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Expedient Stereoselective Synthesis of Coronafacic Acid Through Intramolecular Diels−Alder Cyclization

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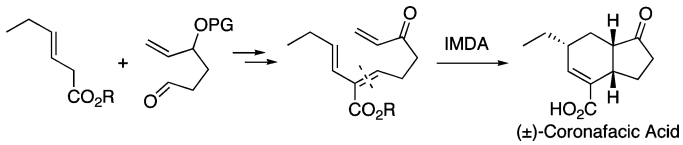

A stereoselective synthesis of coronafacic acid, a natural component of the phytotoxin coronatin, was achieved using an intramolecular Diels−Alder reaction as the key step. The triene precursor bearing a substituted diene and a vinylketone as dienophile was synthesized and then tested in the thermal intramolecular cyclization. We have devised a new strategy to assemble the *E,Z*-diene through the stereoselective aldol reaction of an ester enolate followed by a stereoselective dehydration. Following the thermal cyclization, the corresponding hydrindanone thereby obtained with the desired relative stereochemistry could easily be converted into the natural product. The synthesis of the coronafacic acid was accomplished in six steps in 29% overall yield.

Introduction

Considerable interest has been drawn to coronatin (**1**),[1] a natural phytotoxin, due to its unique structure and biological activities. Coronatin is the most potent phytotoxin of a wide range of phytotoxic compounds produced by *Pseudomonas syringae*, a bacteria that has been abundantly studied and is well characterized.[2] *Pseudomonas syringae* is known to induce a variety of diseases on a number of plants, including leaf spots, blights and galls. Plant infection by *P. syringae* induces chlorosis on Italian rye grass,[3] hypertrophy, root tuberization and cell expansion on potato (at a concentration of 10^{-7} mol/L),[4] biosynthesis of plant hormone ethylene in tobacco leaves,[5] and inhibition of cell growth in soy seeds. Moreover, it induces the biosynthesis of volatile compounds such as ethylene in many plants.[6] Many derivatives possessing different amino acids (Leu, Ile, Val) have also been found but are much less active.

Isolated back in 1977, coronatin has since attracted the attention of several synthetic organic chemistry groups. It exists as two isomers depending upon the recrystallization conditions that are used. The *trans* isomer can easily be converted into its *cis* isomer through equilibration upon silica treatment. Coronatin's unique structure is composed of two distinct fragments: coronafacic acid (**2**), a bicyclic core with three stereogenic centers, and coronamic acid (**3**),[7] a cyclopropane amino acid[8] derived from isoleucine (Figure 1).[9] Many research groups have

* Corresponding author.

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(5) Kenyon, J. S.; Turner, J. G. *Plant Physiol.* **1992**, *100*, 219−224.

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(9) (a) Parry, R. J.; Mafoti, R. *J. Am. Chem. Soc.* **1986**, *108*, 4681−4682. (b) Parry, R. J.; Lin, M.-H.; Walker, A. E.; Mhaskar, S. *J. Am. Chem. Soc.* **1991**, *123*, 1849−1850.

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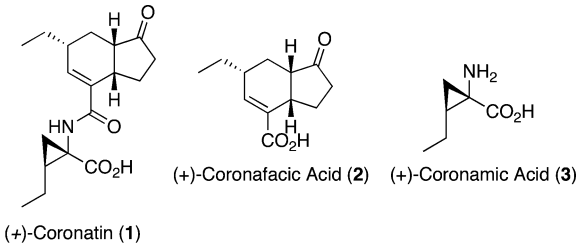
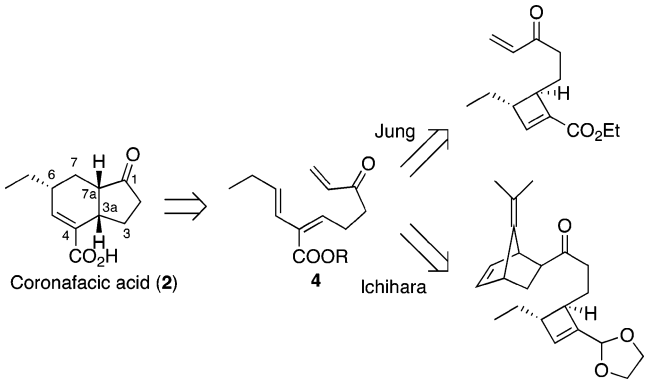


FIGURE 1. Coronatin and its components.

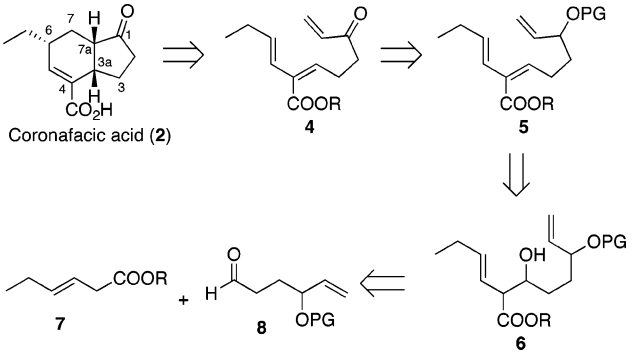
noticed the remarkable structural and functional homology of coronatin with methyl jasmonate, a growth factor produced by plants subjected to biological stress.[10] Both natural products induce analogous biological responses in several plants, which suggests a similar action mode. However, because coronatin also possesses biological activities different from those of methyl jasmonate, it does not serve only as a mimic of methyl jasmonate.[11] It was also found that the coronamic acid is essential for retaining the biological activity of coronatin.

The synthesis of the bicyclic core of coronatin, the coronafacic acid, represents a great challenge due to the necessity to control both the relative and absolute stereochemistry of the three stereogenic centers. To this day, 14 total syntheses of the coronafacic acid have been reported in the literature,[12] as well as a formal synthesis.[13] There are 12 syntheses leading to the racemic product, one enantioselective synthesis,[12m] and a synthesis in which the racemic mixture of an advanced intermediate was resolved to obtain the two enantiomers separately.[12h] In addition to inter- and intramolecular Diels−Alder cyclization, other methods such as an oxy-Cope rearrangement, a cyclopropane ring opening, a Dieckman condensation, a Haller−Bauer-type cleavage, a metathesis, a radical cyclization, and a conjugated addition have been used as key steps for the synthesis of the coronafacic acid. In this paper, we report a total synthesis of (±)-coronafacic acid that features an intramolecular Diels−Alder reaction.

SCHEME 1



SCHEME 2



Results and Discussion

The diversity of the approaches that have been used illustrates the high level of interest generated for the synthesis of this unique hydrindane skeleton. One of the key elements to consider is that the synthetic strategy must include a control over the relative stereochemistry at C_{3a} and C_6 centers. This was accomplished with high selectivity by using an intramolecular Diels−Alder approach (Scheme 1).[12d,e] In both cases, the triene precursor was generated at elevated temperatures as part of a tandem sequence involving a ring opening of an appropriately substituted cyclobutene. The triene was never isolated, and it underwent a [4 + 2] cycloaddition to generate the corresponding hydrindane ring system.

Our strategy to achieve the synthesis of the coronafacic acid, with control over the relative stereochemistry, is based on a similar intramolecular Diels−Alder (IMDA) reaction for the simultaneous construction of the three stereogenic centers. For a rapid access to the natural product, the design of an achiral triene precursor should ideally include a vinyl ketone as dienophile and a diene bearing an acid under masked form at the 2-position (Scheme 2). We speculated that access to the triene would allow us to test the chiral Lewis acid catalyzed cycloaddition reactions that would lead to the enantioenriched product.[14] We planned to introduce the vinyl ketone dienophile moiety at a late stage of the synthesis by oxidation of allylic alcohol **5** (PG = H). The triene could then come from a

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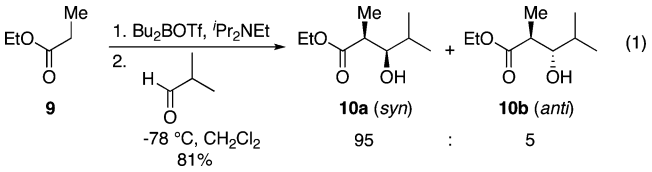
stereoselective dehydration of aldol product **6** obtained from aldehyde **8** and ester **7**.

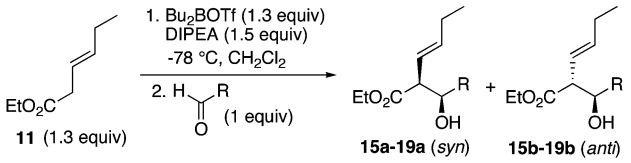
Diene Synthesis. We envisioned the synthesis of the *Z* alkene by the selective dehydration of a diastereomerically pure aldol adduct arising from the condensation of β,γ-unsaturated ester **7** with aldehyde **8**. As opposed to ketones, the aldol reaction of ester enolates is far less developed.[15] For many years, it has been assumed that simple esters could not be enolized using a boron triflate and an amine.[16] Lately, the enolization of esters has been achieved by Abiko[17] after careful choice of a boron triflate coupled with an amine, which allowed for the selective synthesis of either the *syn* or *anti* diastereomer depending upon conditions. The enolization of a propionate ester with dibutylboron triflate and diisopropylamine at low temperature generated the *Z* enolate selectively, which afforded the *syn* diastereomer in 95:5 ratio after a reaction with isobutyraldehyde following a Zimmermann−Traxler transition structure (eq 1).

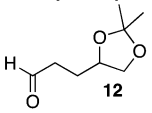
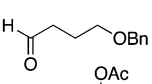
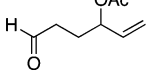


(1)

We wished to use this methodology for the selective synthesis of an aldol product, which could later be eliminated to form the unsaturated ester. Unfortunately, the developed conditions were only reported for the reaction of propionates with isobutyraldehyde. Moreover, since the aldehyde had previously been used in excess for the study, we had to revisit the reaction conditions. We began our investigation by the enolization of ethyl (3*E*)-hex-3-enoate (**11**), a β,γ-unsaturated ester, in the presence of dibutylboron triflate and Hunig's base to generate the *Z* enolate. The stoichiometry of the reagents was adjusted to allow for the aldehyde to serve as a limiting reagent. When reacted with isobutyraldehyde, the expected *syn* diastereomer aldol product **15a** was obtained in good yield (87%) and with excellent stereocontrol (98:2) (Table 1). Moreover, the integrity of the *E* alkene was preserved during the reaction. We then studied the effect of various aldehydes on the diastereoselectivity of the aldol reaction. When functionalized aldehyde **12** was used instead of isobutyraldehyde, a surprising reversal in selectivity was observed, as the *anti* adduct was obtained as a major diastereomer (22:78 *syn*:*anti*) in 82% yield (entry 2). This trend was also observed in the case of an aldehyde **13** that led to a 18:82 *syn*:*anti* ratio (entry 3). The use of butyraldehyde provided poorer selectivity (32:68 *syn*:*anti*) in favor of the *anti* diastereomer (entry 5). These results showed that the nature of the aldehyde has a considerable effect on diastereoselectivity, and an α-branched aldehyde appeared to be required for high *syn* selectivity. Using linear aldehydes, it could be possible that the

TABLE 1. Aldol Reaction of Ethyl (3*E*)-Hex-3-enoate with Various Aldehydes



entry	aldehyde	yield (%)[a]	*syn*:*anti*[b]	major product
1	Isobutyraldehyde	87	98:2	**15a**
2	 **12**	82	22:78	**16b**
3	 **13**	66	18:82	**17b**
4	 **14**	85	13:87	**18b**
5	Butyraldehyde	67	32:68	**19b**

[a] Combined yield of both diastereomers. [b] Ratio determined by ^{1}H NMR of the crude reaction mixture.

Lewis acid catalyzed reaction proceeds through an open transition structure.[18]

For the purpose of the synthesis, we introduced the vinyl ketone functionality under the masked form of a protected allylic alcohol. In the case of aldehyde **14**, which conveniently allowed for the deprotection of the acetate under a wide range of conditions, the aldol product was obtained in 85% yield with 13:87 *syn*:*anti* selectivity (entry 4). Diastereomers **18a** and **18b** were easily separated by flash chromatography.

The selective dehydration of an aldol product in a stereoselective fashion would provide the desired *Z* alkene. Although typical dehydration procedures often lead to the formation of the thermodynamic product, the selective dehydration of a diastereomerically pure aldol product allows for the stereoselective synthesis of unsaturated carbonyls. Upon treatment of an aldol adduct with diethyl azodicarboxylate and triphenylphosphine, the *anti* elimination product was observed.[19] A phosphonium intermediate was first obtained, followed by an abstraction of the acidic hydrogen accompanied by the elimination of the triphenylphosphine oxide. Complementarily, the use of dicyclohexylcarbodiimide with a catalytic copper halide source provided the *syn* elimination product.[20] In this case, a carbamimidate intermediate was formed, which underwent an intramolecular abstraction of the acidic hydrogen, and the formation of a urea. These methods proved extremely useful for the stereoselective synthesis of trisubstituted alkenes.

The selective dehydration of diastereomers **18a** and **18b** by different elimination methods would result in a stereoconver-

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(16) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099−3111.

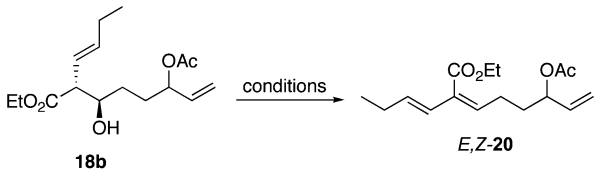
(17) (a) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Org. Chem.* **1996**, *61*, 2590−2591. (b) Inoue, T.; Liu, J.-F.; Buske, D. C.; Abiko, A. *J. Org. Chem.* **2002**, *67*, 5250−5256.

(18) An open transition state has been postulated when an excess of boron triflate is present in the aldol reaction of the boron enolate of an oxazolidinone: Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173−181.

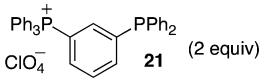
(19) (a) von der Ohe, F.; Brückner, R. *Tetrahedron Lett.* **1998**, *39*, 1909−1910. (b) Bradbury, R. H.; Walker, K. A. M. *J. Org. Chem.* **1983**, *48*, 1741−1750.

(20) (a) Corey, E. J.; Andersen, N. H.; Carlson, R. M.; Paust, J.; Vedejs, E.; Vlatas, I.; Winter, R. E. K. *J. Am. Chem. Soc.* **1968**, *90*, 3245−3247. (b) Alexandre, C.; Rouessac, F. *Tetrahedron Lett.* **1970**, *13*, 1011−1012. (c) Alexandre, C.; Rouessac, F. *Bull. Soc. Chim. Fr.* **1971**, *5*, 1837−1842.

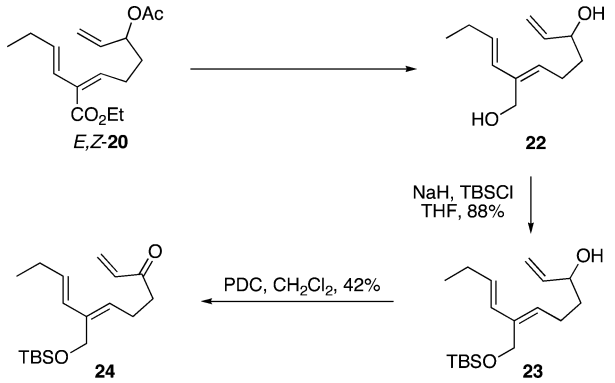
TABLE 2. Diastereoselective Dehydration Reaction



18b *E,Z*-**20**

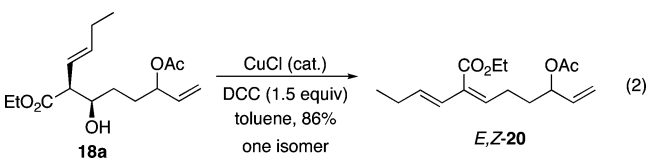
entry	conditions	yield (%)	*E,Z*:*E,E*
1	DEAD (2 equiv), PPh_3 (2 equiv) THF, -40 °C to rt	88	97:3
2	DEAD (2 equiv), PPh_3 (2 equiv) THF, 0 °C to rt	86	94:6
3	DEAD (2 equiv), CH_2Cl_2, 0 °C to rt  (2 equiv)	71	95:5

SCHEME 3



gent synthesis of diene *E*,*Z*-**20**. Treatment of *anti* diastereomer **18b** with DEAD and PPh_3 at −40 °C, afforded the *Z* isomer in high yield (88%) and selectivity (97:3), following an *anti* elimination pathway (Table 2, entry 1). The dehydration could also be accomplished at 0 °C; however, a small erosion in the diastereoselectivity was observed (entry 2). The elimination was also performed using a phosphonium supported triphenylphosphine reagent **21**,[21] which provided the desired product in 71% yield and a 95:5 *Z*/*E* ratio (entry 3). The use of this reagent was advantageous, since the phosphine oxide side product was easily precipitated upon ether addition and was removed by simple filtration.

Conversely, *syn* diastereomer **18a** was treated with DCC in the presence of a catalytic amount of copper chloride, to afford the desired isomer *E*,*Z*-**20** exclusively in 86% yield (eq 2). Products from both diastereoselective dehydrations could then be combined for the continuation of the synthesis.

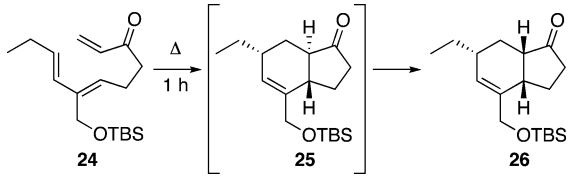


18a *E,Z*-**20** (2)

We elected to initially examine the synthesis of a Diels−Alder precursor bearing a protected alcohol as the masked form

(21) Poupon, J.-C.; Boezio, A. A.; Charette, A. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 1415−1420.

TABLE 3. Thermal Cycloaddition of Triene 24

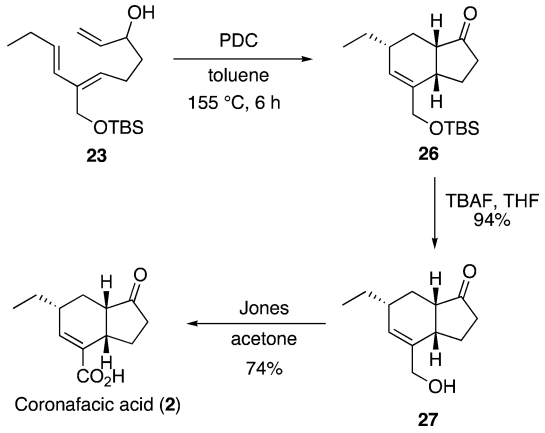


24 **25** **26**

entry	temp (°C)	solvent	conversion (%)[a]
1	100	CD_3SOCD_3	0
2	120	CD_3SOCD_3	decomp
3	135 (sealed tube)	C_6D_6	0
4	145 (sealed tube)	C_6D_6	25
5	155 (sealed tube)	C_6D_6	>95

[a] Determined by ^1H NMR using an internal standard.

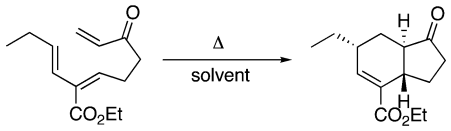
SCHEME 4



of the carboxylic acid at C-4. The reduction of both esters with DIBAL-H afforded corresponding diol **22** in 79% yield (Scheme 3). The protection of the primary alcohol as a TBS ether was achieved in 88% yield. Finally, the oxidation of alcohol **23** using PDC provided the desired triene **24** in 42% yield. Although the triene decomposed slowly over time, it did not undergo spontaneous cycloaddition reaction.

With triene **24** in hand, we tested the thermal cycloaddition (Table 3). The Diels−Alder reaction was first conducted in deuterinated solvent and monitored by ^1H NMR. When the reaction was performed in DMSO-d_6, we observed the degradation of triene **24** beginning at ca. 120 °C. Under these conditions only small amounts of cycloadduct **25** could be detected by NMR. When the reaction was run in benzene-d_6 at 145 °C, triene **24** was slowly converted into **25** (25% conversion after 1 h). Heating the mixture at 155 °C for 1 h led to full consumption of the starting material, and a significant amount of the desired product was formed. The relative stereochemistry at C_6 and C_{3a} was *trans*, resulting from the favored *exo* cycloaddition. However, the product epimerized to the desired *cis* hydrindane **26** upon purification on silica gel, albeit in low yield (24%). This epimerization to the more thermodynamically stable *cis* isomer has been observed in previous total syntheses.[12] The low isolated yield is due to the thermal unstability of triene **24** that starts to decompose at temperature lower than the cycloaddition. Significant improvement in the yield was observed if the oxidation of the allylic alcohol and the cycloaddition were

TABLE 4. Intramolecular Diels−Alder Reaction of Triene 29

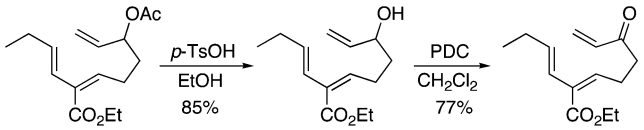


29 **30**

entry	temp (°C)	time	solvent	conversion (%)[a]
1	135	1 h	C_6D_6	40
2	145	1 h	C_6D_6	80
3	100	1 h	CD_3SOCD_3	30
4	120	1 h	CD_3SOCD_3	93
5	140	12 h	CD_3SOCD_3	98 (78)[b]
6	180	5 min	CD_3SOCD_3/C_6D_6	96 (78)[c]

[a] Determined by ^{1}H NMR. [b] Isolated yield of the *cis* ring junction product **31** in parentheses. [c] Microwave irradiation.

SCHEME 5



E,Z-**20** **28** **29**

performed in a one-pot procedure. Under these conditions, hydrindanone **26** was obtained in an improved yield of 61% (Scheme 4).

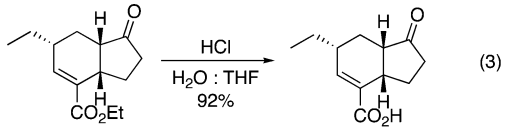
Following its thermal cycloaddition, adduct **26** could be converted into coronafacic acid in a straightforward process (Scheme 4). Deprotection of hydrindanone **26** upon treatment with TBAF followed by an oxidation led to coronafacic acid (**2**) in 19% overall yield over a seven-step synthesis.

Alternatively, the intramolecular Diels−Alder of triene **29** would lead directly to an ester at C-6 instead of a protected alcohol. The synthesis of triene **29** simply involved the acetate deprotection of **20** under mild acidic conditions followed by a PDC oxidation (Scheme 5).

For the sake of comparison with the reaction involving **24**, the Diels−Alder reaction of triene **29** was initially tested in benzene-d_6. NMR monitoring of the reaction indicated that triene **29** was slowly converted into **30** when heated at 135 °C (40% conversion after 1 h) (Table 4). The conversion increased to 80% when the temperature was raised to 145 °C (entry 2). The reaction also proceeded well in DMSO-d_6, as 30% conversion was observed within 1 h at 100 °C and 93% conversion at 120 °C after an additional 1 h (entries 3 and 4). The optimal reaction time and temperature for the cycloaddition were 140 °C for 12 h (entry 5). Under these conditions, the cycloaddition adduct **31** was isolated in 78% yield. Alternatively, the reaction could be carried in a microwave apparatus at 180 °C in a mixture of DMSO/benzene and was complete after only 5 min (entry 6).

In contrast to triene **24**, which underwent cycloaddition at 155 °C (>95% conversion), triene **29** reacted at 130 °C (80% conversion). The lower activation energy required for the Diels−Alder reaction of triene **29** could be explained by the additional stabilization brought by the ester to the new forming double bond in the transition state.[22] As before, hydrindane **30** epimerized to the *cis* ring junction product **31** upon purification.

Hydrindanone **31** was hydrolyzed under acidic conditions to afford coronafacic acid (**2**) in 92% yield (eq 3). Following this route, an improved overall yield of 29% in only six steps was necessary for the synthesis of (±)-coronafacic acid (**2**).



31 Coronafacic acid (**2**)

Conclusion

In summary, the stereoselective synthesis of coronafacic acid, a component of coronatin, was achieved using an intramolecular Diels−Alder reaction as the key step. We have devised a new strategy for the construction of trisubstituted alkenes by a two-step sequence involving a diastereoselective aldol reaction and a subsequent dehydration. Using this methodology, we devised a concise synthesis of a triene, which was then cyclized under thermal conditions to afford the hydrindanone core. Control over the relative stereochemistry at centers C_{3a} and C_6 was successfully achieved during the cyclization step. The coronafacic acid was isolated in 29% overall yield for the six-step sequence. The development of an asymmetric synthesis of the coronafacic acid through a chiral Lewis acid catalyzed Diels−Alder reaction using these trienes is under way and will be reported in due course.

Experimental Section

General Procedure for Aldol Reactions of Ethyl (3*E*)-Hex-3-enoate with Aldehydes. Ethyl (3*E*)-hex-3-enoate (5.2 mmol, 1.3 equiv) was dissolved in CH_2Cl_2 (16 mL), then freshly distilled diisopropylethylamine (6 mmol, 1.5 equiv) was added, and the solution was cooled to −78 °C. Freshly prepared dibutylboron triflate (5.2 mmol, 1.3 equiv) was slowly added to the solution, which was then stirred for 2 h at −78 °C. The aldehyde (4 mmol, 1 equiv) was dissolved in CH_2Cl_2 (8 mL) and added to the solution, which was stirred at −78 °C for 1 h, then at 0 °C for an additional 1 h. Work up: a phosphate buffer solution at pH = 7 (8 mL) was added along with methanol (12 mL) and hydrogen peroxide (30% aqueous, 4 mL), and the solution was stirred at room temperature for 12 h. After this period of time, water was added, and the organic layer was extracted with CH_2Cl_2. The organic layer was washed with brine, dried on Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford separately the diastereomers of the aldol product.

Ethyl (2,3-*syn*)-6-(Acetyloxy)-2-[(1*E*)-but-1-enyl]-3-hydroxyoct-7-enoate (18a) and Ethyl (2,3-*anti*)-6-(Acetyloxy)-2-[(1*E*)-but-1-enyl]-3-hydroxyoct-7-enoate (18b). Following the general procedure for aldol reactions using aldehyde **14** (4 mmol) and purification by flash chromatography on silica gel (20% EtOAc/hexanes) afforded separately the diastereomers of product **18** as colorless oils (1.01 g, 85%, 13:87 *syn*:*anti*); HRMS (ESI, Pos): calcd for $C_{16}H_{26}O_5Na$ $(M + Na)^+$ 321.1673, found 321.1660. **18a**: R_f = 0.23 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81−5.67 (m, 2H, CH_2=C*H*CHOAc, CH_2CH=CHCH), 5.54−5.47 (ddd, J = 15.4, 9.4, 1.4 Hz, 1H, CH_2CH=C*H*CH), 5.30−5.15 (m, 3H, C*H*$_2$=CHC*H*OAc), 4.19−4.13 (dq, J = 7.1, 1.9 Hz, 2H, $CO_2CH_2CH_3$), 3.88−3.82 (m, 1H, C*H*OH), 2.98−2.95 (dd, J = 9.1, 4.7 Hz, 1H, C*H*CO_2Et), 2.78−2.67 (b, 1H, O*H*), 2.11−2.01 (m, 5H, CH=CHC*H*$_2$CH$_3$, O_2CCH$_3$), 1.89−1.79 (m, 1H, AcOCHC*H*$_2$-CH_2CHOH), 1.71−1.61 (m, 1H, AcOCHC*H*$_2$CH$_2$CHOH), 1.55−1.35 (m, 2H. AcOCHCH$_2$C*H*$_2$CHOH), 1.29−1.24 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.02−0.98 (t, J = 7.4 Hz, 3H, CH=$CHCH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 170.3, 138.9, 136.3, 136.2, 121.9, 116.9, 116.8, 74.7, 74.3, 71.1, 70.9, 60.9, 54.8, 54.7, 30.3, 30.1, 29.5, 29.3, 25.7, 21.2, 14.1, 13.5; IR (neat) 3456, 2961, 2934,

(22) Spino, C.; Pesant, M.; Dory, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 3262−3266.

1731 (C=O), 1371, 1236, 1021 cm^{-1}. **18b**: $R_f = 0.18$ (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.78−5.65 (m, 2H, CH_2=C*H*CHOAc, CH_2C*H*=CHCH), 5.42−5.33 (ddd, J = 15.3, 9.1, 1.6 Hz, 1H, CH_2CH=C*H*CH), 5.25−5.15 (m, 3H, C*H*$_2$=CHC*H*OAc), 4.21−4.13 (dq, J = 7.1, 1.9 Hz, 2H, $CO_2CH_2CH_3$), 3.80−3.77 (m, 1H, C*H*OH), 3.03−2.98 (t, J = 7.7 Hz, 1H, C*H*CO_2Et), 2.7−2.5 (b, 1H, O*H*), 2.07−2.00 (m, 5H, CH_3CH_2CH=CH, O_2CCH_3), 1.86−1.82 (m, 1H, AcOCHC*H*$_2$CH$_2$CHOH), 1.72−1.53 (m, 2H, AcO−CHC*H*$_2$CH$_2$CH−OH, AcO−CHCH$_2$C*H*$_2$CH−OH), 1.39−1.34 (m, 1H, AcO−CHCH$_2$C*H*$_2$CH−OH), 1.29−1.24 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.00−0.95 (t, J = 7.4 Hz, 3H, CH=CHCH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 136.7, 136.6, 123.5, 117.4, 117.2, 75.2, 74.7, 72.7, 72.5, 61.3, 56.3, 56.1, 30.6, 30.4, 30.3, 26.0, 21.6, 14.6, 13.8; IR (neat) 3487 (O−H), 2963, 1738 (C=O), 1241 cm^{-1}.

Ethyl (2*Z*)-6-(Acetyloxy)-2-[(1*E*)-but-1-enyl]octa-2,7-dienoate (20). Alcohol **18a** (385 mg, 1.29 mmol) was dissolved in toluene (10 mL), DCC (400 mg, 1.94 mmol), CuBr (19 mg, 0.13 mmol), and molecular sieves (about 200 mg) were added at once, and the solution was warmed to 80 °C and stirred at this temperature for 15 h. Work up: the solution was filtered on Celite then washed with brine. The organic layer was extracted with EtOAc, dried on $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/hexanes) to afford product **20** as a colorless oil (311 mg, 86%, *Z* isomer exclusively). $R_f = 0.30$ (10% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 6.03−5.97 (d, J = 16 Hz, 1H, C*H*CO_2Et), 5.82−5.69 (m, 3H, CH_2=C*H*CHOAc, CH_2C*H*=C*H*CH), 5.28−5.15 (m, 3H, C*H*$_2$=CHC*H*OAc), 4.31−4.24 (q, J = 7.4 Hz, 2H, $CO_2CH_2CH_3$), 2.31−2.23 (m, 2H, C*H*$_2$CH=CCO$_2$-Et), 2.16−2.06 (m, 2H, CH_3CH_2CH=CH), 2.06 (s, 3H, O_2CCH_3), 1.81−1.69 (m, 2H, AcO−CHC*H*$_2$), 1.36−1.31 (t, J = 7.4 Hz, 3H, $CO_2CH_2CH_3$), 1.03−0.98 (t, J = 7.3 Hz, 3H, CH=CHCH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 168.4, 136.4, 134.8, 134.6, 134.2, 127.0, 117.4, 74.6, 61.0, 34.0, 26.3, 25.8, 21.6, 14.7, 13.7; IR (neat) 2964, 2934, 1735 (C=O), 1731 (C=O), 1372, 1233 (C=C), 1154, 1021, 963 cm^{-1}; HRMS (ESI, Pos): calcd for $C_{16}H_{24}O_4$-Na $(M + Na)^+$ 303.1567, found 303.1558 (100%); also $C_{16}H_{25}O_4$ $(M + H)^+$ 281.1747, found 281.1734 (5%).

Ethyl (2*Z*)-6-(Acetyloxy)-2-[(1*E*)-but-1-enyl]octa-2,7-dienoate (20). Alcohol **18b** (193 mg, 0.65 mmol) was dissolved in THF (3.2 mL), PPh_3 (338 mg, 1.29 mmol) was added, and the solution was cooled to −40 °C. DEAD (225 mg, 1.29 mmol) was added dropwise to the solution, which was stirred for 3 h. Work up: $NaHCO_3$ (saturated aqueous solution) was added, and the organic layer was extracted with CH_2Cl_2 and then washed with brine. The organic layer was dried on Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/hexanes) to afford product **20** as a colorless oil (160 mg, 88%, 97:3 *Z*/*E*). $R_f = 0.30$ (10% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 6.03−5.97 (d, J = 16 Hz, 1H, C*H*CO_2Et), 5.82−5.69 (m, 3H, CH_2=C*H*CHOAc, CH_2C*H*=C*H*CH), 5.28−5.15 (m, 3H, C*H*$_2$=CHC*H*OAc), 4.31−4.24 (q, J = 7.4 Hz, 2H, $CO_2CH_2CH_3$), 2.31−2.23 (m, 2H, C*H*$_2$CH=CCO$_2$-Et), 2.16−2.06 (m, 2H, CH_3CH_2CH=CH), 2.06 (s, 3H, O_2CCH_3), 1.81−1.69 (m, 2H, AcO−CHC*H*$_2$), 1.36−1.31 (t, J = 7.4 Hz, 3H, $CO_2CH_2CH_3$), 1.03−0.98 (t, J = 7.3 Hz, 3H, CH=CHCH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 168.4, 136.4, 134.8, 134.6, 134.2, 127.0, 117.4, 74.6, 61.0, 34.0, 26.3, 25.8, 21.6, 14.7, 13.7; IR (neat) 2964, 2934, 1735 (C=O), 1731 (C=O), 1372, 1233 (C=C), 1154, 1021, 963 cm^{-1}; HRMS (ESI, Pos): calcd for $C_{16}H_{24}O_4$-Na $(M + Na)^+$ 303.1567, found 303.1558 (100%); also $C_{16}H_{25}O_4$ $(M + H)^+$ 281.1747, found 281.1734 (5%).

(3a,6-*trans*;3a,7a-*cis*)-4-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-6-ethyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-1-one (26). Triene **24** (5 mg, 0.016 mmol) was dissolved in C_6D_6 (1 mL) in a sealed tube, and then the solution was warmed to 155 °C for 3 h. Work up: the solvent was evaporated under reduced pressure, and then the residue was purified by flash chromatography on silica gel (5% EtOAc/hexanes) to afford product **26** as a colorless oil (1.2 mg, 24%). $R_f = 0.35$ (5% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 5.63−5.59 (b, 1H), 4.24−4.09 (m, 2H), 2.8−2.71 (m, 1H), 2.49−2.17 (m, 3H), 2.09−1.88 (m, 2H) 1.86−1.80 (dt, J = 12.4, 4.1 Hz, 1H), 1.66−1.49 (m, 1H), 1.44−1.23 (m, 2H), 1.10−0.99 (m, 1H), 0.92 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 221.5, 138.0, 127.1, 65.7, 47.0, 38.2, 37.1, 36.7, 28.7, 27.5, 27.2, 25.9 (3C), 18.4, 11.1, −5.3, −5.4; IR (neat) 2956, 2927, 2855 1743 (C=O), 1462, 1253, 1137, 1069, 836, 775 cm^{-1}; HRMS (ESI, Pos): calcd for $C_{18}H_{33}O_2Si_1$ $(M + H)^+$ 309.2244, found 309.2255 (100%); also $C_{18}H_{32}O_2Si_1Na$ $(M + Na)^+$ 331.2064, found 331.2075 (60%).

(3a,6-*trans*;3a,7a-*cis*)-4-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-6-ethyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-1-one (26). Optimized Procedure: Tandem Oxidation and Cyclization. Triene **23** (97 mg, 0.313 mmol) was dissolved in toluene (10 mL) in a Schlenk flask, PDC (176 mg, 0.469 mmol) was added, and the solution was heated to 155 °C for 4 h. Work up: the solvent was evaporated under reduced pressure, and then the residue was purified by flash chromatography on silica gel (5% EtOAc/hexanes) to afford product **26** as a colorless oil (59 mg, 61%). $R_f = 0.35$ (5% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 5.63−5.59 (bs, 1H), 4.24−4.09 (m, 2H), 2.80−2.71 (m, 1H), 2.49−2.17 (m, 3H), 2.09−1.88 (m, 2H) 1.86−1.80 (dt, J = 12.4, 4.1 Hz, 1H), 1.66−1.49 (m, 1H), 1.44−1.23 (m, 2H), 1.10−0.99 (m, 1H), 0.92 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 221.5, 138.0, 127.1, 65.7, 47.0, 38.2, 37.1, 36.7, 28.7, 27.5, 27.2, 25.9 (3C), 18.4, 11.1, −5.3, −5.4; IR (neat) 2956, 2927, 2855, 1743 (C=O), 1462, 1253, 1137, 1069, 836, 775 cm^{-1}; HRMS (ESI, Pos): calcd for $C_{18}H_{33}O_2Si_1$ $(M + H)^+$ 309.2244, found 309.2255 (100%); also $C_{18}H_{32}O_2Si_1Na$ $(M + Na)^+$ 331.2064, found 331.2075 (60%).

Ethyl (3a,6-*trans*;3a,7a-*cis*)-6-Ethyl-1-oxo-2,3,3a,6,7,7a-hexahydro-1*H*-indene-4-carboxylate (31). Triene **29** (30 mg, 0.127 mmol) was dissolved in benzene (1 mL) and DMSO (1 mL) in a sealed tube, and then the solution was heated to 180 °C for 5 min in a microwave apparatus. NMR monitoring of the reaction indicated that **30** was initially formed by complete epimerization to **31** upon purification. Work up: the solvent was evaporated under reduced pressure, and then the residue was purified by flash chromatography on silica gel (10% EtOAc/hexanes) to afford product **31** as a colorless oil (23.4 mg, 78%). $R_f = 0.25$ (10% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 6.93−6.91 (bs, 1H, H_5), 4.30−4.16 (m, 2H, $CO_2CH_2CH_3$), 3.13−3.05 (m, 1H, H_{3a}), 2.61−2.53 (m, 1H, H_3), 2.44−2.25 (m, 3H, H_2 (2H), H_{7a}), 2.23−2.14 (m, 1H, H_6), 1.89−1.84 (dt, J = 12.7, 5 Hz, 1H, H_7), 1.64−1.47 (m, 2H, CHC*H*$_2$-CH$_3$, H_3), 1.45−1.37 (m, 1H, CHC*H*$_2$CH$_3$), 1.34−1.30 (t, J = 7 Hz, 3H, $CO_2CH_2CH_3$), 1.12−1.02 (m, 1H, H_7), 1.00−0.96 (t, J = 7.5 Hz, 3H, CHCH$_2$C*H*$_3$). Product was identical in all respects to authentic material.[12m]

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Supporting Information Available: Experimental procedures for the preparation of all the compounds and characterization data for each reaction and detailed structural assignment. This material is available free of charge via the Internet at http://pubs.acs.org.

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