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An Enantioselective Synthesis of the ABD Tricycle for (−)-Phomactin A Featuring Rawal's Asymmetric Diels–Alder Cycloaddition

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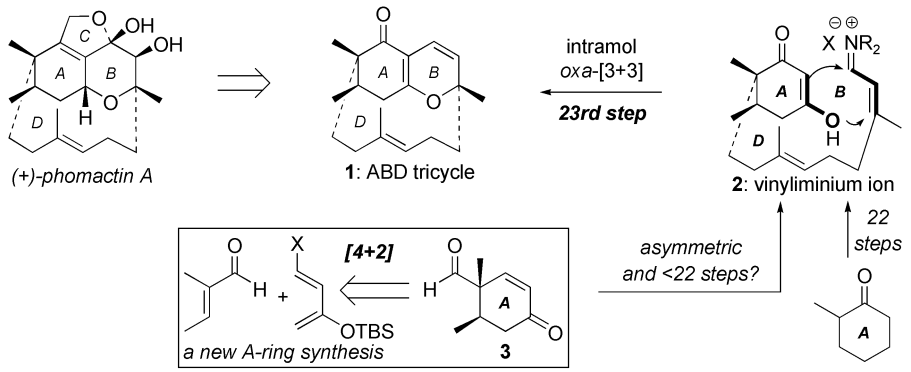
Abstract: An enantioselective synthesis of the ABD ring of (−)-phomactin A is described here. The sequence features Rawal's asymmetric Diels–Alder cycloaddition. The overall length is significantly reduced from our previous attempt.

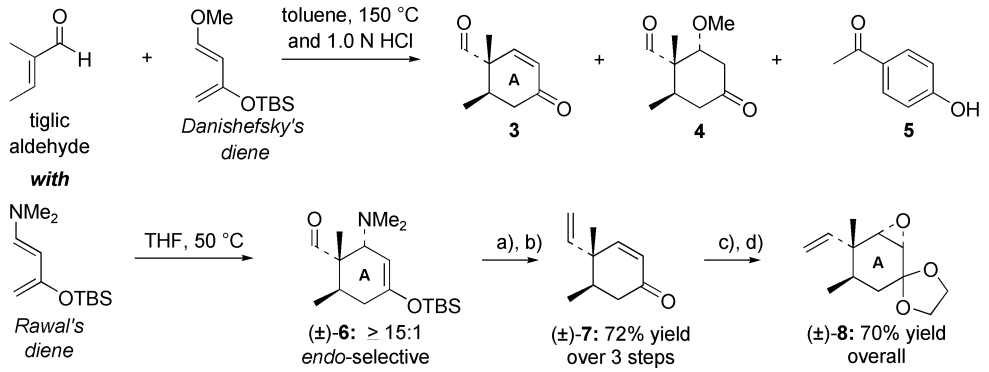
Keywords: asymmetric Diels–Alder cycloaddition; chromium(II)-salen catalyst; intramolecular *oxa*-[3+3]annulation; phomactin A; Rawal's 1-amino-3-siloxy-1,3-butadiene

We have been pursuing the total synthesis of phomactin A, a biologically interesting and structurally unique natural product from the culture filtrate of a parasitic fungus *Phoma* sp. [SANK 11486] found on the shell of *Chinoecetes opilio* off the coast of Fukui prefecture in Japan.[1,2,3] In the last 15 years, phomactin A and its other family members have attracted a number of impressive synthetic efforts[4,5] including Yamada's synthesis of (+)-phomactin D,[6] total syntheses of (±)- and (+)-phomactin A by Pattenden[7] and Halcomb,[8] respectively, and most recently, Wulff's total synthesis of (±)-phomactin B2.[9] We[10] disclosed our synthetic approach to (±)-phomactin A potentially through the ABD tricycle **1**,[11] which can be accessed from an intramolecular *oxa*-[3+3]annulation of vinyliminium salt **2**.[12,13,14]

However, our total synthesis efforts have been seriously compromised by the fact that the annulation precursor **2** required 22 steps from 2-methylcyclohexanone, adopting a route not amenable for asymmetric total synthesis (Scheme 1). Therefore, we have been exploring a conceptually different strategy. Specifically, by constructing the A ring from a Diels–Alder cycloaddition instead of buying from 2-methylcyclohexanone, we hope to establish a much shorter and asymmetric synthesis of **1**. We report herein an enantioselective synthesis of the ABD tricycle for (−)-phomac-



Scheme 1. A synthetic approach to phomactin A.



Scheme 2. Danishefsky's diene *versus* Rawal's diene. *Reaction conditions:* a) Ph_3PBrCH_3, *n*-BuLi, THF, 0 °C to room temperature. b) 4.0 M HF in THF, 0 °C to room temperature. c) K_2CO_3, H_2O_2, MeOH, 0 °C to room temperature. d) $HOCH_2CH_2OH$, *p*-TsOH, PhH, 80 °C.

tin A featuring Rawal's asymmetric Diels–Alder cycloaddition.

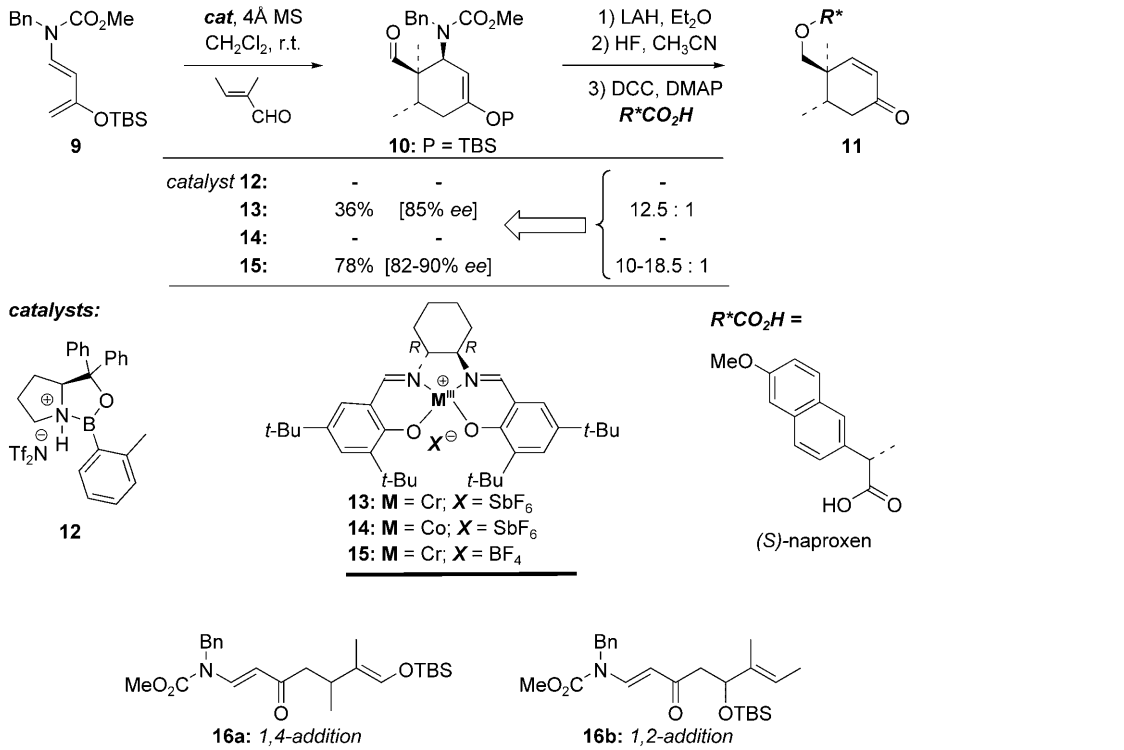
Our initial efforts quickly identified that Diels–Alder cycloaddition of tiglic aldehyde with Danishefsky's diene proceeded only at high temperatures (Scheme 2). After acidic work-up, this cycloaddition afforded, with variable yields, a complex mixture of products **3–5** including *para*-hydroxyacetophenone **5**,[15] likely derived from dimerization of the diene. On the other hand, cycloaddition with Rawal's diene[16,17,18,19,20] did occur with remarkable ease. Although the reaction was slow at −10 °C [ice/acetone], on a 0.22 mol scale, it was complete within 20 h at 50 °C in THF to afford the desired cycloadduct (±)-**6** in high yields as a single *endo* isomer.

It is noteworthy that the better reactivity towards tiglic aldehyde is likely a consequence of the dimethylamino group possessing stronger donating ability into the diene (significantly raising its HOMO level) relative to Danishefsky's diene.[18] This key *endo*-selective cycloaddition sets up a majority of the stereochemistry in the A ring, and provides extensive oxygenation for subsequent transformations. However, attempts to append a tethering fragment through nucleophilic addition to the aldehydic motif in (±)-**6** were not fruitful, and (±)-**6** was rather unstable to chromatography, and underwent clean elimination to give the enone under acidic conditions. With the knowledge of Halcomb's success in adopting Suzuki–Miyaura coupling,[8] we proceeded to olefinate the aldehyde in
(±)-**6**, and after hydrolysis, enone (±)-**7** was attained in 72% yield (Scheme 2). A nucleophilic epoxidation and ketone protection gave vinyl epoxy acetal (±)-**8**, which was used for investigating the Suzuki–Miyaura coupling (*vide infra*).

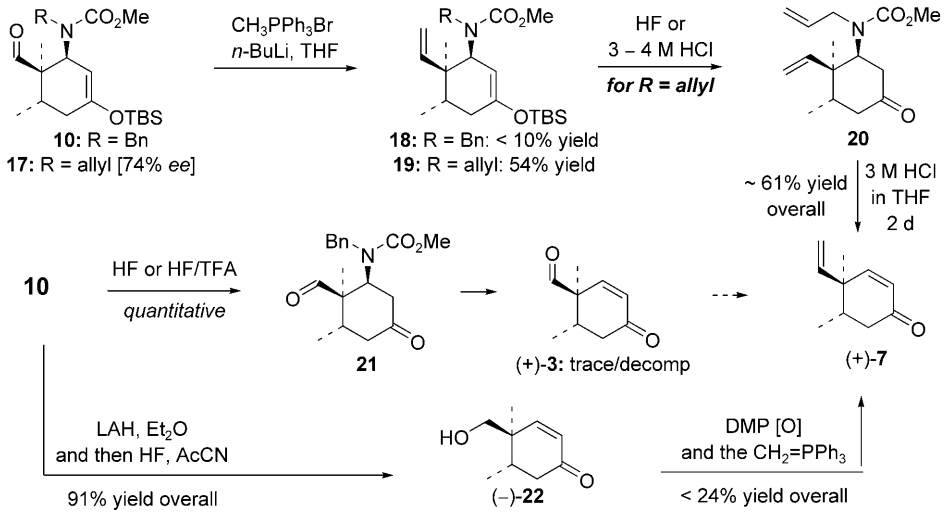
We then turned our attention to pursuing an asymmetric Diels–Alder cycloaddition of tiglic aldehyde with the Rawal's carbamate diene **9**[18–22] (Scheme 3). Screening Corey's oxazaborolidine catalyst **12**[21] only led to 1,4-addition and 1,2-addition products **16a** and **16b**.[23] Rawal[19] had reported a related cycloaddition of tiglic aldehyde that gave 62% yield with 93% *ee* when using Jacobsen's Cr(III)-salen catalyst[24] (see **13** with SbF_6 as counter anion). However, our attempts using diene **9** again resulted in **16a** and **16b** with the best yield for the desired cycloadduct **10** being 36%. The use of Co(III)-salen catalyst **14** was also not useful and gave products related to 1,4-addition and 1,2-addition.[23] Ultimately, we were able to obtain **10** in 78% yield with *ee* up to 90% by using the (*R*,*R*)-Cr(III)-salen catalyst **15** with BF_4 as counter anion. The *ee* was determined by making the (*S*)-naproxen ester **11** (not crystalline and so no X-ray structure could be attained).

With optically enriched cycloadduct **10** in hand, we had trouble transforming it into enone (±)-**7**. As shown in Scheme 4, unlike that of **6**, Wittig olefination of **10** proceeded with <10% yield. While a related DA cycloadduct **17** (R = allyl, only 74% *ee*) gave an improved yield for the olefination, and while hydrolysis to alkene **19** was fast, the elimination of resulting ketone **20** to (±)-**7** was neither efficient nor clean. Subsequently, we examined the possibility of first pursuing a hydrolysis/elimination sequence. However, while treating **10** with HF or HF/TFA quantitatively gave **21**, the elimination was again slow and sluggish, leading to enone (+)-**3** in low yields accompanied with significant decompositions.

Intriguingly, only after we reduced the aldehyde using LAH, the hydrolysis/elimination sequence could be achieved to cleanly give alcohol (−)-**22**. However, subsequent Dess–Martin periodinane (DMP) oxidation and Wittig olefination were again disastrous in an attempt to synthesize (+)-**7**. On the other hand, alcohol (−)-**22** proved to be useful in accessing vinyl epoxy acetal (+)-**8** through epoxy acetal (−)-**23** in an overall 4 steps (Scheme 5). LAH reduction of the epoxide in **8** followed by TES protection led to vinyl acetal (+)-**24** in 87% overall yield.



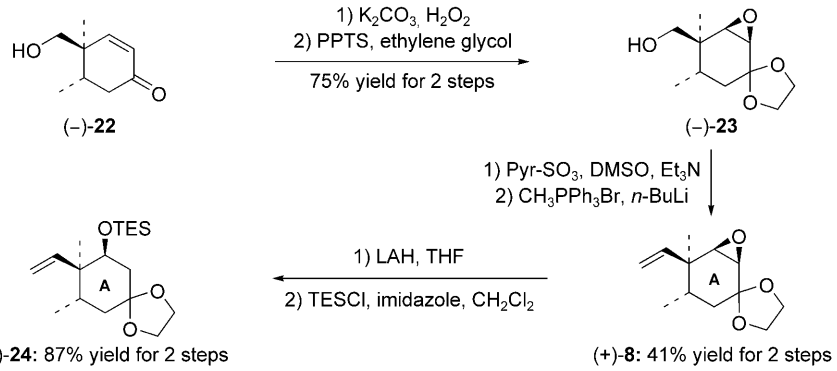
Scheme 3. Rawal's asymmetric Diels–Alder cycloaddition.



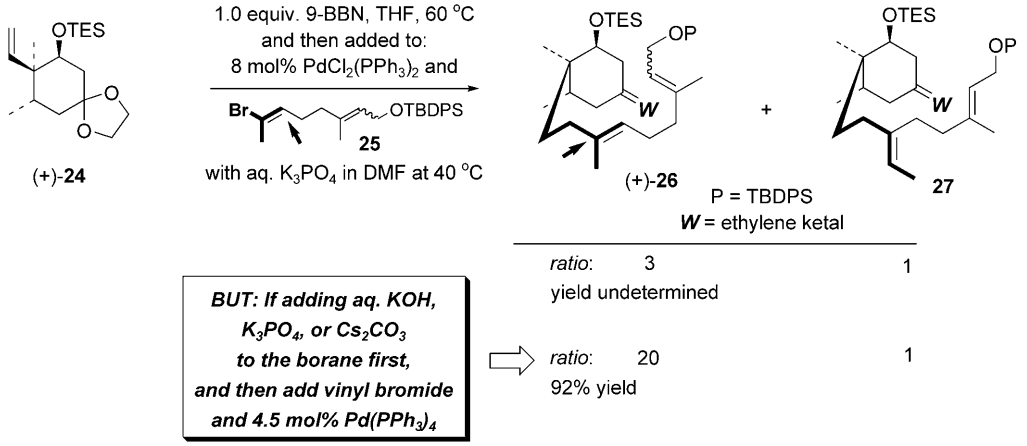
Scheme 4. Struggles in accessing enone (+)-7.

At this point, although we have already examined Suzuki–Miyaura coupling of (±)-**8** with vinyl bromide **25**,[15] it was not very desirable. Thus, we focused on the cross-coupling of vinyl acetal (+)-**24** with **25** (Scheme 6). Upon closer examination of the reaction mixture, we were disturbed to find significant quantities of the unexpected olefin **27** (*E/Z* unassigned) in addition to the desired Suzuki–Miyaura cross-product (−)-**26**. It was extremely difficult to separate **27** from (−)-**26**.[25]

We were certain that this compound was not coming from contamination during the preparation of vinyl bromide **25**.[15] The use of exotic bases such as Cs_2CO_3, Tl_2CO_3, Ag_2CO_3, Ag_2O, or $Tl(OEt)_2$,[24] often critical to the success of these reactions, did not seem to help matters. After trying the $PdCl_2$dppf and finding it produced a larger amount of by-product **27**, we stuck to our traditional mode of employing $PdCl_2(PPh_3)_2$ for the reaction. While we remain uncertain of the mechanism for this unusual crossed



Scheme 5. A suitable path to vinyl epoxy acetal (+)-8.



Scheme 6. A strange Suzuki–Miyaura coupling.

product, it appears that the addition order mattered. After the 9-BBN hydroboration had occurred, a respective base must be added first to the borane solution before the addition of the palladium/vinyl bromide solution. The most effective catalyst was $Pd(PPh_3)_4$, and when it was used at 4.5 mol% along with 2.0 M aqueous KOH, the formation of **27** was just barely observable by ^{1}H NMR.

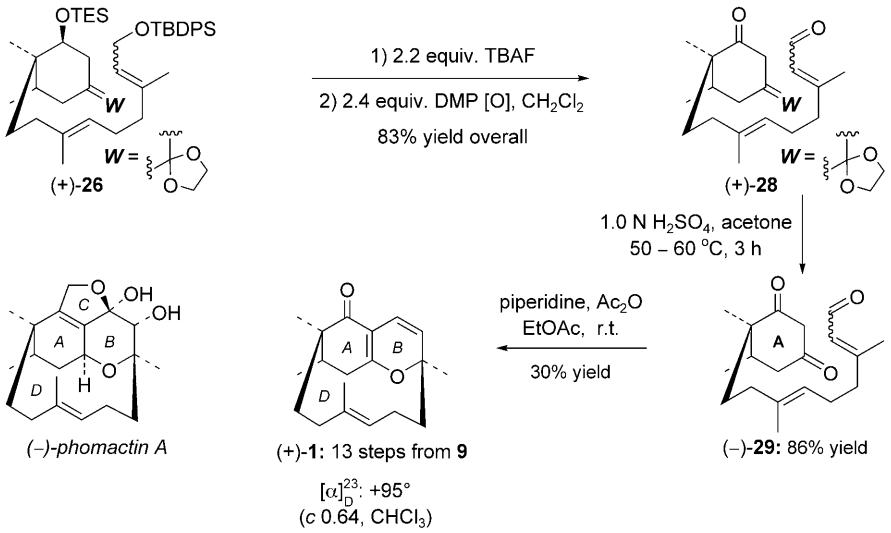
Resolving this quagmire in the Suzuki–Miyaura coupling allowed us to complete an asymmetric synthesis of the ABD tricycle. As shown in Scheme 7, desilylation followed by DMP oxidation led to acetal enal (+)-**28**, and a careful hydrolysis of acetal (+)-**28** with 1.0 N H_2SO_4 gave the annulation precursor (−)-**29**. Under the *oxa*-[3+3]annulation conditions,[10,13] ABD tricycle (+)-**1** was attained in 30% yield[27] in an overall 13 steps from diene **9**. The absolute configuration at this point is solely based on Rawal's assignment of related asymmetric Diels–Alder cycloadducts.

We have described here an enantioselective synthesis of the ABD ring for constructing (−)-phomactin A. The synthetic sequence features Rawal's asymmetric Diels–Alder cycloaddition. The overall length of this new approach is significantly reduced from our previous attempt. Completion of a total synthesis of (−)-phomactin A is in progress.

Experimental Section

Asymmetric Diels–Alder Reaction

To a solution of tiglic aldehyde (3.95 mL, 41.0 mmol, 2.0 equiv.) in CH_2Cl_2 (20 mL) were added 4 Å molecular sieves (16.5 g), (*R,R*)-Cr(III)-salen BF_4 (697.0 mg, 1.02 mmol, 5 mol%) and then diene **9** (7.12 g, 20.5 mmol, 1.0 equiv.) and the reaction was stirred at room temperature for 2 d. The reaction mixture was then filtered through a plug of silica gel. The filtrate was concentrated to give a light brown oil. This crude oil was purified *via* silica gel flash column chromatography (gradient eluent: 5–10% EtOAc in hexanes) to afford the cycloadduct Diels–Alder product **10** as a yellow oil; yield: 6.90 g (78%); R_f = 0.56 (25% EtOAc in hexanes); $[\alpha]_D^{23}$: +48.0° (*c* 2.50, $CHCl_3$); ^{1}H NMR (400 MHz $CDCl_3$): δ = −0.15 (s, 3H,), −0.06 (s, 3H), 0.67–0.93 (m, 12H), 1.16 (s, 3H), 1.69–1.77 (m, 1H), 2.11–2.17 (m, 1H), 2.23–2.46 (m, 1H), 3.57 (s, 3H), 4.45 (s, 1H), 4.58–4.61 (m, 2H), 4.84 (s, 1H), 7.08–7.23 (m, 5H), 9.58 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = −4.6, 14.1, 16.6, 18.1, 25.8 28.4, 35.0, 48.5, 53.0, 53.6, 59.7, 99.5, 126.2,



Scheme 7. Synthesis of ABD ring (+)-**1** for (−)-phomactin A.

126.7, 128.3, 139.8, 154.8, 158.0, 205.9; IR (neat): $\nu = 2956$ (w), 2931 (w), 2859 (w), 1721 (w), 1692 (w), 1670 (w), 1451 (w), 1393 (m), 1373 (m), 1219 (w), 1201 (w), 1169 (m), 835 (w), 780 cm^{-1} (m); MS (APCI): *m/e* (% relative intensity) = 267 (13) $(M+1)^+$, 432 (100).

LAH Reduction and HF Hydrolysis

To a solution of the Diels–Alder cycloadduct **10** (6.89 g, 16.0 mmol) in 160 mL of Et_2O at 0 °C was added LAH (1.21 g, 32.0 mmol) portion wise. The reaction mixture was then warmed to room temperature and stirred overnight. The reaction was cooled to 0 °C, and H_2O (1.21 mL), 10% aqueous NaOH (1.21 mL) and H_2O (3.63 mL) were added slowly in that order. The mixture was stirred for 1–2 h, and then the white precipitate was formed. The white solid was removed by filtration. The filtrate was concentrated under reduced pressure to give a pale yellow oil.

The above crude oil was taken up in CH_3CN (32 mL) and to this solution was added an HF solution (1.10 mL, 48%, 29.0 M, 32.0 mmol) and the reaction was stirred at room temperature overnight. The reaction solution was neutralized by addition of aqueous Na_2CO_3 until the CO_2 bubbles stopped forming. The solid (mostly NaF) was removed by filtration and the filtrate was concentrated under vacuum. The crude oil was purified *via* silica gel flash column chromatography eluting with 10% EtOAc in hexanes to give alcohol (−)-**22** as a pale yellow oil; yield: 2.26 g (91% for two steps from the Diels–Alder cycloadduct **10**). Upon standing, colorless crystals can be formed from crystallization. $R_f = 0.19$ (40% EtOAc in hexanes); $[\alpha]_D^{20} = -18.0$ (*c* 2.50, $CHCl_3$]; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.97$ (s, 3H), 0.98 (d, 3H, $J = 7.0$ Hz), 1.73 (brs, 1H), 2.29 (dd, 1H, $J = 13.5$, 17.0 Hz), 2.36–2.44 (m, 2H), 3.59 (d, 1H, $J = 11.0$ Hz), 3.62 (d, 1H, $J = 11.0$ Hz), 6.01 (d, 1H, $J = 10.0$ Hz), 6.82 (d, 1H, $J = 10.0$ Hz); ^{13}C NMR (500 MHz, $CDCl_3$): $\delta = 15.2$, 15.5, 31.8, 41.6, 41.8, 68.1, 128.7, 158.1, 200.1; IR (neat): $\nu = 3448$ (s), 2965 (m), 1662 cm^{-1} (s); MS (APCI): *m/e* (% relative intensity) = 155 (100) $(M+1)^+$.

Naproxen Ester Formation for Analyzing Isomeric Ratios

To a solution of alcohol (−)-**22** (10.0 mg, 0.067 mmol) in CH_2Cl_2 (2 mL) were added (*S*)-naproxen (15.0 mg, 0.067 mmol), DMAP (0.080 mg, 0.0067 mmol), and DCC (14.0 mg, 0.067 mmol). The resulting mixture was stirred for at room temperature for 18 h. The reaction mixture was simply filtered through a Celite™ plug and the clear filtrate was concentrated under vacuum to give the crude ester **11** as a solid that was subjected to crude NMR analysis for the assessment of diastereomeric ratios. $R_f = 0.62$ (40% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.80$ (d, 3H, $J = 6.6$ Hz), 0.91 (s, 3H), 1.54–1.61 (m, 1H), 1.57 (d, 3H, $J = 6.8$ Hz), 1.66–1.71 (m, 1H), 1.88–1.96 (m, 1H), 1.99–2.17 (m, 1H), 2.17 (d, 2H, $J = 9.2$ Hz), 3.91 (s, 3H), 4.03 (d, 2H, $J = 3.6$ Hz), 5.85 (d, 1H, $J = 10.4$ Hz), 6.59 (d, 1H, $J = 10.4$ Hz), 7.10–7.15 (m, 2H), 7.35 (dd, 1H, $J = 1.6$, 8.0 Hz), 7.63–7.68 (m, 3H).

The *Oxa*-[3+3] Annulation: Asymmetric Synthesis of ABD Ring (+)-1

To a solution of enal (−)-**29** (107.0 mg, 0.35 mmol) in anhydrous EtOAc (15 mL; distilled from CaH_2) was added anhydrous piperidine (42.0 μL, 0.422 mmol, 1.2 equiv.; distilled from and stored with CaH_2) at −10 °C. The solution was stirred to −10 °C for 5 min, and then, acetic anhydride (200.0 μL, 2.11 mmol, 6.0 equiv.) was added carefully dropwise. The resulting mixture was stirred at room temperature for 3–4 h before it was washed with an equal volume of 1.0 N aqueous NaOH. The organic layer was dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude product was purified using silica gel flash column chromatography (gradient eluent: 0–25% EtOAc in hexanes) to give, yield along with by-product **30a/b** (yield: 27.0 mg, 25%), the desired ABD tricycle (+)-**1**; yield: 32.0 mg (30%); $R_f = 0.41$ (10% EtOAc/hexanes); $[\alpha]_D^{23}$: +95° (*c* 0.64, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.45$ (d, 1H, $J = 10.5$ Hz), 5.15 (brd, 1H, $J = 10.5$ Hz), 4.99 (d, 1H, $J = 10.5$ Hz), 2.87 (dd, 1H, $J = 6.5$, 20.0 Hz), 2.29–2.40 (m,

2H), 2.12 (m, 1H), 2.10 (d, 1H, $J=19.5$ Hz), 2.06 (ddd, 1H, $J=1.5$, 7.5, 14.5 Hz), 1.94 (dt, 1H, $J=3.5$, 14.0 Hz), 1.94 (ddd, 1H, $J=2.0$, 4.0, 14.5 Hz), 1.89 (ddd, 1H, $J=3.5$, 12.5, 15.0 Hz), 1.80 (td, 1H, $J=3.5$, 14.5 Hz), 1.70 (ddd, 1H, $J=3.0$, 6.0, 15.0 Hz), 1.47 (s, 3H), 1.38 (brm, 3H), 1.07 (s, 3H), 1.02 (d, 3H, $J=7.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=198.6$, 169.1, 134.6, 125.3, 119.8, 118.0, 116.0, 82.9, 47.1, 46.1, 39.5, 37.0, 35.7, 34.5, 31.3, 25.2, 24.6, 20.0, 16.1; IR (neat): $\nu=2976$ (m), 2929 (m), 2901 (m), 2835 (w), 1640 (vs), 1607 (s), 1449 (m), 1416 cm^{-1} (s); MS (ESI): *m/e* (% relative intensity) = 309.2 $(M+Na)^+$ (100), 197.0 (13); HR-MS: *m/e* = 309.1818, calcd. for $C_{19}H_{26}O_2Na$ $(M+Na)^+$: 309.1830 [$\delta=3.89$ ppm].

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