9,11,12,13,13a,14,14a-decahydro-1*H*-7,14-methanobenzo[4,5]cyclodeca[1,2-*d*][1,3]dioxine (34). Freshly cut lithium slices (28.0 mg, 4.0 mmol) were added rapidly to a solution of **31** and **32** (68.4 mg, 0.2 mmol) in ethylamine (5 mL) at 25 °C. The mixture turned blue and was vigorously stirred for further 45 min. The reaction was quenched with cyclopentadiene (1 mL) and saturated NH_4Cl (aq) (3 mL). Water (1 mL) was added to the mixture, which was extracted with EtOAc (100 mL). The combined organic extracts were washed with 1 M HCl (aq), brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a crude product of **33** (hard to purify), which was used in the next step.

The crude product was dissolved again in DCM (5 mL) at rt. Then, 2,2-dimethoxypropane (0.24 mL, 2.0 mmol) and *p*-toluenesulfonic acid (PTSA, 8.6 mg, 0.05 mmol) were added to the solution sequence, and the resulting mixture was stirred at the same temperature overnight. The reaction was quenched with saturated $NaHCO_3$ (1 mL) and filtered with Celite. The solution was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solution was concentrated in vacuo, and the residue was chromatographed on silica gel (hexane/EtOAc = 8:1) to afford a mixture of **34** (18 mg, 70% for two steps from **32**) as a foam: R_f = 0.50 (hexane/EtOAc = 2:1); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{35}O_2$ 343.2632, found 343.2630; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38−5.34 (m, 1H), 4.75 (t, J = 1.8 Hz, 1H), 4.53 (s, 1H), 4.07 (td, J = 7.8, 3.4 Hz, 1H), 3.89−3.77 (m, 2H), 2.91 (dt, J = 12.7, 3.7 Hz, 1H), 2.63−2.50 (m, 2H), 2.39 (dt, J = 14.7, 7.5 Hz, 1H), 2.21−2.16 (m, 2H), 2.04−1.89 (m, 3H), 1.86−1.78 (m, 4H), 1.72 (d, J = 1.3 Hz, 3H), 1.70−1.65 (m, 2H), 1.62 (s, 3H), 1.44 (s, 3H), 1.42 (s, 3H), 1.40−1.36 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 147.5, 145.2, 130.0, 128.4, 117.6, 110.2, 98.6, 70.0, 63.3, 49.2, 47.0, 43.5, 37.5, 36.6, 36.1, 32.0, 31.7, 29.9, 28.7, 28.7, 22.3, 22.0, 19.2.

(2*S*,3*S*,4*S*)-3-((*E*)-3-(Benzyloxy)prop-1-en-1-yl)-2-((*S*)-2-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)furan-3-yl)-1-hydroxyethyl)-4-((*S*)-6-methylhept-5-en-2-yl)cyclohexan-1-one (49). *n*-BuLi (2.4 M in hexanes, 10.5 mL, 25 mmol) was added dropwise to a solution of (*E*)-(3-(benzyloxy)prop-1-en-1-yl)tributylstannane **47** (10.6 g, 24.5 mmol) in anhydrous THF (80 mL) at −50 °C, and the mixture was stirred at the same temperature for 1 h. The resultant solution was transferred via cannula to another flask containing a suspension of copper cyanide (CuCN, 2.1 g, 24.5 mmol) in anhydrous THF (50 mL, also cooled to −50 °C). The mixture was stirred for 15 min and then treated with MeLi (1.6 M in diethyl ether, 15.5 mL, 24.5 mmol), stirred for an additional 15 min, and cooled to −78 °C. A solution of enone **42** (2.5 g, 12 mmol) in THF (15 mL) was added over 30 min, and the mixture was stirred for an additional 30 min. Chlorotrimethylsilane (TMSCl, 2.1 mL, 24.5 mmol) was then added, and after 15 min, this was followed by TEA (4.2 mL, 30 mmol). The reaction was quenched by pouring into a 10% aqueous solution of NH_4Cl (100 mL). The mixture was filtrated through a pad of Celite with the aid of EtOAc. The organic layer of the filtrate was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was passed through a short silica gel column with EtOAc/hexane (1:100−1:50) quickly. The eluate was concentrated to give the trimethylsilyl enol ether **48**, which was used for the next step without further purification.

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To a solution of the crude trimethylsilyl enol ether **48** (about 20 mmol) in anhydrous THF (40 mL) was added *n*-BuLi (2.4 M in hexanes, 5.0 mL, 12 mmol) at −78 °C, and stirring was continued at −30 °C for 1 h. Then, the mixture was cooled to −78 °C, and a solution of $ZnBr_2$ (3.0 g, 13.2 mmol) in THF (15 mL) was added dropwise. After the mixture was stirred at the same temperature for 30 min, a solution of aldehyde **41** (3.1 g, 12 mmol) in THF (6 mL) was added over 30 min, and the mixture was stirred for an additional 5 min. The reaction was quenched by pouring into a saturated aqueous solution of $NaHCO_3$ (100 mL) at 0 °C. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. The dried solution was filtered and concentrated. The residue obtained was purified by flash column chromatography on silica gel (hexane/EtOAc = 10:1) to afford **49** (about 45−60% for two steps) as a foam: R_f = 0.45 (hexane/EtOAc = 5:1); HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{37}H_{56}NaO_5Si$ 631.3789, found 631.3787; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.28 (m, 5H), 7.12 (s, 1H), 6.03 (s, 1H), 5.71 (dt, *J* = 15.5, 5.5 Hz, 1H), 5.30 (ddt, *J* = 15.6, 9.7, 1.6 Hz, 1H), 5.08−5.00 (m, 1H), 4.52 (d, *J* = 11.5 Hz, 4H), 4.03 (dd, *J* = 5.5, 1.6 Hz, 2H), 3.87−3.77 (m, 1H), 3.17 (d, *J* = 11.4 Hz, 1H), 2.87 (ddd, *J* = 14.4, 7.0, 1.2 Hz, 1H), 2.76−2.66 (m, 2H), 2.36 (tt, *J* = 13.1, 7.1 Hz, 2H), 2.24 (d, *J* = 11.4 Hz, 1H), 2.06−1.99 (m, 2H), 1.84−1.75 (m, 2H), 1.74−1.68 (m, 1H), 1.64 (d, *J* = 1.4 Hz, 3H), 1.55 (d, *J* = 1.3 Hz, 3H), 1.49−1.40 (m, 2H), 0.94 (d, *J* = 7.0 Hz, 4H), 0.89 (s, 9H), 0.06 (s, 6H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 215.2, 154.7, 139.3, 138.4, 133.8, 131.6, 130.3, 128.5, 127.7, 127.7, 124.7, 122.7, 108.9, 72.1, 70.9, 70.0, 58.4, 55.6, 48.9, 47.4, 43.2, 32.8, 32.0, 29.9, 26.4, 26.3, 26.0, 25.9, 18.7, 18.6, 17.7, −5.1.

(*S*)-1-((1*S*,2*S*,3*S*)-2-((*E*)-3-(Benzyloxy)prop-1-en-1-yl)-3-((*S*)-6-methylhept-5-en-2-yl)-6-oxocyclohexyl)-2-(5-(hydroxymethyl)furan-3-yl)ethyl Acetate (51). To a solution of **49** (1.4 g, 2.3 mmol) in DCM (30 mL) at 0 °C was added Et_3N (0.49 mL, 3.5 mmol) and DMAP (146 mg, 1.2 mmol) subsequently. Then Ac_2O (0.24 mL, 2.5 mmol) was added to the solution and stirred at rt for 15 min before the reaction was quenched by saturated NH_4Cl (10 mL). Then the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. The dried solution was filtered and concentrated. The residue obtained was purified by flash column chromatography on silica gel (hexane/EtOAc = 15:1) to afford the corresponding acetate as a foam.

The acetate prepared above (1.1 g, 1.6 mmol) was dissolved in CH_3CN (30 mL) and cooled to 0 °C. Then, imidazole (1.6 g, 23 mmol) and triethylamine trihydrofluoride (1.5 g, 9.2 mmol) were added subsequently. After the mixture was stirred at the same temperature for 2 h, the reaction was quenched by a saturated aqueous solution of $NaHCO_3$ (20 mL) at 0 °C. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. The dried solution was filtered and concentrated. The residue obtained was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to afford **51** (789 mg, 64% for two steps) as a foam: R_f = 0.2 (hexane/EtOAc = 2:1); HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{33}H_{45}O_6$ 537.3211, found 537.3210; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 5.6 Hz, 4H), 7.15 (s, 1H), 6.13 (s, 1H), 5.51 (dt, *J* = 15.5, 5.5 Hz, 1H), 5.36−5.27 (m, 1H), 5.13 (td, *J* = 7.5, 1.8 Hz, 1H), 5.04 (tt, *J* = 6.5, 5.0, 2.0 Hz, 1H), 4.57−4.50 (m, 2H), 4.47−4.44 (m, 2H), 4.03 (ddd, *J* = 5.5, 3.9, 1.4 Hz, 2H), 2.99 (dd, *J* = 14.0, 7.9 Hz, 1H), 2.81 (dd, *J* = 14.1, 6.9 Hz, 1H), 2.47−2.37 (m, 3H), 2.31−2.24 (m, 1H), 2.03 (s, 3H), 1.95 (ddd, *J* = 9.4, 6.1, 3.2 Hz, 1H), 1.88 (t, *J* = 6.2 Hz, 1H), 1.82−1.72 (m, 2H), 1.56 (d, *J* = 1.2 Hz, 3H), 1.47 (ddd, *J* = 24.5, 12.2, 3.8 Hz, 2H), 1.34−1.21 (m, 3H), 0.93 (d, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 209.6, 170.7, 154.6, 140.1, 138.4, 133.5, 131.7, 129.6, 128.5, 127.8, 127.8, 124.6, 121.7, 109.5, 72.9, 72.1, 70.2, 57.7, 54.0, 47.0, 46.7, 42.1, 32.6, 29.7, 27.0, 26.3, 25.9, 24.5, 21.4, 18.5, 17.8.

(3a*S*,3a1*R*,6*S*,6a*S*,7*S*,13a*S*,14*R*)-8-((Benzyloxy)methyl)-2,2,14-trimethyl-6-((*S*)-6-methylhept-5-en-2-yl)-3a,3a1,4,5,6,6a,7,8,13,13a-decahydro-1,3-dioxa-7,12-methanocyclodeca[*de*]naphthalen-14-ol (62). To a solution of **61** (30.0 mg, 0.05 mmol) in Et_2O (5 mL) at −78 °C was added *t*-BuLi (1.6 M, 0.24 mL, 0.15 mmol). Then, the mixture was stirred at the same temperature for 15 min before the reaction was quenched by saturated NH_4Cl (5 mL). Then the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. The dried solution was filtered and concentrated. The residue obtained was purified by flash column chromatography on silica gel (hexane/EtOAc = 15:1) to afford **62** (7.8 mg, 30%) as a foam: R_f = 0.5 (hexane/EtOAc = 5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.27 (m, 5H), 6.33 (d, *J* = 10.1 Hz, 1H), 6.18−6.12 (m, 1H), 5.90 (s, 1H), 5.09 (d, *J* = 7.2 Hz, 1H), 4.58−4.42 (m, 2H), 4.14−4.01 (m, 2H), 3.68−3.59 (m, 1H), 3.50 (d, *J* = 3.2 Hz, 2H), 2.61 (dd, *J* = 11.0, 3.2 Hz, 1H), 2.46 (d, *J* = 5.0 Hz, 3H), 2.15 (s, 1H), 2.03−1.91 (m, 2H), 1.75 (d, *J* = 11.2 Hz, 2H), 1.70−1.68 (m, 3H), 1.62 (d, *J* = 1.3 Hz, 3H), 1.57−1.46 (m, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 1.28−1.15 (m, 4H), 1.06 (dd, *J* = 12.3, 4.8 Hz, 1H), 0.90 (d, *J* = 6.7 Hz, 3H).

(1*S*,3a*S*,3a1*R*,6a*S*,8a*R*,11*R*,11a*S*,11b*R*)-5,5-Dimethyl-1-((*S*)-6-methylhept-5-en-2-yl)-1,2,3,3a,3a1,6a,7,8a,10,11,11a,11b-dodecahydro-4,6,9-trioxa-8,11-(epipropan[1]yl[3]ylidene)-naphtho[1,8-*ef*]azulene (71). To a solution of **64** (43.2 mg, 0.1 mmol) in DCM (10 mL) at rt was added triphenylphosphine (39.3 mg, 0.15 mmol) and iodide (30.5 mg, 0.12 mmol) subsequently. Then, the mixture was stirred at rt for 50 min before the reaction was quenched by saturated Na_2SO_3 (5 mL). Then the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. The dried solution was filtered and concentrated. The residue obtained was purified by flash column chromatography on silica gel (hexane/EtOAc = 15:1) to afford **71** (34.4 mg, 83%) as a foam: R_f = 0.5 (hexane/EtOAc = 10:1). Compound **71** was isolated as a byproduct from the deprotection reaction of compound **72**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.71 (dd, *J* = 9.0, 4.1 Hz, 1H), 5.14 (tt, *J* = 7.0, 1.5 Hz, 1H), 4.50 (d, *J* = 7.9 Hz, 1H), 4.09 (d, *J* = 7.8 Hz, 1H), 3.97−3.89 (m, 2H), 3.31 (ddd, *J* = 10.9, 9.4, 5.4 Hz, 1H), 2.68 (dd, *J* = 16.5, 12.8 Hz, 1H), 2.55 (q, *J* = 5.1 Hz, 1H), 2.42 (dd, *J* = 11.3, 5.4 Hz, 1H), 2.16−2.05 (m, 3H), 1.93−1.71 (m, 8H), 1.69 (d, *J* = 1.4 Hz, 3H), 1.60 (s, 3H), 1.52 (ddd, *J* = 14.0, 6.5, 3.3 Hz, 2H), 1.44−1.38 (m, 3H), 1.37 (s, 3H), 1.33 (s, 3H), 1.16−1.13 (m, 1H), 0.96 (d, *J* = 6.8 Hz, 3H).

(*S*,*E*)-2-Methyl-6-((1*R*,1a*R*,4a*S*,8*S*,8a*S*,8b*R*)-1-methyl-5-methylene-1a,3,4,4a,5,6,7,8,8a,8b-decahydro-1*H*-1,2-(epipropan[1]yl[3]ylidene)benzo[*a*]cyclopropa[*c*][7]annulen-8-yl)hept-2-enoic Acid (1).[8] To a solution of **35** in anhydrous DCM (20 mL) were added methacrylaldehyde (0.29 mL, 3.5 mmol) and Grubbs II catalyst (81 mg, 0.1 mmol) subsequently. The reaction was sealed and heated at 52 °C for 15 h. After the mixture was cooled to 25 °C, the volatiles were removed under vacuo, and the residue was redissolved in EtOH (10 mL). To the vigorously stirred solution was added Ag_2O (prepared in situ from a solution of silver nitrate (82 mg, 0.48 mmol) in water (1 mL) by the addition of a solution of sodium hydroxide (38 mg, 0.96 mmol) in water (1 mL) dropwise). After stirring for 1 h, the mixture was carefully acidified with AcOH and filtered. The filtrate was concentrated in vacuo, and the residue was extracted with ether. The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. The dried solution was filtered and concentrated. The residue obtained was purified quickly by flash column chromatography on silica gel (hexane/EtOAc = 3:1) to afford **1** as a colorless oil (32 mg, 27% for three steps): R_f = 0.45 (hexane/EtOAc = 5:1); $[\alpha]_D^{25}$ −38 (*c* 0.32, CH_2Cl_2); HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{37}O_2$ 369.2788, found 369.2788; ^1H NMR (500 MHz, CD_2Cl_2) δ 6.90 (t, *J* = 7.6 Hz, 1H), 5.69−5.62 (m, 1H), 4.76 (d, *J* = 2.0 Hz, 1H), 4.70 (d, *J* = 2.1 Hz, 1H), 2.49−2.42 (m, 1H), 2.34−2.29 (m, 1H), 2.29−2.23 (m, 1H), 2.25−2.08 (m, 5H), 2.03−1.94 (m, 1H), 1.84 (m, 1H), 1.83 (s, 3H), 1.81−1.76 (m, 1H), 1.72−1.60 (m, 3H), 1.59−1.53 (m, 2H), 1.50−1.45 (m, 1H), 1.39−1.32 (m, 1H), 1.21−1.17 (m, 1H), 1.16−1.12 (m, 1H), 1.10 (s, 3H), 0.96 (d, *J* = 9.2 Hz, 1H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.68 (t, *J* = 9.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, CD_2Cl_2) δ 173.2, 152.3, 146.1, 140.9, 127.1, 124.6, 106.4, 45.0, 40.8, 36.5, 33.0, 32.9, 32.8, 32.6, 31.2, 29.1, 28.9, 27.5, 27.1, 25.0, 24.3, 24.2, 21.0, 18.2, 12.3.

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Methyl (*S*,*E*)-2-Methyl-6-((1*R*,1a*R*,4a*S*,8*S*,8a*S*,8b*R*)-1-methyl-5-methylene-1a,3,4,4a,5,6,7,8,8a,8b-decahydro-1*H*-1,2-(epipropan[1]yl[3]ylidene)benzo[*a*]cyclopropa[*c*][7]annulen-8-yl)hept-2-enoate (2).[8] To a solution of **1** (10 mg, 0.03 mmol) in hexane (2.5 mL) and MeOH (2.5 mL) was added a solution of $TMSCHN_2$ (2 M in hexane, 27 μL, 0.05 mmol). The solution was stirred at rt for 40 min and quenched with AcOH until no bubbles came out. The volatiles were removed under a vacuum, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 20:1) to afford the cerorubenic acid-III methyl ester (**2**) as a colorless oil (9.8 mg, 95%): R_f = 0.59 (hexane/EtOAc = 20:1); $[\alpha]_D^{25}$ −50 (*c* 1.0, CH_2Cl_2), $[\alpha]_D^{25}$ −22 (*c* 0.16, $CHCl_3$); −28 (*c* 0.054, $CHCl_3$); {lit.[6g] $[\alpha]_D^{20}$ −139 (*c* 0.16, $CHCl_3$); lit.[6g] −124 (*c* 0.001, $CHCl_3$); lit.[3] $[\alpha]_D^{24}$ −60 (*c* 0.001, $CHCl_3$)}; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{39}O_2$ 383.2945, found 383.2944; ^1H NMR (500 MHz, C_6D_6) δ 6.93 (dt, *J* = 1.5, 8.0 Hz, 1H), 5.71−5.65 (m, 1H), 4.95 (s, 1H), 4.89 (d, *J* = 1.8 Hz, 1H), 3.45 (s, 3H), 2.53−2.46 (m, 1H), 2.25−2.13 (m, 5H), 2.11−2.03 (m, 1H), 2.00 (m, 1H), 1.90 (m, 1H), 1.87 (s, 3H), 1.83 (dt, *J* = 10.3, 5.2 Hz, 1H), 1.80−1.73 (m, 1H), 1.66−1.31 (m, 8H), 1.19 (dt, *J* = 6.7, 4.4 Hz, 1H), 1.05 (s, 3H), 0.92 (d, *J* = 8.5 Hz, 1H), 0.81 (d, *J* = 6.7 Hz, 3H), 0.71 (dd, *J* = 10.5, 9.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, C_6D_6) δ 168.1, 151.3, 142.6, 140.5, 127.7, 124.4, 106.9, 51.3, 44.9, 40.6, 36.3, 32.9, 32.8, 32.6, 32.2, 31.1, 28.9, 28.6, 27.3, 26.5, 24.8, 24.2, 23.9, 20.7, 18.1, 12.6. (127.7, the signal of the enoate carbon 19, is obscured by solvent peaks, and it was elucidated by the correlations of H21 and C19 in the HMBC spectrum).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00185.

Comparison of spectroscopic data of our synthetic cerorubenic acid-III ester (**2**) with that of Paquette's reports; reference; X-ray crystallography data for compounds **25**, **29**, **60**; and copies of NMR spectra of synthesized compounds **15**, **18**−**32**, **34**, **49**, **51**, **62**, **71**, **1**, and **2** (PDF)

Accession Codes

CCDC 1869291 and 2052612−2052613 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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