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Construction of the Tricyclic Furanochroman Skeleton of Phomactin A via the Prins/Conia-Ene Cascade Cyclization Approach

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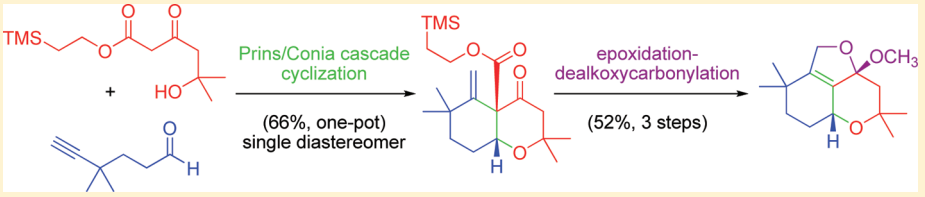
Supporting Information

ABSTRACT:



A substrate-controlled asymmetric Prins/Conia-ene cascade cyclization has been developed with $In(OTf)_3$ in CH_3CN from 0 to 70 °C. These conditions afforded very good yields of the 1-oxadecalin product in one pot and effectively suppressed the racemization of the 1-oxadecalin product with almost no enantiomeric excess (ee) loss. This cascade cyclization has been successfully employed for the construction of the highly functionalized 1-oxadecalin unit of phomactin A with an acyclic β-keto ester and an alkynal as the substrates via a one-pot operation (66% yield, single diastereomer). The 1-oxadecalin moiety has been readily converted to the tricyclic furanochroman skeleton of phomactin A via the epoxidation/dealkoxycarbonylation protocol under very mild conditions with 52% yield in three steps.

INTRODUCTION

Prins reaction[1,2] involves addition of an alkene to a Brønsted or Lewis acid-activated aldehyde substrate followed by trapping of a nucleophile (or a solvent molecule) or regeneration of an alkene via deprotonation. This class of reactions has been developed into a very useful cyclization method for construction of highly functionalized tetrahydropyrans and tetrahydropyranones.[3−10] Recently, we have reported an efficient Prins/Conia-ene cascade cyclization for construction of highly functionalized 1-oxadecalins using $InCl_3$ with simple acyclic substrates.[11,12] As shown in Figure 1, condensation of the β-keto ester[13−19] and alkynal substrates with $InCl_3$ provided the oxocarbenium ion intermediate,[20] which underwent Prins cyclization and formed the tetrahydropyran-4-one intermediate. Subsequent Conia-ene reaction provided very good yields of the 1-oxadecalin product with excellent diastereoselectivity in one pot. We herein report the development of a substrate-controlled asymmetric Prins/Conia-ene cascade cyclization and the utility of this highly convergent cascade cyclization approach in the synthesis of the tricyclic furanochroman skeleton of phomactin A.

Phomactins represented a new class of platelet activating factor (PAF) antagonists isolated from a marine fungus *Phoma* sp. and exhibited inhibition against PAF-induced platelet aggregation.[21−26] Phomactin A is structurally the most complex member in the phomactin family and has attracted a tremendous amount of synthetic effort[27−39] including three elegant total syntheses reported by Pattenden,[40−44] Halcomb,[45−47] and Hsung.[48−51] To realize an asymmetric total synthesis of phomactin A via the

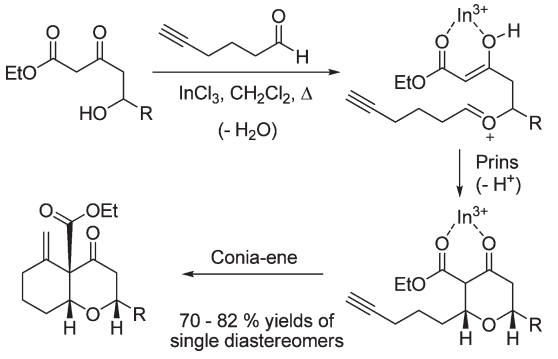


Figure 1. Prins/Conia-ene cascade cyclization reaction.

Prins/Conia-ene cascade cyclization approach, we have decided to develop this cascade cyclization into an asymmetric transformation through substrate control and consider two model compounds (**1** and **2**) that bear the tricyclic furanochroman skeleton with two all-carbon quaternary centers at C2 and C6 (Figure 2). The C-ring of the model compounds is anticipated to be established from (±)-**3** or **4** using an epoxidation/dealkoxycarbonylation protocol. The A,B-ring subunit could be readily prepared via a one-pot process by the Prins/Conia-ene cascade cyclization of β-keto esters **5** or **6** with alkynal **7**.

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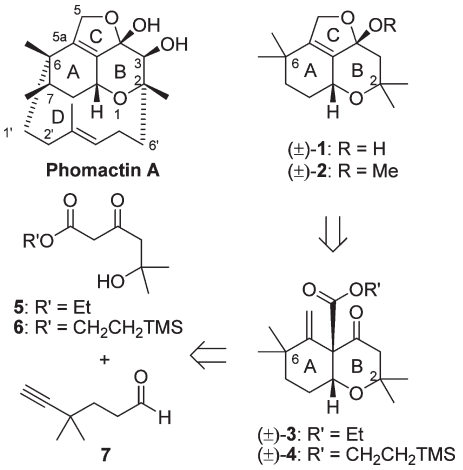


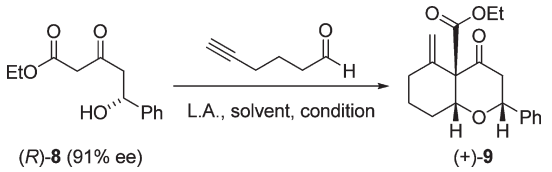
Figure 2. Construction of the tricyclic furanochroman skeleton of phomactin A via the Prins/Conia-ene cascade cyclization approach.

RESULTS AND DISCUSSION

Development of Asymmetric Prins/Conia-ene Cascade Cyclization via Substrate Control. Since the Prins/Conia-ene cascade cyclization can provide the 1-oxadecalin product with excellent diastereocontrol, we have decided to develop an asymmetric cascade cyclization via substrate control which could become a useful tool for synthesis of 1-oxadecalin containing natural products. However, side reactions associated with this type of process including partial racemization and the exchange of aldehyde and alcohol side chains leading to mixtures of products have been reported recently.[52−63] Thus, racemization of the 1-oxadecalin product was studied using the reaction between optically enriched (*R*)-**8**[64] and hex-5-ynal.[65] As shown in Table 1, $InCl_3$ in refluxing CH_2Cl_2[11] provided 1-oxadecalin (+)-**9** in good yields, but more than 10% loss of the enantiomeric excess (ee) value (entry 1) resulted. According to the literature, racemization of Prins reactions can be suppressed by lowering the reaction temperature with an appropriate Lewis acid.[66] Thus, a variety of Lewis acids in CH_2Cl_2 at low reaction temperature were examined. Prins reaction with $InCl_3$ proceeded very slowly at 0 °C, and the substrates decomposed slowly under the reaction condition (entry 2). Switching to a stronger Lewis acid ($InBr_3$) at 0 °C led to a complete reaction in one hour. Subsequent Conia-ene reaction was achieved at 40 °C and gave 62% of the cascade cyclization product ((+)-**9**) in one pot with only 3% ee loss (entry 3). The yield of (+)-**9** was improved to 83% by using $In(OTf)_3$ with a similar level of racemization (entry 4). $Zn(OTf)_2$ gave a result similar to that of $InCl_3$ (entry 5). Racemization was almost completely suppressed by using $SnCl_4$ (89% ee), but a very poor yield of the product resulted (entry 6). After a brief survey of the solvent effect (entries 7−9), the results were optimized by using $In(OTf)_3$ in CH_3CN, which afforded 85% yield of **9** with almost no ee loss (entry 9).

To determine the racemization-involving steps in the cascade cyclization reaction, the effects of extending the reaction time at different reaction temperatures with $In(OTf)_3/CH_3CN$ were studied. Interestingly, no significant change in yields or ee values was observed by extending the reaction time from 1 to 5 h for the Prins cyclization step at 0 °C. Moreover, similar results were obtained by extending the reaction time from 5 to 12 h for the Conia-ene reaction at 70 °C, and the 1-oxadecalin product bearing

Table 1. Racemization Study of Prins/Conia-Ene Cascade Cyclization[a]



entry	L.A.	solvent	temperature	yields[b] (%)	% ee[c] (**9**)
1	$InCl_3$	CH_2Cl_2	40 °C	73	80
2	$InCl_3$	CH_2Cl_2	0−40 °C	trace	n.d.[d]
3	$InBr_3$	CH_2Cl_2	0−40 °C	62	88
4	$In(OTf)_3$	CH_2Cl_2	0−40 °C	83	87
5	$Zn(OTf)_2$	CH_2Cl_2	0−40 °C	trace	n.d.[d]
6	$SnCl_4$	CH_2Cl_2	0−40 °C	42	89
7	$In(OTf)_3$	THF	0−70 °C	34	84
8	$In(OTf)_3$	toluene	0−110 °C	60	86
9	$In(OTf)_3$	CH_3CN	0−70 °C	85	89

[a] The general procedures were followed with the indicated Lewis acid and reaction conditions. [b] Isolated yields (%) after silica gel column chromatography. [c] The ee values were determined by Daicel Chiracel OD-H column (hexanes: *i*-propanol = 98:2, 0.3 mL/min: t_1 = 38.61 min, t_2 = 44.12 min). [d] n.d. = not determined.

the 2,6-*trans*-substituted tetrahydropyran was not observed. These results suggested that racemization could occur only before the tetrahydropyran ring formation, and once the 1-oxadecalin has been established, ring opening and closing of the tetrahydropyran could not be effective even at high reaction temperature. The effects of the Lewis acid on the *β*-keto ester substrate alone were investigated. Upon treatment of $InCl_3$ in CH_2Cl_2, a 20% decrease in the ee value of (*R*)-**8** was observed after 1 h at 40 °C. On the other hand, the racemization was completely suppressed under $In(OTf)_3$ in CH_3CN at 0 °C. These results indicated that the racemization of the cascade reaction could occur via a stabilized carbocation intermediate.

Thus, a racemization mechanism base on Willis's work[58] was proposed. As shown in Figure 3, the stabilized carbocation (**10**) could be generated upon treatment of a Lewis acid at high reaction temperature. The resulting carbocation (**10**) could be either attacked by the carbonyl moiety of the aldehyde to form (±)-**11** or converted to (±)-**8** followed by condensation with the aldehyde and formed the same oxocarbenium ion intermediate. Since the racemization of (*R*)-**8** can be effectively suppressed under our optimal conditions ($In(OTf)_3/CH_3CN$, 0 °C), the 1-oxadecalin product ((+)-**9**) can be obtained with almost no ee loss. According to Rychnovsky's mechanistic studies,[67] another racemization mechanism could also be effective at high reaction temperature. As shown in Figure 4, condensation between (*R*)-**8** and hex-5-ynal provided oxocarbenium ion **12**, which could undergo either a Prins reaction (cyclization followed by loss of a proton) and form the expected tetrahydropyran product (**14**) or an oxocarbenium ion isomerization followed by a 3,3-sigmatropic rearrangement and give **18**. After a series of C−C bond rotations, oxocarbenium ion **19** could undergo either a Prins reaction and give **22** (the enantiomer of **15**) or a 3,3-sigmatropic rearrangement and afford **20**, which could also lead to **22** via a Prins reaction.

In contrast to the modified Maitland−Japp reaction (Figure 5)[13−18] between *β*-keto esters and aldehydes that afford the *trans*-tetrahydropyran ring as the minor product with no racemization being

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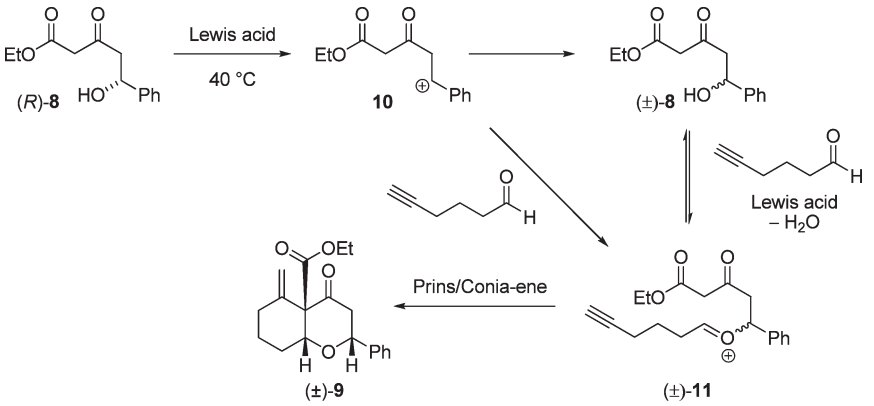

Figure 3. Proposed racemization mechanism for the Prins/Conia-ene cascade cyclization based on a stabilized carbocation intermediate.

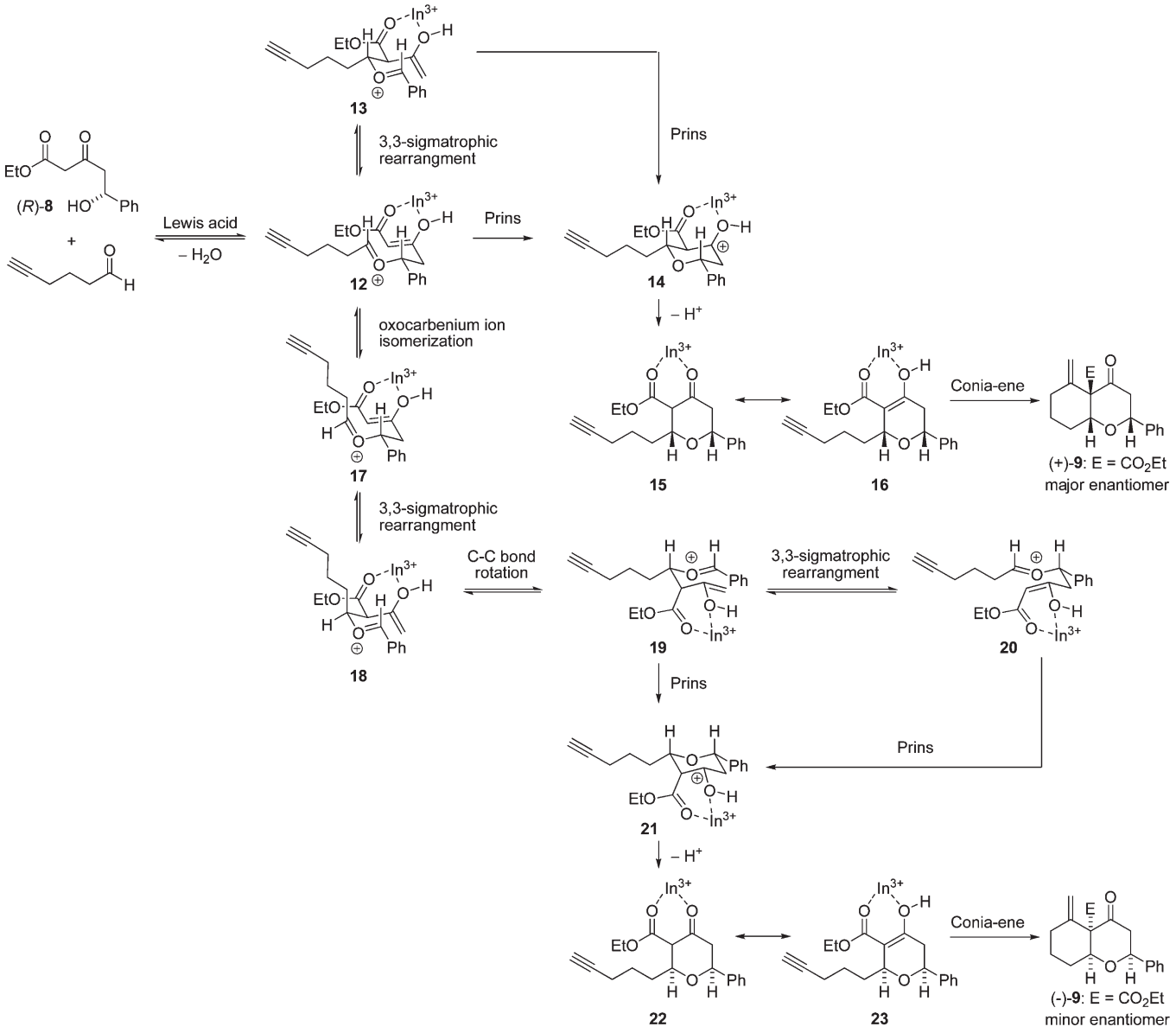

Figure 4. Proposed racemization mechanism for the Prins/Conia-ene cascade cyclization based on an oxocarbenium ion isomerization and a 3,3-sigmatropic rearrangement.

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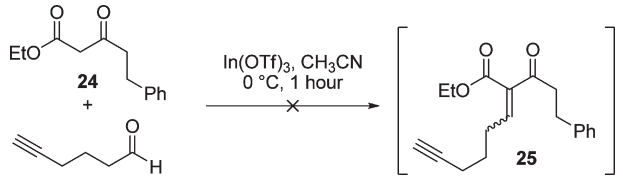


Figure 5. Study on the modified Maitland−Japp mechanism.

observed,[16] the *trans*-tetrahydropyran isomers were not observed in our system. This result indicated that reopening and closing of the tetrahydropyran ring could be unfavorable under our reaction conditions. Moreover, Knoevenagel condensation between β-keto ester **24**[68] (the dehydroxy derivative of **8**) and hex-5-ynal did not provide the condensation product (**25**) under our optimal condition and led to decomposition of the aldehyde substrate. This result suggested that the modified Maitland−Japp mechanism (Knoevenagel/oxa-Michael) is unlikely under our reaction conditions.

Synthesis of the Tricyclic Core of Phomactin A. In our previous study, the Prins/Conia-ene cascade cyclization of sterically hindered substrate (Scheme 1) provided only modest yields even in high reaction temperature.[11] Thus, the Prins/Conia-ene cascade cyclization between two sterically demanding substrates, β-keto ester **5**[69] and alkynal **7**,[70] was studied. Fortunately, our optimal condition ($In(OTf)_3/CH_3CN$) provided 80% yield of 1-oxadecalin **3** as a single diastereomer.[71] The β-keto ester moiety of (±)-**3** could be converted to the β-hydroxyl ketone for construction of the tricyclic furanochroman skeleton of phomactin A via Totah's epoxidation/retro-Aldol protocol.[31] However, this approach required a number of functional and protecting group manipulations. Alternatively, direct dealkoxycarbonylation of (±)-**26** should lead to intermediate **27**, which could undergo epoxide ring opening and gave the tricyclic core of phomactin A (**28** or (±)-**1**) in one pot. To study this direct dealkoxycarbonylation approach, (±)-**3** was first converted to (±)-**26** (a 4:1 diastereomeric mixture) using *m*CPBA. Unfortunately, (±)-**26** was found to be inert with a variety of dealkoxycarbonylation conditions[72−77] and decomposed upon prolonged heating.

By replacing the ethyl ester with a 2-(trimethylsilyl)ethyl ester, (±)-**31** was anticipated to undergo dealkoxycarbonylation under a much milder condition.[78,79] As shown in Scheme 2, synthesis of (±)-**31** began with Mukaiyama aldol reaction between **29**[80] and acetone. Lactone ring opening of **30** with 2-trimethylsilyl ethanol provided β-keto ester **6** in good yields. However, Prins/Conia-ene cascade cyclization of **6** with alkynal **7** using $In(OTf)_3$ in CH_3CN did not give the expected cyclized product ((±)-**4**). The dealkoxycarbonylation product (**32**) was obtained as the major side product, which may result from hydrolysis of the 2-(trimethylsilyl)ethyl ester. This side reaction was suppressed by removing water from the reaction mixture by addition of 4 Å molecular sieves, and the cascade cyclization afforded (±)-**4** in 66% yield. Epoxidation of (±)-**4** using *m*CPBA afforded the dealkoxycarbonylation precursor ((±)-**31**), which was treated with TBAF and afforded the expected crude dealkoxycarbonylation product ((±)-**1** or **28**). The crude product ((±)-**1**) was found to be unstable, and it underwent dehydration rapidly in the purification process to give the furan derivative (**33**). This observation is consistent with that reported by Pattenden.[40] The crude product was then treated with a catalytic amount of TsOH in methanol and afforded the stable tricyclic model compound ((±)-**2**) in decent yields, which has been characterized unambiguously by ^1H, ^{13}C NMR, and HRMS. The relative configurations of (±)-**2** were determined by NOESY (Scheme 2).

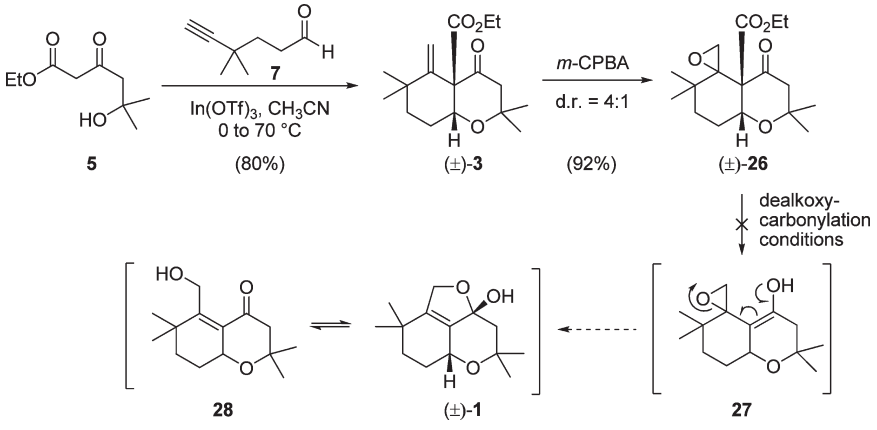
CONCLUSION

In summary, we have successfully developed an asymmetric Prins/Conia-ene cascade cyclization via substrate control. The cyclization has been optimized by using $In(OTf)_3$ in CH_3CN from 0 to 70 °C. These conditions afforded the 1-oxadecalin product in good yields and effectively suppressed the racemization of the 1-oxadecalin product with almost no ee loss. The racemization-involving steps have been investigated by varying the reaction conditions. The optimal reaction condition also provided good yields for (±)-**4** (66%, single diastereomer) in one pot by addition of 4 Å molecular sieves for removing water from the reaction. The 2-trimethylsilyl ethyl moiety of (±)-**4** was successfully converted to the tricyclic furanochroman skeleton of phomactin A in 52% yield (for three steps) via the epoxidation/dealkoxycarbonylation protocol under a very mild condition. We are currently employing this cascade cyclization strategy for the total synthesis of phomactin A.

EXPERIMENTAL SECTION

General Remarks. All air- and water-sensitive reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Reactions were monitored by thin-layer

Scheme 1. Prins/Conia-Ene Cascade Cyclization of Sterically Hindered Substrates



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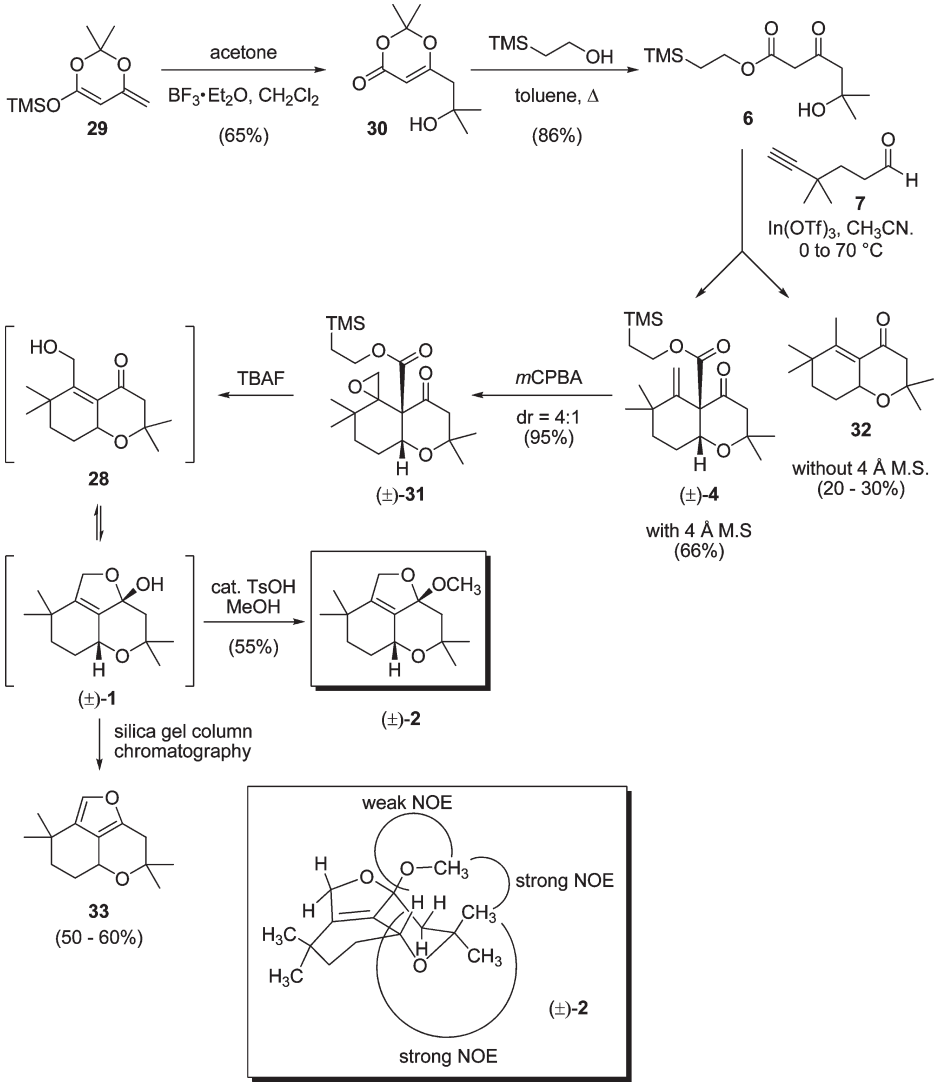
Scheme 2. Synthesis of the Tricyclic Furanochroman Skeleton of Phomactin A and the Important NOESY Correlations of (±)-2



chromatography (TLC) carried out on 0.25 mm silica gel plates (60F-254) that were analyzed by fluorescence upon 254 nm irradiation or by staining with anisaldehyde (450 mL of 95% EtOH, 25 mL of conc. H_2SO_4, 15 mL of acetic acid, and 25 mL of anisaldehyde). Silica gel (60, particle size 0.040−0.063 mm) was used for flash column chromatography. All the chemicals were purchased commercially and used without further purification. Anhydrous THF was distilled from sodium-benzophenone. Toluene was distilled over Na. CH_3CN and CH_2Cl_2 were distilled from calcium hydride. Molecular sieves were activated by heating at 200 °C for 12 h at ~1.0 Torr. Yields refer to chromatographically, unless otherwise stated. NMR spectra were recorded on either a 300 (^{1}H: 300 MHz, ^{13}C: 75.5 MHz) or 500 MHz (^{1}H: 500 MHz, ^{13}C: 125.8 MHz). The NOESY experiments were performed on a 600 MHz spectrometer. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High-resolution mass spectra were obtained from a MALDI-TOF Mass Spectrometer. High-performance liquid chromatography analysis was performed using an OD-H column (250 × 4.6 mm) or AD column (250 × 4.6 mm) with *i*PrOH/hexanes as the eluent. Optical rotations were measured on a digital polarimeter in $CHCl_3$.

General Procedures for Asymmetric Prins/Conia-Ene Cascade Cyclization. To a stirred suspension of In(OTf)$_3$ (0.066 g, 0.12 mmol) in CH_3CN (2 mL) at 0 °C was added a solution of hex-5-ynal (0.015 g, 0.16 mmol) and *β*-keto ester **8** (0.025 g, 0.11 mmol, 91% ee) in CH_3CN (1 mL) via a cannula. The resulting mixture was stirred at 0 °C for 1 h and 70 °C for 5 h. The reaction mixture was then cooled to room temperature and diluted with a saturated aqueous solution of $NaHCO_3$ (1 mL). The aqueous layer was extracted with ethyl acetate (5 mL × 3), and combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated. Silica gel flash column chromatography (hexanes:ethyl acetate = 30:1) of the residue afforded a colorless oil (0.029 g, 0.092 mmol, 85%) as the product (**9**). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.39−7.32 (m, 5H), 5.23 (d, *J* = 2 Hz, 1H), 4.85 (dd, *J* = 12, 3 Hz, 1H), 4.58 (d, *J* = 2 Hz, 1H), 4.56 (m, 1H), 4.34−4.26 (m, 2H), 2.93 (dd, *J* = 15, 12 Hz, 1H), 2.63 (dd, *J* = 15, 3 Hz, 1H), 2.52−2.46 (m, 1H), 2.31−2.14 (m, 2H), 2.09−1.93 (m, 1H), 1.67−1.53 (m, 2H), 1.30 (t, *J* = 7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 204.5, 169.2, 143.0, 140.9, 128.6, 128.1, 125.6, 115.6, 79.1, 78.0, 69.0, 61.6, 47.1, 33.5, 28.6, 20.2, 14.1. IR (neat, cm^{-1}): 3065, 1731, 1710, 1641, 1496, 1455, 1228. **8**: $[\alpha]_D^{20}$ = +32.3° (91% ee (*R*), *c* = 0.1, $CHCl_3$). **9**: $[\alpha]_D^{20}$ = +188.1° (89% ee, *c* = 0.1, $CHCl_3$), HRMS (+ESI) *m*/*z* calcd. for $C_{19}H_{22}O_4Na^+$ (M + Na^+) 337.1416, found 337.1406.

*Synthesis of Racemic Ethyl 2,2,6,6-Tetramethyl-5-methylene-4-oxooctahydro-2H-chromene-4a-carboxylate (**3**).* The general procedures

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were followed with $In(OTf)_3$ (0.093 g, 0.16 mmol), alkynal **7** (0.031 g, 0.25 mmol), and β-keto-ester **5** (0.031 g, 0.16 mmol). A colorless oil (0.038 g, 0.13 mmol, 80%) was obtained as the product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.36 (s, 1H), 4.64 (s, 1H), 4.62 (m, 1H), 4.30−4.13 (m, 2H), 2.91 (d, J = 13 Hz, 1H), 2.16 (d, J = 13 Hz, 1H), 1.95−1.92 (m, 2H), 1.88−1.76 (m, 1H), 1.31 (s, 3H), 1.29−1.25 (t, J = 7 Hz, 3H), 1.25−1.20 (m, 1H), 1.20 (s, 6H), 0.96 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ206.9, 170.1, 149.8, 116.6, 75.5, 71.3, 67.6, 61.3, 50.3, 35.9, 33.1, 30.9, 30.5, 29.2, 25.0, 23.7, 13.9. IR (neat, cm^{-1}): 1722, 1710, 1631, 1224. HRMS (+ESI) m/z calcd for $C_{17}H_{26}O_4Na$ $(M + Na)^+$ 317.1723, found 317.1725.

*Synthesis of Racemic Ethyl 2,2,6,6-Tetramethyl-4-oxooctahydrospiro-[chromene-5,2′-oxirane]-4a-carboxylate (**26**).* To a stirred solution of **3** (0.035 g, 0.12 mmol) in CH_2Cl_2 (4 mL) was added *m*-CPBA (0.088 g, 0.36 mmol, 70%). The resulting mixture was stirred at 40 °C for 24 h. The mixture was then cooled to room temperature and treated with a saturated aqueous solution of $Na_2S_2O_3$ (3 mL) and $NaHCO_3$ (1 mL). After stirring for 1 h, the aqueous layer was extracted with ethyl acetate (10 mL × 3), and the combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated. Silica gel flash column chromatography of the residue (hexanes:ethyl acetate = 30:1) to afford a colorless oil as the product (0.033 g, 0.11 mmol, 92%, a 4:1 mixture of diastereomers). Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.68 (t, J = 3 Hz, 1H), 4.30−4.16 (m, 2H), 2.92 (d, J = 14 Hz, 1H), 2.76 (d, J = 4 Hz, 1H), 2.53 (d, J = 4 Hz, 1H), 2.23 (d, J = 14 Hz, 1H), 2.21−2.09 (m, 1H), 2.15 (dt, J = 13, 5 Hz, 1H), 1.38 (s, 3H), 1.30 (t, J = 7 Hz, 3H), 1.25 (s, 3H), 1.23−1.18 (m, 1H), 0.98 (s, 3H), 0.81 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 204.0, 169.5, 73.9, 69.3, 63.6, 61.4, 58.2, 52.2, 46.0, 34.0, 31.1, 30.8, 25.8, 24.9, 24.8, 13.9. IR (neat, cm^{-1}): 1744, 1720, 1257. HRMS (+ESI) m/z calcd for $C_{17}H_{26}O_5Na$ $(M + Na)^+$ 333.1672, found 333.1673. Minor isomer: δ 4.93 (q, J = 3 Hz, 1H), 4.29−4.17 (m, 2H), 2.84 (d, J = 4 Hz, 1H), 2.68 (d, J = 4 Hz, 1H), 2.53 (m, 2H), 2.07−1.96 (m, 1H), 1.92−1.82 (m, 1H), 1.79−1.69 (m, 1H), 1.51−1.43 (m, 1H), 1.33−1.24 (m, 9H), 0.93 (s, 3H), 0.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 201.8, 167.8, 74.8, 73.8, 65.1, 61.9, 59.4, 50.8, 47.9, 34.4, 34.0, 30.4, 28.8, 27.1, 25.7, 24.7, 13.9. IR (neat, cm^{-1}): 1748, 1729, 1259. HRMS (+ESI) m/z calcd for $C_{17}H_{26}O_5Na$ $(M + Na)^+$ 333.1672, found 333.1673.

*Synthesis of 6-(2-Hydroxy-2-methylpropyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (**30**).* To a stirred solution of acetone (0.093 g, 1.6 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added $BF_3 \cdot Et_2O$ (0.14 mL, 1.1 mmol). The resulting mixture was stirred at −78 °C for 0.5 h. Then a solution of silyl dienolate **29** (0.23 g, 1.1 mmol) in CH_2Cl_2 was added slowly via a cannula at −78 °C. The mixture was stirred at room temperature for 1 h. Then a saturated aqueous solution of $NaHCO_3$ (2 mL) was added. The aqueous layer was extracted with ethyl acetate (10 mL × 3), and the combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated. Silica gel flash column chromatography of the residue (hexanes:ethyl acetate = 5:1) afforded a colorless oil (0.14 g, 0.70 mmol, 65%) as the product. ^{1}H NMR (300 MHz, CD_3OD): δ 5.35 (s, 1H), 2.43 (s, 2H), 1.71 (s, 6H), 1.29 (s, 6H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 168.8, 160.9, 106.6, 96.0, 70.5, 47.2, 29.7, 25.2. IR (neat, cm^{-1}): 3434, 1718, 1628, 1203. HRMS (+ESI) m/z calcd for $C_{10}H_{17}O_4$ $(M + H)^+$ 201.1121, found 201.1125.

*Synthesis of 2-(Trimethylsilyl)ethyl 5-Hydroxy-5-methyl-3-oxohexanoate (**6**).* A solution of **30** (1.1 g, 5.5 mmol) and 2-(trimethylsilyl)-ethanol (0.97 g, 8.2 mmol) in toluene (40 mL) was stirred at 110 °C in a sealed tube for 16 h. After removal of the volatiles, silica gel flash column chromatography (hexanes:ethyl acetate = 1:5) of the residue afforded a colorless oil (1.2 g, 4.7 mmol, 86%) as the product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.38 (s, 0.1H), 5.00 (s, 0.1H), 4.26−4.20 (m, 2H), 3.43 (s, 1.8H), 3.39 (s, 1H), 2.74 (s, 1.8H), 2.37 (s, 0.2H), 1.28 (s, 6H), 1.04−0.98 (m, 2H), 0.04 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 204.1, 175.1, 172.6, 166.9, 92.1, 70.1, 69.6, 63.7, 62.3, 53.7, 50.7, 48.2, 29.2, 17.2, −1.7. IR (neat, cm^{-1}): 3525, 1739, 1708, 1252, 862, 839. HRMS (+ESI) m/z calcd for $C_{12}H_{24}O_4NaSi$ $(M + Na)^+$ 283.1336, found 283.1339.

*Synthesis of Racemic 2-(Trimethylsilyl)ethyl 2,2,6,6-Tetramethyl-5-methylene-4-oxooctahydro-2H-chromene-4a-carboxylate (**4**).* The general procedures were followed with $In(OTf)_3$ (0.078 g, 0.14 mmol), 4 Å molecular sieves (0.050 g), alkynal **7** (0.026 g, 0.21 mmol), and β-keto-ester **6** (0.036 g, 0.14 mmol). A colorless oil (0.034 g, 0.093 mmol, 66%) was isolated as the product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.36 (s, 1H), 4.63 (s, 1H), 4.62 (m, 1H), 4.29−4.19 (m, 2H), 2.91 (d, J = 13 Hz, 1H), 2.16 (d, J = 13 Hz, 1H), 1.95−1.92 (m, 2H), 1.88−1.77 (m, 1H), 1.31 (s, 3H), 1.25−1.20 (m, 1H), 1.20 (s, 6H), 1.07−0.98 (m, 2H), 0.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 200.0, 170.3, 149.7, 116.6, 75.5, 71.4, 67.7, 63.7, 50.3, 36.0, 33.2, 30.9, 30.5, 29.3, 25.0, 23.7, 17.1, −1.6. IR (neat, cm^{-1}): 1724, 1708, 1630, 1226, 1205, 862, 837. HRMS (+ESI) m/z calcd for $C_{20}H_{34}O_4NaSi$ $(M + Na)^+$ 389.2119, found 389.2115.

*Synthesis of Racemic 2-(Trimethylsilyl)ethyl 2,2,6,6-Tetramethyl-4-oxooctahydrospiro[chromene-5,2′-oxirane]-4a-carboxylate (**31**).* The procedures for the synthesis of **26** were followed with (±)-**4** (0.033 g, 0.090 mmol) and *m*-CPBA (0.060 g, 0.27 mmol, 70%). A colorless oil (0.033 g, 0.086 mmol, 95%, a 4:1 mixture of diastereomers) was obtained as the product. Major product: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.68 (t, J = 3 Hz, 1H), 4.33−4.19 (m, 2H), 2.92 (d, J = 14 Hz, 1H), 2.76 (d, J = 4 Hz, 1H), 2.54 (d, J = 4 Hz, 1H), 2.23 (d, J = 14 Hz, 1H), 2.15 (dt, J = 13, 5 Hz, 1H), 1.87−1.84 (m, 1H), 1.38 (s, 3H), 1.26 (s, 3H), 1.23−1.18 (m, 1H), 1.08−1.02 (m, 2H), 0.99 (s, 3H), 0.81 (s, 3H), 0.06 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 204.0, 169.6, 73.9, 69.3, 63.9, 63.6, 58.3, 52.2, 46.1, 34.0, 31.1, 30.8, 25.9, 24.99, 24.96, 24.9, 17.3, −1.6. IR (neat, cm^{-1}): 1721, 1250, 863, 836. HRMS (+ESI) m/z calcd for $C_{20}H_{34}O_5NaSi$ $(M + Na)^+$ 405.2068, found 405.2069. Minor product: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.93 (q, J = 3 Hz, 1H), 4.31−4.16 (m, 2H), 2.83(d, J = 4 Hz, 1H), 2.70 (d, J = 4 Hz, 1H), 2.52 (m, 2H), 2.02−1.96 (m, 1H), 1.92−1.84 (m, 1H), 1.78−1.68 (m, 1H), 1.51−1.43 (m, 1H), 1.29 (s, 6H), 1.07 (m, 2H), 0.93 (s, 3H), 0.88 (s, 3H), 0.04 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 201.8, 167.8, 74.9, 73.9, 65.3, 64.4, 59.5, 50.8, 47.8, 34.3, 34.0, 30.4, 28.9, 27.2, 25.7, 24.9, 17.2, −1.6. IR (neat, cm^{-1}): 1721, 1250, 860, 838. HRMS m/z calcd for $C_{20}H_{34}O_5NaSi$ $(M + Na)^+$ 405.2068, found 405.2068.

*Synthesis of Racemic 3a-Methoxy-2,2,6,6-tetramethyl-2,3,3a,5,6,7,8,8a-octahydrofuro[2,3,4-de]chromene (**2**).* To a stirred solution of (±)-**31** (0.028 g, 0.073 mmol) in THF (2 mL) was added TBAF (0.11 mL of a 1 M solution in THF, 0.11 mmol). The mixture was stirred at room temperature for 1 h. After removal of volatiles, the residue was dissolved in MeOH (2 mL) and treated with *p*TsOH (0.0014 g, 0.0073 mmol). The mixture was stirred at room temperature until TLC analysis showed consumption of the crude product (**1** or **28**). The solution was then treated with 4−5 drops of triethylamine and concentrated. The residue was purified by flash column chromatography with basic aluminum oxide (hexanes:dichloromethane = 5:1) to afford a colorless oil (0.010 g, 0.040 mmol, 55%) as the product. ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.61 (dd, J = 13, 3 Hz, 1H), 4.38 (dd, J = 13, 1 Hz, 1H), 4.15−4.13 (m, 1H), 3.01 (s, 3H), 1.98−1.94 (m, 2H), 1.52−1.41 (m, 4H), 1.22 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H), 1.03 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 146.4, 128.4, 110.1, 73.2, 73.0, 64.7, 49.4, 48.9, 37.1, 32.7, 32.6, 29.4, 27.6, 26.4, 24.3. IR (neat, cm^{-1}): 1708, 1466, 1201, 1157. HRMS (+ESI) m/z calcd for $C_{15}H_{24}O_3Na$ $(M + Na)^+$ 275.1618, found 275.1629.

*2,2,5,6,6-Pentamethyl-6,7,8,8a-tetrahydro-2H-chromen-4(3H)-one (**32**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.42−4.36 (m, 1H), 2.48 (m, 2H), 1.96 (s, 3H), 1.95 (m, 1H), 1.71−1.49 (m, 3H), 1.29 (s, 6H), 1.13 (s, 3H), 1.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 200.6, 153.1, 131.2, 73.5, 70.2, 53.9, 37.0, 35.9, 30.5, 28.6, 26.5, 26.4, 25.6, 16.2. IR (neat, cm^{-1}): 1687, 1604, 1220. HRMS (+ESI) m/z calcd for $C_{14}H_{23}O_2$ $(M + H)^+$ 223.1693, found 223.1698.

2,2,6,6-Tetramethyl-2,3,6,7,8,8a-hexahydrofuro[2,3,4-de]chromene (***33***). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.35 (s, 1H), 4.39−4.36 (m, 1H), 2.56−2.46 (m, 2H), 1.88−1.85 (m, 1H), 1.59−1.57 (m, 2H), 1.33 (s, 3H), 1.29 (s, 3H), 1.31−1.26 (m, 1), 1.26 (s, 3H), 1.13 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 145.7, 137.1, 130.7, 119.7, 73.6, 66.5, 38.6, 36.4, 32.1, 31.7, 31.0, 30.9, 28.0, 25.2. IR (neat, cm^{-1}): 1666, 1463, 1072. HRMS (+ESI) *m*/*z* calcd for $C_{14}H_{21}O_2$ $(M + H)^+$ 221.1536, found 221.1538.

■ ASSOCIATED CONTENT

Supporting Information. HPLC analysis of (±)- and (+)-**9**, ^{1}H, ^{13}C NMR, and IR spectra of (+)-**9**, (±)-**2**−**4**, **26**, **31**, and **6**, **30**, **32**−**33**, and NOESY spectrum of (±)-**2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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