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Total synthesis of (+)-crocacin C

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ABSTRACT

Two approaches toward the total synthesis of cytotoxic polyketide natural product (+)-crocacin C (**1**) are described. The first approach, which was ultimately unsuccessful, was replaced altogether with a second that afforded target **1** in 10 linear steps from commercially available Evans' chiral propionimide (5% overall yield). No protecting groups were utilized in the total synthesis of **1**.

1. Introduction

Jansen and co-workers in 1944 reported the isolation and structure determination of a group of electron transport inhibitors from the myxobacterium *Chondromyces crocatus* possessing moderate inhibition of Gram-positive bacterial growth, in addition to antifungal and cytotoxic activity.[1] In 1999, the relative stereochemistry of crocacin C (**1**) and its congeners crocacins A (**2**), B (**3**) and D (**4**) was established (Fig. 1).[2]

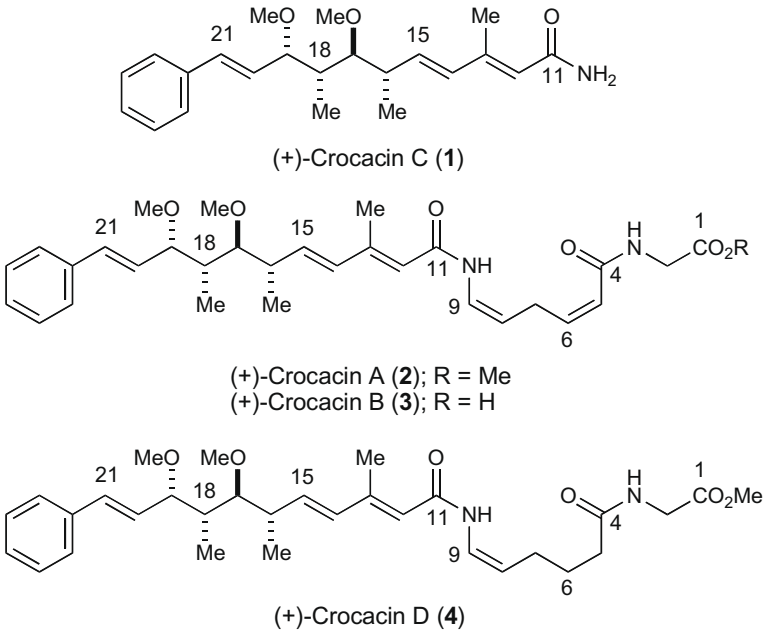

Figure 1. Structures of crocacins A–D (**1**–**4**).

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The crocacins have recently been identified as novel agricultural pesticide leads, which have led to a renewed interest in these natural products.[3] By inspection, crocacin C (**1**) is composed of a polyketide fragment possessing the challenging *anti–anti–syn* stereotetrad (C16–C19) in addition to a conjugated (*E*,*E*)-dienamide system (C11–C15). Crocacins A (**2**), B (**3**) and D (**4**) are further characterized by an acid-sensitive (*Z*)-*N*-acylenamine motif (C7–C11) tethered to a glycine residue. These structural features coupled with an interesting bioactivity profile have made these natural products attractive targets for synthesis.

The first enantioselective total synthesis of (+)-crocacin C (**1**) was reported in 2000 by Rizzacasa and co-workers,[4] which was quickly followed by both Chakraborty and Jayaprakash[5] and Dias and de Oliveira[6] in 2001. In 2008, we reported a concise synthesis of **1**,[7] which was shortly followed by Gillis and Burke.[8] In addition, there are five formal synthesis of **1** by Gurjar et al.,[9] Raghavan,[4] Furstner and co-workers[10] and Yadav et al. (two approaches).[11,12] Recently, all syntheses of the crocacins were reviewed.[13] Herein we report the first generation approach to **1**, which was not successful, in addition to a detailed description of the second successful approach to crocacin C (**1**).

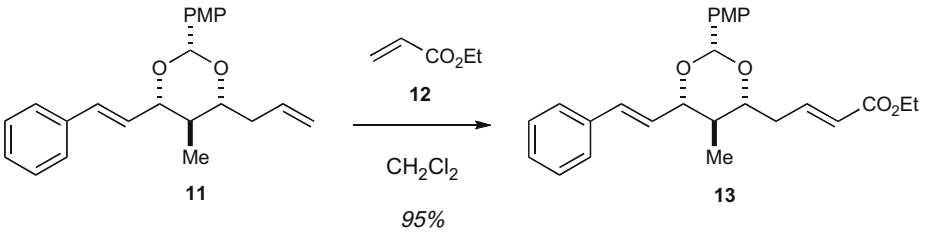
2. Results and discussion

Current natural product total synthesis places a high premium on synthetic efficiency, which is characterized by economy (e.g., atom,[14] step[15] and redox[16]) and selectivity (e.g., regio-, stereo- and chemo-),[17] among other metrics.[18] The realization of an *efficient* total synthesis therefore mandates the attendant synthetic strategy maximize both economy and selectivity.

2.1. First generation retrosynthesis

The retrosynthetic analysis of crocacin C (**1**) is shown in Scheme 1. To maximize convergence we opted for a chemoselective cross-metathesis reaction between known dienamide **5**[19] and diene **6**.

It is important to note that the presence of a cyclic protecting group (i.e., acetonide) would be essential to the success of the proposed chemoselective cross-metathesis step. In its absence, the 1,7-diene system would certainly cyclize to form a cyclohexene derivative and styrene via a ring-closing metathesis (RCM) pathway. As such, we hypothesized an acetonide (or related cyclic protecting group) would preclude RCM and enable a cross-metathesis pathway by eliminating conformational isomers capable of cyclizing. A survey of the literature revealed Crimmins had employed this tactic to effect a cross-metathesis reaction between diene **11** and ethyl acrylate (**12**), isolating dienoate **13** in near quantitative yield and validating our hypothesis (Eq. 1.[20]



(1)

Diene **6**, in turn, would be prepared via a reagent-controlled asymmetric crotylboration reaction utilizing Brown's reagent **9**[21] or Roush's reagent **10**[22] and an aldehyde derived from the Crimmins aldol reaction[23] of propionate synthon **8** and *trans*-cinnamaldehyde (**7**).

2.2. Attempted synthesis of crocacin C (1)

The forward synthesis began with a Crimmins aldol reaction of commercially available thiazolidinethione propionimide **8** and *trans*-cinnamaldehyde (**7**). Enolization of **8** with $TiCl_4$ and Hunig's base afforded *non-Evans syn* aldol **14** in 50% isolated yield (dr >20:1). Protection of the free alcohol as its TBS ether with TBSOTf and 2,6-lutidine proceeded in 75% yield. Reductive removal of the auxiliary furnished requisite aldehyde **15** in 82% yield (Scheme 2).

At this juncture, we began exploring options for executing the asymmetric crotoylboration reaction with **15**. Mindful of the fact the desired product was the *anti-Felkin* diastereomer, we subjected **15** to two well-known asymmetric crotylboration reagents known for their ability to override substrate-derived bias in double asymmetric reactions.[24] In the event, reaction with Brown's reagent **9** gave a 61% yield of two inseparable diastereomers **16** and **17** (3:1 ratio by ^{1}H NMR spectroscopy) (Scheme 3). Roush's reagent **10** performed similarly in the crotylboration reaction, albeit in 60% yield (dr = 4:1).

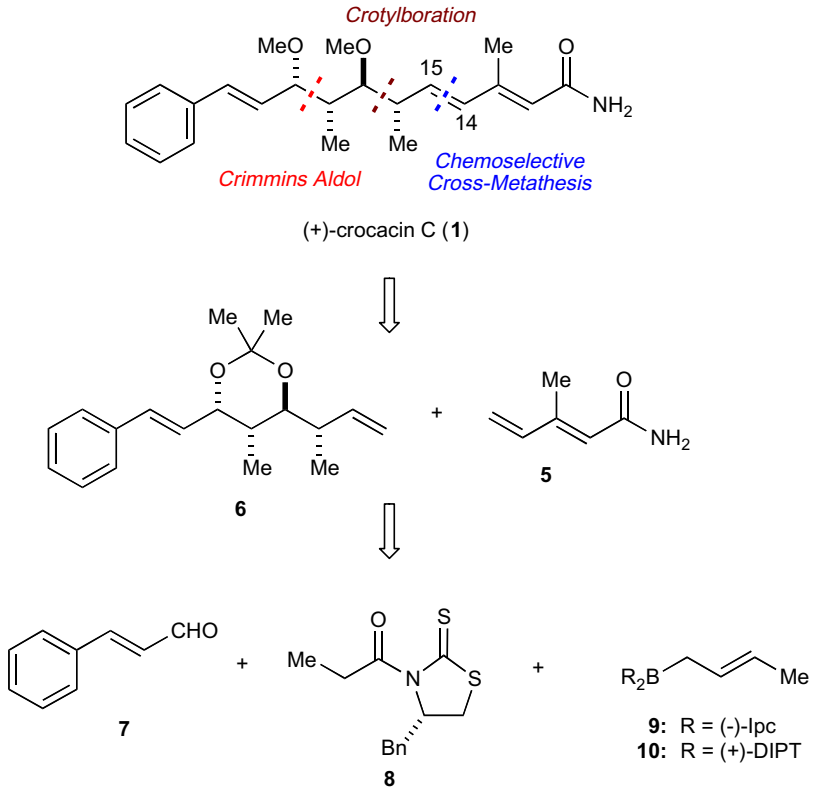
Structural assignment of diastereomers **16** and **17** was achieved by ^{13}C acetonide analysis.[25] Toward this end, the inseparable isomers were treated with TBAF to remove the silyl ether, affording intermediary diols in 88% yield, which were carried forward. Isopropylidenation with dimethoxypropane and PPTS afforded chromatographically separable acetonide diastereomers **18** and **19** in 76% and 19% yields, respectively. Analysis of the ^{13}C NMR spectra of **18** and **19** revealed that major isomer **18** was the 1,3-*syn* diastereomer with the ketal carbon resonating at 99.2 and methyls at 19.6 (*axial* Me) and 30.0 (*equatorial* Me), which are consistent with the chair-like conformation adopted by 1,3-*syn* acetonides. *anti*-Diastereomer **19**, on the other hand, possessed a ketal carbon at 100.6 ppm and acetonide methyls at 25.5 and 23.6, which are characteristic of the twist-boat conformation of 1,3-*anti* acetonides (Scheme 4).[25]

The results clearly indicated chiral reagents **9** and **10** were unable to overcome the stereochemical bias of aldehyde **15** to furnish the desired *anti-Felkin* diastereomer. In light of these unfortunate results, recourse was made to an entirely different synthetic plan.

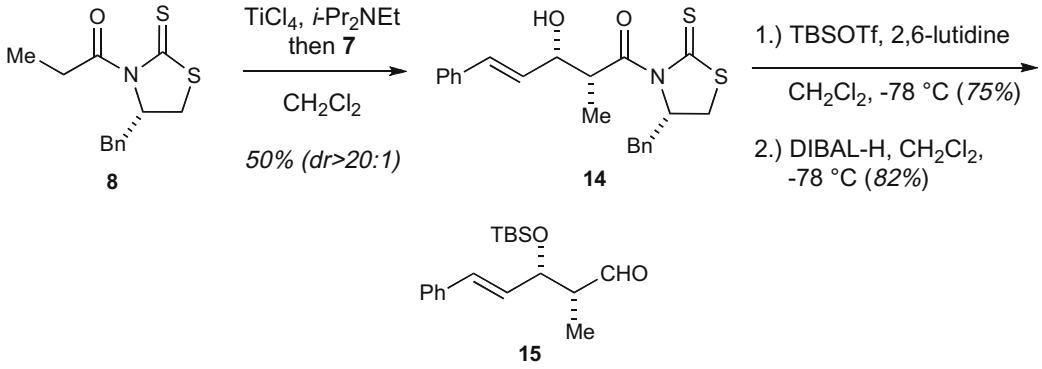
2.3. Second generation retrosynthesis

Our second approach to (+)-crocacin C (**1**) wanted to retain the high levels of convergence from the first; therefore, we maintained the disconnection at the C14–C15 olefin (Scheme 5). Chakraborty and Jayaprakash[5] employed the vinylogous Horner–Wadsworth–Emmons olefination with phosphonate **20**[26] to efficiently forge this bond, so our challenge lied in the concise preparation of aldehyde **21**. Access to homochiral **21** was thought to proceed from Evans' dipropionate synthon **22** and commercially available *trans*-cinnamaldehyde (**7**).[27]

The power of this method lies in its ability to (1) exert stereocontrol in the aldol reaction to access either *syn* aldol diastereo-



Scheme 1. First-generation retrosynthesis of **1**.



Scheme 2. Synthesis of aldehyde **15**.

mer; and (2) utilize the newly formed hydroxyl to direct the stereochemical course of the reduction by proper reagent selection, leading to either a 1,3-*syn* or 1,3-*anti* diol.[28]

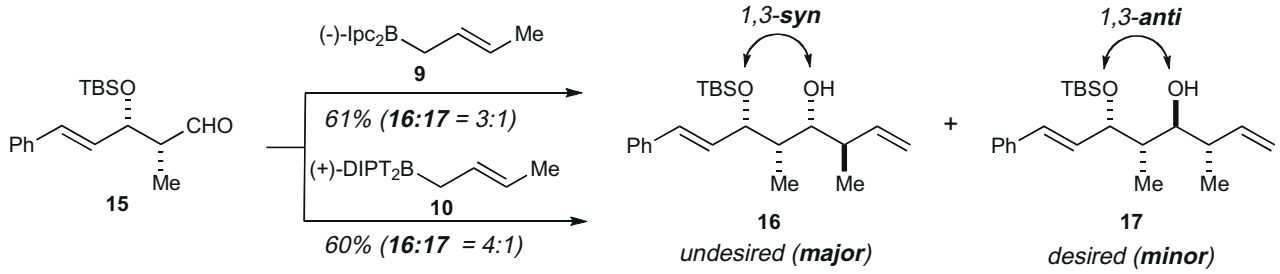
2.4. Total synthesis of crocacin C (1)

The synthesis commenced with the preparation of ketoimide **22** by an Evans aldol reaction[29] of oxazolidinone **23** and propionaldehyde (dr >20:1), followed by Parikh–Doering oxidation,[30] which proceeded in 71% overall yield. Enolization of **22** with $TiCl_4$ and *i*-Pr_2NEt and subsequent addition of *trans*-cinnamaldehyde (**7**) afforded desired aldol **25** (dr >20:1) in 75% yield (Scheme 6).

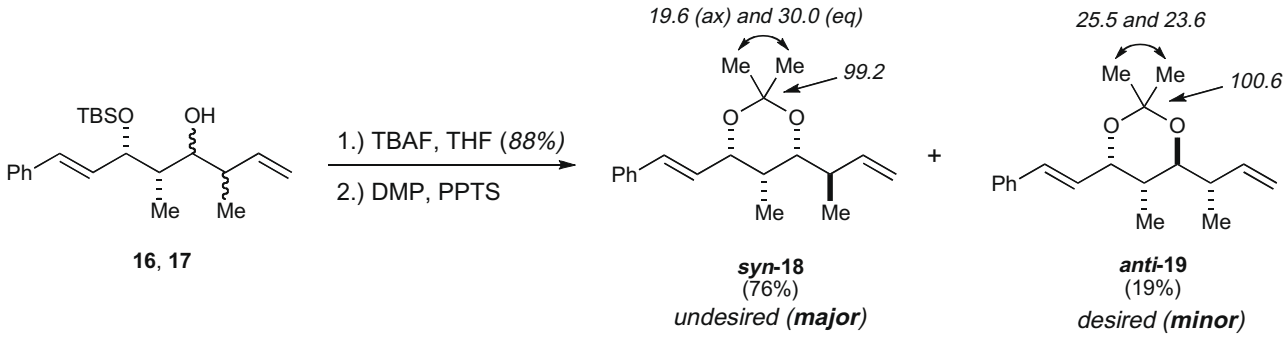
Stereoselective substrate-based reduction of the C17 ketone with $NMe_4BH(OAc)_3$ afforded desired 1,3-*anti* diol **26** in 88% yield as a single diastereomer.[28] To confirm the relative 1,3-*anti* stereochemistry, diol **26** was converted into acetonide **27** following standard conditions and subjected to ^{13}C NMR analysis. Resonances from the ^{13}C NMR of **27** (23.5 and 25.8 ppm for the methyls; 100.8 ppm for the ketal carbon) were consistent with those found in a twist-boat conformation, which is indicative of a 1,3-*anti* diol disposition (Scheme 7).[25]

With **26** in hand, we turned our attention to installing the methyl ethers in target **1**. Toward this end, we reductively removed the oxazolidinone auxiliary with $LiBH_4$ (66% yield) and differentiated the primary from the secondary alcohols with the bulky TBDPS group (90% yield). The latter tactic had been utilized by Rizzacasa and co-workes[4] and Dias and de Oliveira (Scheme 8).[6]

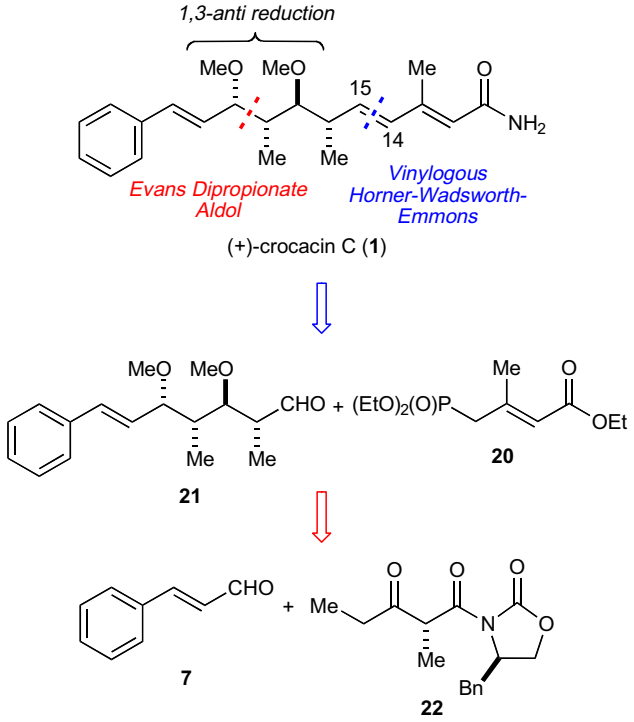
After some consideration, we opted for a shorter route to alcohol **31** that avoided protecting groups, such as silyl ethers, altogether. Methylation of diol **26** would directly accomplish our goal. Thus, various methylation protocols were screened to install both requisite methyl ethers.[30] Ultimately, the combination of



Scheme 3. Double asymmetric crotylboration reaction with aldehyde **15**.



Scheme 4. Structural assignment of diastereomers **18** and **19** via ^{13}C acetonide analysis.



Scheme 5. Second-generation retrosynthesis of **1**.

MeOTf and 2,6-di-*tert*-butyl-4-methylpyridine at 0 °C provided **32** in 49% yield with unproductive elimination accounting for the remaining mass balance (Scheme 9).

Reductive removal of the chiral auxiliary in **32** with $LiBH_4$ and subsequent oxidation of the intermediary alcohol with the Dess–Martin periodinane[31] provided aldehyde **21** in 59% yield over two steps. Endgame began with a stereoselective, vinylogous Horner–Wadsworth–Emmons reaction with phosphonate **20** to prepare conjugated *E*,*E*-dienoate **33** in 57% yield as one diastereomer. Saponification of the ester, activation of the intermediary acid with methyl chloroformate and treatment with aqueous ammonia delivered crocacin C (**1**) in 63% yield from **33**.[5]

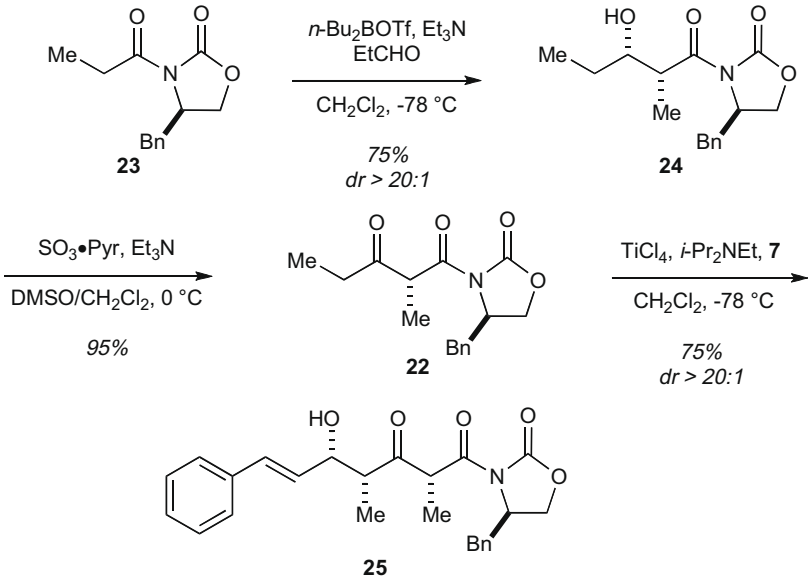
3. Conclusion

Two synthetic strategies for the concise asymmetric synthesis of (+)-crocacin C (**1**) have been presented. The first was unsuccessful due to undesired substrate control in the asymmetric crotylboration reaction, which resulted in an undesired diastereomer. The second-generation strategy, based on Evans' dipropionate synthon methodology, enabled a concise total synthesis of **1** in ten steps from commercially available Evans' propionimide **22** and cinnamaldehyde (**7**) in (5% overall yield) without recourse to protecting groups.

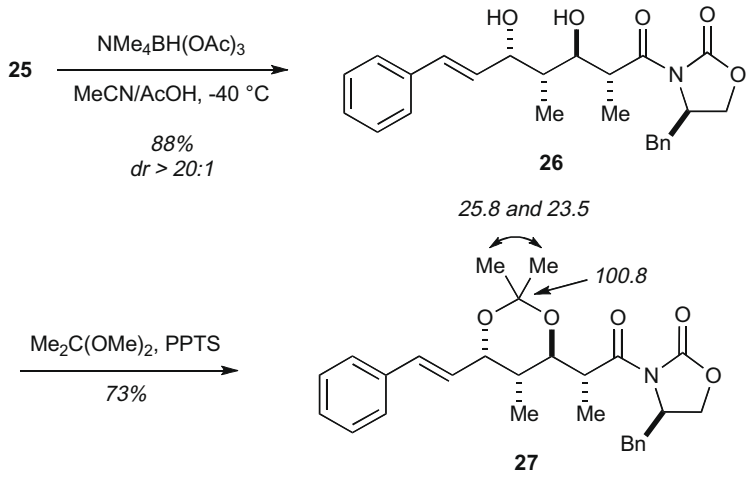
4. Experimental

4.1. General

All reactions containing water or air sensitive reagents were performed in oven-dried glassware under nitrogen or argon. Tetrahydrofuran and dichloromethane were passed through two columns of neutral alumina. Toluene was passed through one column of neutral alumina and one column of Q5 reactant. Diisopropylamine, chloroform and 2,6-lutidine were distilled from CaH_2 prior to use. Preparation of **9** and use in Brown crotylation reaction with **15** were performed according to Ref. 21 Reagent **10** was prepared according to Ref. 22. *trans*-Cinnamaldehyde (**7**) was distilled prior to use. All other reagents were purchased from commercial sources and used without further purification. All solvents for work-up procedures were used as received. Flash column chromatography was performed according to the procedure of Still (see Ref. 32) using ICN Silitech 32-63 D 60Å silica gel with the indicated solvents. Thin layer chromatography was performed on Analtech $60F_{254}$ silica gel plates. Detection was performed using UV light,



Scheme 6. Evans dipropionate aldol reaction with **7**.



Scheme 7. ^{13}C NMR acetonide analysis of diol **26**.

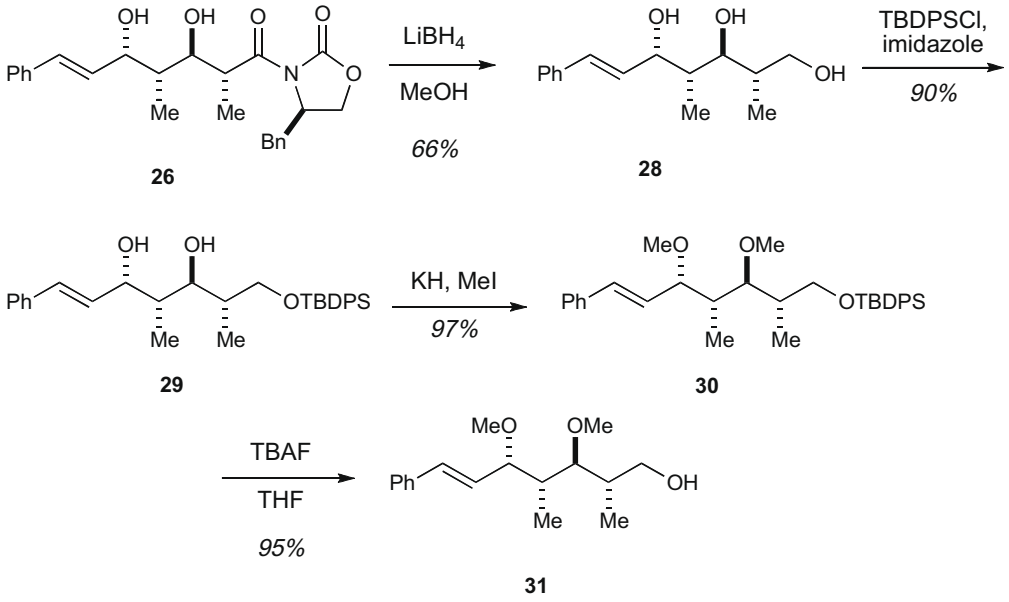
$KMnO_4$ stain, PMA stain and subsequent heating. ^{1}H and ^{13}C NMR spectra were recorded at the indicated field strength in $CDCl_3$ at rt. Chemical shifts are indicated in parts per million (ppm) downfield from tetramethylsilane (TMS, d = 0.00) and referenced to the $CDCl_3$. Splitting patterns are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), comp (overlapping signals of chemically nonequivalent protons), br (broad).

4.2. Aldol 14

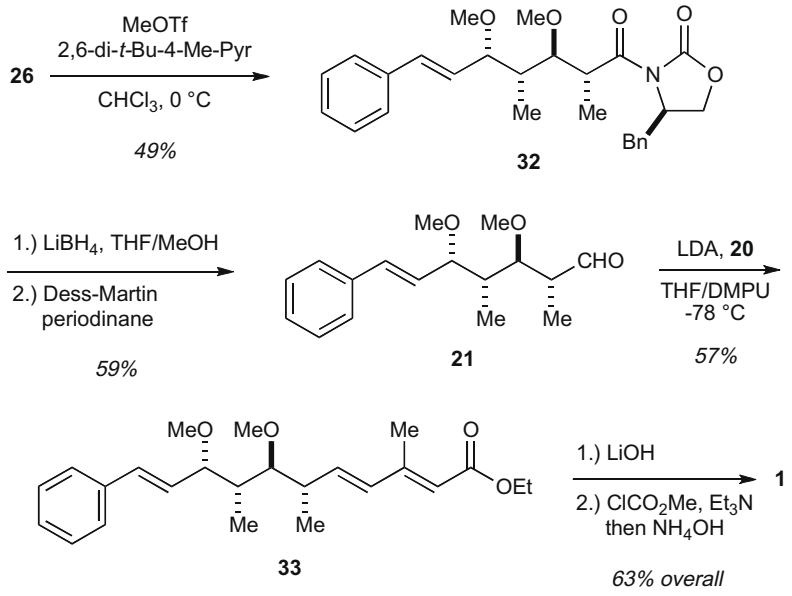
To a solution of propionimide **8** (507 mg, 1.91 mmol) in CH_2Cl_2 (12 mL) at 0 °C was added $TiCl_4$ (725 mg, 3.82 mmol) and the yellow slurry was stirred for 5 min. Freshly distilled i-Pr_2NEt (271 mg, 2.10 mmol) was slowly added at 0 °C to give a red solution, which was stirred for an additional 20 min at 0 °C. The reaction mixture was cooled to −78 °C, and freshly distilled *trans*-cinnamaldehyde **7** (278 mg, 2.10 mmol) was added dropwise. After stirring at −78 °C for 1 h, the mixture was warmed to 0 °C over 3 h. The reaction mixture was quenched by the addition of saturated NH_4Cl (12 mL) and stirred for 5 min at 0 °C. The reaction mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine solution (20 mL), dried (Na_2SO_4) and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (1:9) to afford 380 mg (50%) of **14** as a yellow oil. ^{1}H and ^{13}C NMR consistent with reference (see Ref. 33).

4.3. Aldol 14 *O*-TBS ether

To a solution of aldol **14** (225 mg, 0.57 mmol) in CH_2Cl_2 (6.0 mL) at −78 °C were added distilled 2,6-lutidine (152 mg, 1.42 mmol) and TBSOTf (164 mg, 0.62 mmol). After stirring the reaction mixture for 1 h at −78 °C, water (3.0 mL) was added. The reaction mixture was stirred an additional 5 min at rt and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (10 mL), brine solution (15 mL), dried (Na_2SO_4) and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (0.4:9.6) to afford 217 mg (75%) of product as a yellow oil. $[\alpha]_D^{20}$ +63.2 (c 0.5, CH_2Cl_2); IR (neat) 3154, 2930, 2857, 2360, 2254, 1793, 1694, 1471, 1376, 1259 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.23 (m, 10H), 6.56 (d, J = 16.0 Hz, 1H), 6.18 (dd,



Scheme 8. Synthesis of alcohol **31**.



Scheme 9. Completion of the synthesis.

J = 15.6, 7.6 Hz, 1H), 5.42–5.37 (m, 1H), 5.20–4.89 (m, 1H), 4.70 (t, J = 8.0 Hz, 1H), 3.33 (dd, J = 11.2, 7.2 Hz, 1H), 3.24 (dd, J = 13.2, 3.2 Hz, 1H), 3.05 (dd, J = 13.2, 10.8 Hz, 1H), 2.85 (d, J = 11.6 Hz, 1H), 1.12 (d, J = 6.8 Hz, 3H), 0.87 (s, 9H), 0.10 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0, 176.3, 136.8, 136.7, 132.1, 130.4, 129.4, 128.9, 128.6, 127.7, 127.2, 126.5, 75.9, 69.1, 45.3, 37.1, 31.3, 25.9, 25.7, 18.1, 14.4, −3.8, −4.6; HRMS (FAB) calcd for $C_{28}H_{37}NS_2SiO_2$+Na^+ = 534.1933, found 534.1945.

4.4. Aldehyde 15

To a solution of TBS-protected aldol **14** (205 mg, 0.40 mmol) in CH_2Cl_2 (4.0 mL) at −78 °C was added DIBAL-H (0.8 mL, 1.0 M in hexanes, 0.8 mmol) and stirred for 30 min. Additional DIBAL-H (0.4 mL, 1.0 M in hexanes, 0.4 mmol) was added at −78 °C and stirred for another 20 min, and the reaction was quenched with saturated aqueous Rochelle's salt solution (4.0 mL) and stirred for 45 min at rt. The reaction mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed brine solution (10 mL), dried (Na_2SO_4) and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (0.3:9.7) to afford 100 mg (82%) of aldehyde **15** as a yellow oil. ^{1}H and ^{13}C NMR consistent with reference (see Ref. 34).

4.5. Homoallylic alcohols 16 and 17

A solution of (*E*)-crotylboronate **10** (0.49 mL, 1.0 M solution in toluene, 0.49 mmol) in toluene (1.0 mL) was treated with powdered 4 Å molecular sieves and then cooled to −78 °C. A solution of freshly prepared aldehyde **15** (100 mg, 0.33 mmol) in toluene (1.0 mL) was slowly added over a period of 10 min. After stirring

the reaction mixture for 20 h, at −78 °C, it was treated with 2 N NaOH (3.0 mL) to hydrolyze DIPT. The biphasic mixture was warmed to 0 °C and stirred for 20 min at 0 °C, the reaction mixture was extracted with ether (2 × 20 mL). The combined organic layers were washed brine solution (10 mL), dried (K_2CO_3) and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (0.3:9.7) to afford 70 mg (60%) of alcohols **16** and **17** as a colorless foam. IR (neat) 3155, 2958, 2931, 2250, 1471, 1383, 1257 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.27–7.09 (m, 5H), 6.39 (d, J = 16.0 Hz, 1H), 6.10 (dd, J=16.0, 7.2 Hz, 1H), 5.69–5.60 (m, 1H), 5.0–4.91 (m, 2H), 4.24 (t, J = 6.4 Hz, 1H), 3.38 (d, J = 7.6, 1H), 2.20–2.14 (m, 1H), 2.10 (bs, 1H), 0.88 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 5.2 Hz, 3H), 0.79 (s, 9H), −0.03 (s, 3H), −0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 139.4, 136.9, 136.8, 131.8, 131.4, 130.4, 128.7, 128.6, 127.6, 127.5, 126.5, 126.4, 115.5, 114.9, 78.8, 77.9, 75.7, 42.1, 41.6, 40.6, 25.6, 25.8, 18.1, 18.0, 16.6, 12.7, 7.7, −3.0, −3.6, −4.0, −4.4; HRMS (FAB) calcd for $C_{22}H_{36}SiO_2$–H = 359.2406, found 359.2393.

4.6. Acetonides 18 and 19

TBAF·$3H_2O$ (92 mg, 0.29 mmol) was added to a solution of alcohols **16** and **17** (70 mg, 0.19 mmol) in THF (2.0 mL) at 0 °C. The reaction was warmed to rt and stirred for 12 h, diluted with water (4 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed brine solution (10 mL), dried (Na_2SO_4) and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (2:8) to afford 42 mg (88%) of intermediary diols. The crude diols were dissolved in 2,2-dimethoxypropane (15 mL) and a catalytic amount of PPTS was added. The reaction mixture was stirred for 3 h then filtered through a plug of cotton. The solvent was concentrated under reduced pressure, and the residue was purified by preparative TLC eluting with EtOAc/hexanes (1:9) to afford 32 mg (76%) **18** as a colorless foam and 8 mg (19%) of minor acetonide **19** as a colorless foam.

4.6.1. Major acetonide 18

$[\alpha]_D^{20}$ +29.5 (c 0.5, CH_2Cl_2); IR (neat) 3154, 3082, 2977, 2938, 2360, 2253, 1605, 1452, 1382, 1201 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41–7.39 (m, 2H), 7.33–7.30 (m, 2H), 7.25–7.21 (m, 1H), 6.61 (dd, J = 16.0, 1.5 Hz, 1H), 6.20 (dd, J=16.0, 5.5 Hz, 1H), 5.98–5.91 (m, 1H), 5.09–5.01 (m, 2H), 4.63–4.61 (m, 1H), 3.64 (dd, J = 10.0, 2.0 Hz, 1H), 2.34–2.29 (m, 1H), 1.68–1.64 (m, 1H), 1.48 (s, 3H), 1.47 (s, 3H), 0.95 (d, J = 1.5 Hz, 3H), 0.94 (d, J = 1.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 137.0, 130.2, 129.2, 128.5, 127.4, 126.4, 113.4, 99.2, 74.3, 38.2, 34.6, 30.0, 19.6, 14.5, 5.3; HRMS (CI) calcd for $C_{19}H_{26}O_2 + H^+$ = 287.2011, found 287.2000.

4.6.2. Minor acetonide 19

$[\alpha]_D^{20}$ +50.0 (c 0.2, CH_2Cl_2); IR (neat) 3155, 2986, 2930, 2200, 1458, 1380, 1224, 1172, 1096 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 7.0 Hz, 2H), 7.30 (t, J = 7.5 Hz, 2H), 7.22 (t, J = 7.3 Hz, 1H), 6.57 (d, J = 15.5 Hz, 1H), 6.18 (dd, J = 15.8, 6.3 Hz, 1H), 5.94–5.87 (m, 1H), 5.07–5.02 (m, 2H), 4.50 (dt, J = 6.5, 1.5 Hz, 1H), 3.29 (dd, J = 8.0, 3.5 Hz, 1H), 2.36–2.29 (m, 1H), 2.00–1.93 (m, 1H), 1.40 (s, 3H), 1.39 (s, 3H), 1.10 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 137.0, 130.4, 128.4, 127.6, 127.3, 126.3, 115.0, 100.6, 77.8, 70.7, 41.2, 37.9, 25.5, 23.6, 17.1, 13.1; HRMS (CI) calcd for $C_{19}H_{26}O_2 + H^+$ = 287.2011, found 287.2021.

4.7. Aldol 25

To a solution of dipropionimide **22** (1.38 g, 4.77 mmol) in CH_2Cl_2 (19 mL) at −10 °C was added $TiCl_4$ (1.00 g, 5.25 mmol) then freshly distilled i-Pr_2NEt (0.68 g, 5.25 mmol). After stirring for 1 h, the reaction mixture was cooled to −78 °C and freshly distilled aldehyde **7** (0.69 g, 5.25 mmol) was added drop wise. The reaction mixture was stirred at −78 °C for 30 min then warmed to −40 °C over a period of 1 h. The reaction mixture was warmed to 0 °C and quenched by the addition of phosphate buffer (7.6 mL, pH 7) and stirred an additional 5 min. The reaction mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (15 mL), brine solution (15 mL), dried (Na_2SO_4) and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (1:5) to afford 1.50 g (75%) of **25** as a yellow oil. $[\alpha]_D^{20}$ −165.0 (c 1.0, CH_2Cl_2); IR (neat) 3524, 2252, 1774, 1713, 1391, 1358, 1215, 909, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.13 (m, 10H), 6.63 (dd, J = 16.0, 1.2 Hz, 1H), 6.13 (dd, J = 16.0, 5.6 Hz, 1H), 4.84 (q, J = 7.2 Hz, 1H), 4.78 (bs, 1H), 4.73–4.68 (m, 1H), 4.22–4.12 (m, 2H), 3.24 (dd, J = 13.6, 3.2 Hz, 1H), 3.02–3.00 (m, 2H), 2.74 (dd, J = 13.6, 9.6 Hz, 1H), 1.45 (d, J = 7.6 Hz, 3H), 1.13 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 170.0, 153.9, 136.7, 134.9, 130.9, 129.3, 128.9, 128.5, 127.5, 127.4, 126.5, 71.9, 66.6, 55.3, 52.3, 49.7, 37.8, 13.0, 10.5; HRMS (FAB) calcd for $C_{25}H_{27}NO_5 + Na^+$ 444.1786, found 444.1778.

4.8. Diol 26

To a stirred solution of $Me_4NBH(OAc)_3$ (5.63 g, 21.40 mmol) in MeCN (10 mL) was added glacial AcOH (10 mL). After stirring for 30 min, the reaction mixture was cooled to −40 °C and a solution of **25** (1.50 g, 3.57 mmol) in MeCN (10 mL) was added via cannula. After stirring for 6 h at this same temperature, the reaction mixture was transferred to a refrigerator and allowed to age for 16 h at −20 °C. Aqueous sodium tartrate (0.5 M, 25 mL) was added. The reaction mixture was warmed to rt over 1 h then diluted with additional sodium tartrate (0.5 M, 25 mL) and CH_2Cl_2 (50 mL). The organic layer was separated, and the aqueous layer was back-extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (30 mL), brine solution (30 mL), dried (Na_2SO_4) and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (2:3) to afford 1.32 g (88%) of **26** as a yellow oil. $[\alpha]_D^{20}$ −80.8 (c 1.0, CH_2Cl_2); IR (neat) 3460, 3028, 2976, 2360, 2341, 2252, 1779, 1698, 1455, 1385, 1209, 908, 732; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.20 (m, 10H), 6.64 (dd, J = 16.0, 1.2 Hz, 1H), 6.26 (dd, J = 16.0, 5.6 Hz, 1H), 4.77–4.75 (m, 2H), 4.26–4.16 (m, 3H), 3.98 (d, J = 8.4 Hz, 1H), 3.73 (q, J = 6.9 Hz, 1H), 3.31 (bs, 1H), 3.25 (dd, J = 13.2, 3.4 Hz, 1H), 2.81 (dd, J = 13.2, 9.6 Hz, 1H), 1.97–1.90 (m, 1H), 1.31 (d, J = 7.2 Hz, 3H), 1.04 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 153.3, 136.8, 135.0, 130.5, 130.3, 129.4, 129.0, 128.5, 127.5, 127.4, 126.4, 78.4, 72.8, 66.2, 55.5, 40.3, 39.8, 37.9,15.0, 11.6; HRMS (FAB) calcd for $C_{25}H_{29}NO_5 + Na^+$ 446.1943, found 446.1945.

4.9. Acetonide 27

To a stirred solution of diol **26** (80.0 mg, 0.19 mmol) in dimethoxypropane (19 mL) was added a catalytic amount of PPTS. The reaction mixture was stirred for 3 h. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (1:4) to afford 65.0 mg (73%) of **27** as a yellow oil. $[\alpha]_D^{20}$ −50.2 (c 1.0, CH_2Cl_2); IR (neat) 3154, 3029, 2986, 2253, 1780, 1698, 1455, 1383, 1263, 1222, 1107, 1022, 969, 909, 650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.14 (m, 10H), 6.54 (dd, J = 15.8, 0.8 Hz, 1H), 6.09 (dd, J = 15.8, 6.0 Hz, 1H), 4.66–4.54 (m, 1H), 4.57–4.54 (m, 1H), 4.12–4.11 (m, 2H), 4.04–3.96 (m, 1H), 3.67 (dd, J = 9.2, 6.8 Hz, 1H),

3.20 (dd, J = 13.2, 3.2 Hz, 1H), 2.74 (dd, J = 13.2, 9.6 Hz, 1H), 1.93–1.85 (m, 1H), 1.35 (s, 3H), 1.26 (s, 3H), 1.18 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 153.2, 137.0, 135.3, 130.5, 129.5, 129.0,128.5, 127.4, 127.3, 127.2, 126.4, 100.8, 76.2, 70.0, 66.0, 55.4, 42.9, 38.9, 38.0, 25.8, 23.5, 14.0, 12.8; HRMS (FAB) calcd for $C_{28}H_{33}NO_5 + Na^+$ 486.2256, found 486.2254.

4.10. Imide 32

To a stirred solution of the diol **26** (70.0 mg, 0.17 mmol) in $CHCl_3$ (1.5 mL) at 0 °C, was added 2,6-di-*tert*-butyl-4-methylpyridine (1.19 g, 5.81 mmol) followed by the addition of MeOTf (0.82 g, 4.98 mmol). The reaction mixture was stirred for 28 h at 0 °C, quenched with MeOH (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL), washed with brine solution (5 mL), dried (Na_2SO_4) and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (1:4) to afford 37.0 mg (49%) of **32** as a yellow oil. $[\alpha]_D^{20}$ −74.5 (*c* 1.0, CH_2Cl_2); IR (neat) 3154, 2983, 2253, 1780, 1698, 1470, 1383, 1264, 1094, 907, 733, 650 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.14 (m, 10H), 6.50 (d, J = 21.2, Hz, 1H), 6.08 (dd, J = 21.2, 9.6 Hz, 1H), 4.57–4.56 (m, 1H), 4.13–4.08 (m, 3H), 3.94 (dd, J = 9.6, 4.8 Hz, 1H), 3.41–3.36 (m, 4H), 3.25–3.20 (m, 4H), 2.69 (dd, J = 17.6, 13.0 Hz, 1H), 1.90–1.88 (m, 1H), 1.20 (d, J = 6.4 Hz, 3H), 0.90 (d, J = 9.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 153.1, 136.8, 135.4, 132.3, 129.5, 129.2, 128.9, 128.6, 127.6, 127.3, 126.5, 84.9, 81.8, 66.0, 60.1, 56.5, 55.7, 41.6, 40.7, 37.9, 14.1, 11.0; HRMS (FAB) calcd for $C_{27}H_{33}NO_5$+-Na^+ = 474.2256, found 474.2228.

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