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Total Synthesis

A Chemoenzymatic and Fully Stereocontrolled Total Synthesis of the Antibacterial Natural Product (−)-Platencin

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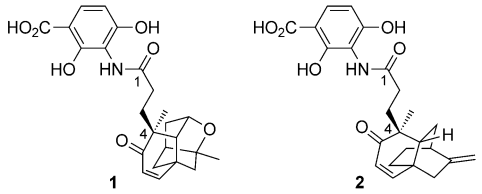
Abstract: The natural product (−)-platencin is a potent antibacterial agent that exerts its effects through a novel mode of action. As such, it is an important lead in the development of next-generation antibacterials that are urgently needed because of the rapidly developing resistance to current therapies. The work reported here concerns the development of a convergent and chemoenzymatic total synthesis of (−)-platencin by methods that should provide access to a range of biologically relevant analogues. The key step involves a thermally promoted and facially selective intramolecular Diels–Alder (IMDA) cycloaddition reaction to give an adduct that embodies the tricarbocyclic core of (−)-platencin. This adduct was elaborated over thirteen steps to the natural product. The substrate for the IMDA reaction was prepared by Stille cross-coupling of a *Z*-configured alkenylstannane with an iodinated diene obtained in an enantiomerically pure form through the whole-cell biotransformation of iodobenzene.

Introduction

The increasingly broad resistance of bacterial pathogens to current frontline antibiotics represents a major public health issue.[1] Indeed, the World Health Organization (WHO) has identified this situation as one of the three most significant threats to human health at the present time.[1b] Accordingly, various efforts are being made to identify next-generation antibacterial agents that possess novel structures and modes of action. In this regard, and between 2006 and 2007, the Singh group at Merck reported the isolation of the structurally related and unusual natural products platensimycin (**1**)[2] and platencin (**2**)[3] from various strains of *Streptomyces platensis* and demonstrated that both compounds are potent inhibitors of certain enzymes involved in bacterial fatty acid biosynthesis.[4] Specifically, platensimycin (**1**) is a selective inhibitor of fatty acid acyl carrier protein synthase II (FabF), whereas congener **2** inhibits both this enzyme and the related one known as FabH. As a result, both compounds show potent in vitro activities against, inter alia, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecalis* (VREF), and extensively drug-resistant *Mycobacterium tuberculosis*.[5] Interestingly, they are also thought to represent promising leads for the development of antidiabetic therapies.[6]



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A wide range of studies has been reported in efforts to address the less-than-optimal pharmacokinetic properties of platensimycin (**1**) and platencin (**2**).[2,3,7,8] These have included the discovery of naturally occurring congeners[4,9] and pathway engineering/combinatorial biosynthesis approaches[10] for the generation of analogues. Of course, chemical synthesis has also played a significant role in the development of a structure–activity relationship (SAR) profile for these compounds and led to the identification of a significant number of active analogues including some rather accessible ones that possess comparable antibacterial properties.[7,11] Much of the recent work on analogues has been underpinned by the various total and formal total syntheses of compounds **1** and **2** that began emerging very soon after their structures were first established.[4,12] Nicolaou and co-workers reported[13] the original total synthesis of platencin (**2**) in 2008, and this involved the assembly of the cyclohexannulated bicyclo[2.2.2]octane framework **3** as a key substructure. Subsequently, both our group[14] and that of Nicolaou[15] used an intramolecular Diels–Alder (IMDA) approach to establish this key substructure in an enantioselective manner. Others reported related routes to com-

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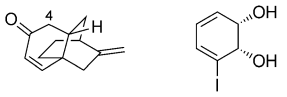

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pound **3** shortly thereafter.[12a,i] A pivotal aspect of the work we reported was the use of the enantiomerically pure *cis*-1,2-dihydrocatechol **4** (which is obtained by the whole-cell biotransformation of iodobenzene using a genetically engineered form of *E. coli*) as the starting material.[16]

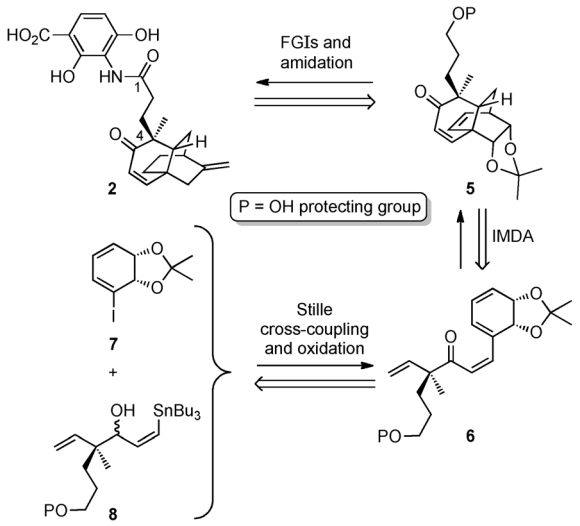
Enone **3** has proven to be a popular synthetic target because it can be converted, by using stereocontrolled *C*-alkylation protocols,[13,17] into platencin (**2**). In our hands, however, this end-game proved difficult to implement with the rather small quantities of substrate **3** available to us as a result of employing the synthetic sequence we established.[14] As such, we sought to modify our original route to generate, in as highly controlled a manner as possible, substrates for the pivotal IMDA reaction that afford, after the cycloaddition event, derivatives of enone **3** that already incorporate a suitably constituted quaternary carbon center adjacent to the carbonyl residue and could, therefore, be more readily elaborated to (−)-platencin. Herein, we report the successful realization of this approach.

Results and Discussion

Retrosynthetic Analysis

The retrosynthetic analysis employed in the present study is shown in Scheme 1 and was informed by our earlier work that led to the tricyclic framework **3** of platencin and which was obtained, as suggested above, through the engagement of a derivative of the enantiomerically pure starting material **4** in an IMDA reaction.

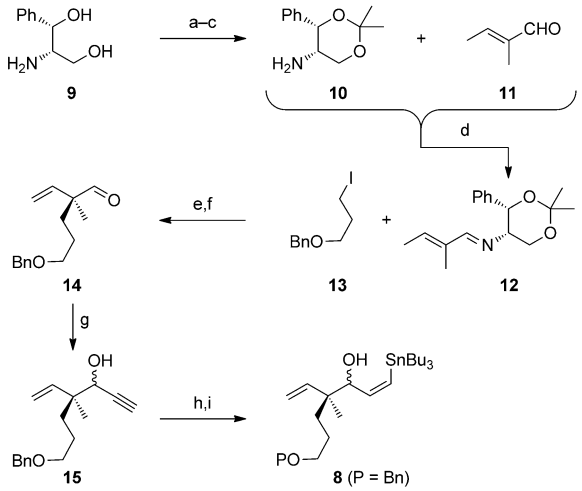
A key objective of the present study was to establish, at a relatively early stage in the synthesis, means by which the propionic acid side chain (or some equivalent thereof) and the methyl group at C4 within the target **2** could be introduced with full stereochemical control. As such, we envisaged that a compound of the general form **5** (and wherein P represents an alcohol protecting group) would be an important and relatively late-stage intermediate and might be accessible in a fully stereocontrolled manner through engagement of the tetraene **6** in a thermally promoted IMDA reaction. It was thought that compound **6** itself could be obtained through Stille cross-coupling of the alkenylstannane **8** with acetonide **7** (a known derivative of diol **4**) followed by oxidation of the alcohol-containing compound formed in this way. Compound **8** embodies two stereochemical elements, namely, a quaternary carbon center (destined to become C4 of platencin) and a *Z*-configured alkene (which corresponds to the endocyclic C–C double bond within target **2**), and thus represents a challenging sub-target. By seeking to implement the synthetic plan defined above, the required stereochemistry at C4 in platencin would be established prior to the assembly of its carbocyclic core and not afterwards. This new approach is potentially advantageous because the (otherwise necessary) twofold *C*-alkylation of compound **3** is not a completely stereoselective process.



Scheme 1. Retrosynthetic analysis of (−)-platencin employed in the present study.

Synthesis of Alkenylstannane 8

The reaction sequence used to prepare sub-target **8** (P = Bn) is shown in Scheme 2 and exploited, in its early stages, chiral auxiliary-based chemistry employed by Yamashita and coworkers[18] in a related context. Thus, the commercially available amino-diol **9** was converted into the corresponding 1,3-dioxane **10** under the conditions defined by Nordin and Thomas[19] (89% yield over three steps). Condensation of the latter compound with aldehyde **11** in the presence of trifluoroacetic anhydride gave the imine **12** that was deprotonated



Scheme 2. Synthesis of alkenylstannane **8** (P = Bn): a) HCO_2H, MeOH, 18 °C, 3.5 h; b) 2-methoxypropene, *p*-TsOH·H_2O, 18 °C, 2 h; c) N_2H_4, 120 °C, 2 h, 89% over three steps; d) $(CF_3CO)_2O$, C_6H_6, 80 °C, 5 h; e) Lithium diisopropylamide (LDA), THF, −78 to 18 °C, 16 h; f) 2 M aq. HCl, THF, 18 °C, 5 h; g) HCCMgBr, THF, −10 °C, 0. 5 h, 44% over three steps; h) $Bu_2Sn(OTf)H$, hexane, 18 °C, 16 h; and i) *n*BuLi, Et_2O, 0 °C, 0.25 h, 54% over two steps.

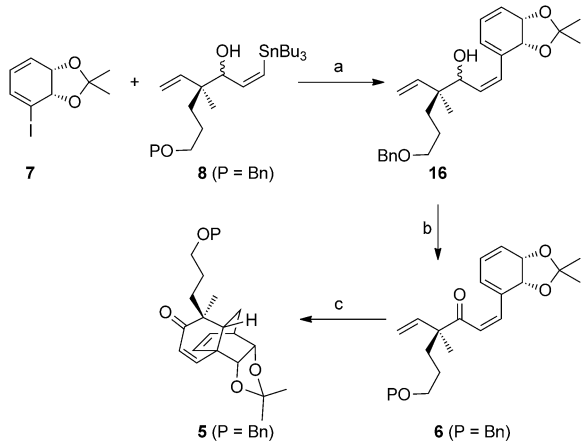
with lithium diisopropylamide and the resulting anion alkylated with the benzyl ether **13**[20] of 3-iodopropan-1-ol. After acidic workup, the desired α-alkylation product, aldehyde **14** (52%), was obtained along with the chromatographically separable (*E*)-7-(benzyloxy)-2-methylhept-2-enal (9%), the product of γ-alkylation. The selective formation of compound **14** by these means is presumed to result from preferential metalation at the α-position (owing to the proximity of coordinating heteroatoms) within the anion derived from precursor **12**.

To determine the enantiomeric excess (*ee*) of compound **14** obtained by the pathway described immediately above, this aldehyde was treated with (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) hydrazine and the ratio of the diastereoisomeric hydrazones formed in this manner was then determined by HPLC analysis. For the purposes of obtaining an appropriate reference material, the racemic modification of compound **14** was synthesized by related means (see the Experimental Section for details) and this too was converted into the corresponding mixture of diastereoisomeric SAMP hydrazones. By such means, and using a Chiracel OD-H column for the separation of the diastereoisomeric hydrazones, the *ee* of compound **14** was determined to be approximately 92%. The illustrated configuration at C2 was initially assigned on the basis of Yamashita's work[18] but ultimately confirmed (see below) through a single-crystal X-ray analysis of a derivative that incorporates a residue of known absolute stereochemistry.

The completion of the synthesis of target stannane **8** (P = Bn; Scheme 2) involved treating compound **14** with ethynylmagnesium bromide in THF and thus generating the anticipated propargyl alcohol **15** (85 or 44% from **12**). This was obtained as an approximately 1:1 mixture of diastereoisomers and no attempts were made to separate these. Sequential treatment of compound **15** with the readily prepared Lewis acidic hydrostannane $Bu_2Sn(OTf)H$[21] then *n*BuLi gave, in a seemingly completely regio- and stereo-controlled process, the required *Z*-configured alkene **8** (P = Bn) (54%) and, once again, as an approximately 1:1 mixture of diastereoisomers. All the data acquired on this material were in accord with the assigned structure, although no attempt was made to record its mass spectrum because of concerns about contamination of the spectrometer by tin residues.

Synthesis of Tetraene 6 (P = Bn) and its Engagement in the IMDA Reaction: Formation of Compound 5 (P = Bn)

With compound **8** (P = Bn) in hand, an examination of its capacity to engage in a Stille cross-coupling reaction with the previously reported[14] acetonide **7** could be undertaken. Given the expected fragile nature of the hoped-for product, this process was carried out under the mildest possible conditions. In the event (Scheme 3), treatment of an approximately 1:1 mixture of these substrates with $[Pd(PPh_3)_4]$ in the presence of CuI and CsF[22] at 18 °C resulted in the generation of the target tetraene **16** as an approximately 1:1 mixture of diastereoisomers in 80% combined yield. These diastereoisomers could be separated chromatographically, and each was subjected to the usual range of spectroscopic analyses. Interestingly, the chromatographically less mobile isomer exhibited a positive specific rotation, whereas the other displayed a negative one.



Scheme 3. Synthesis of the IMDA adduct **5** (P = Bn): a) $[Pd(PPh_3)_4]$, CuI, CsF, dimethylformamide (DMF), 18 °C, 16 h, 80%; b) DMP, pyridine, CH_2Cl_2, 0 to 18 °C, 1.5 h, 53%; and c) toluene, 112 °C, 16 h, 70%.

Neither of the diastereoisomeric forms of compound **16** participated in a thermally promoted IMDA reaction upon heating in toluene. Furthermore, attempts to promote such a process through the addition of a range of Lewis acids simply led to rapid decomposition of the substrates. As a result, and given the observation[23] that in certain related type 1 IMDA reactions the nature of the substituents associated with the side chain can have a dramatic impact on the efficacy of the process, compound **16** was oxidized to the corresponding ketone **6** (P = Bn) (53%) using the Dess–Martin periodinane (DMP) in the presence of pyridine (to prevent acid-catalyzed aromatization of the *cis*-1,2-dihydrocatechol residue). The positive-ion electrospray mass spectrum of this oxidation product displayed the expected $[M+Na]^+$ ion at *m/z* 431 (base peak), whereas the corresponding infrared spectrum displayed a strong carbonyl-stretching band at 1683 cm^{-1}. Similarly, the ^{13}C NMR spectrum revealed a carbonyl carbon resonance at $\delta = 204.4$ ppm as well as an additional 23 higher-field resonances, as would be expected for the assigned structure. The corresponding ^1H NMR spectrum was also in complete accord with the proposed structure. Gratifyingly, when a 2.9 mM solution of compound **6** (P = Bn) in toluene was heated at reflux for 16 h, the desired cycloaddition reaction took place and such that the anticipated IMDA adduct **5** (P = Bn) could be obtained as a white crystalline solid in 70% yield after chromatographic purification. There was no evidence for the accompanying formation of a product or products that arise from an electrocyclization reaction involving the doubly unsaturated ketone moiety embedded within the substrate. The ^{13}C NMR spectrum of the product provided the most convincing early evidence for the assigned structure. In particular, only nine signals due to sp^2-hybridized carbon atoms were apparent, whereas fifteen were observed for their sp^3-hybridized counterparts. However, definitive assignment of structure **5** (P = Bn) to this adduct followed from a single-crystal X-ray analysis. The derived ORTEP diagram is shown in Figure 1, while certain crystal data are provided in

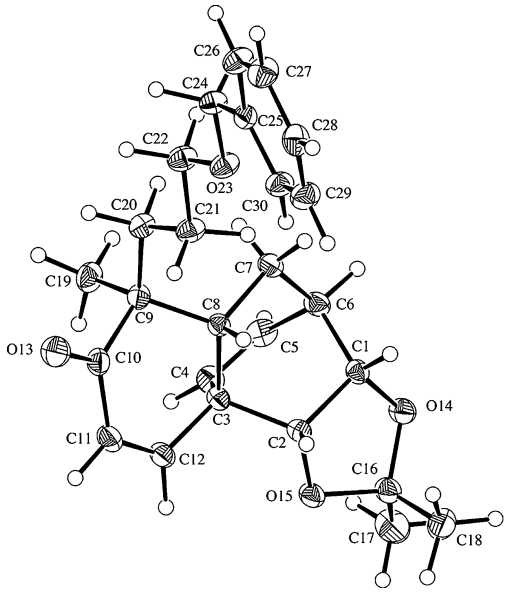


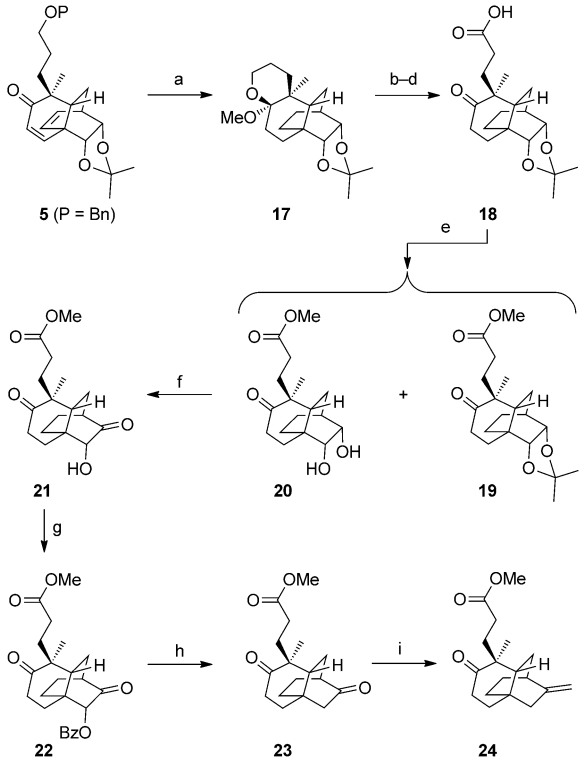
Figure 1. ORTEP diagram derived from the single-crystal X-ray analysis of the IMDA adduct **5** (P = Bn). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

the Experimental Section. Significantly, this analysis unequivocally established the absolute stereochemistry associated with C4 (platencin numbering) of compound **5** (P = Bn) and that was constructed using the chiral auxiliary-mediated and diastereoselective alkylation reaction **12+13→14** shown in Scheme 2. Clearly this configuration at C4 is required for elaboration of the IMDA adduct to (−)-platencin. The following sections delineate how this was achieved.

Synthesis of the Homochiral Form, 24, of Yoshimitsu's Intermediate from IMDA Adduct 5 (P = Bn)

The reaction sequence used for the purposes of elaborating compound **5** (P = Bn) to an established (and advanced) precursor to (−)-platencin is shown in Scheme 4. To such ends, and with a view to cleaving the benzyl ether residue within this substrate as well as reducing the associated nonconjugated carbon–carbon double bond, a solution of compound **5** (P = Bn) in methanol was exposed to dihydrogen in the presence of 5% Pd on C. Although the desired transformations were achieved under these conditions, they were accompanied by the unwanted reduction of the C=C moiety associated with the enone residue. In addition, the liberated primary alcohol cyclized onto the C3 carbonyl moiety and (presumably after methanolysis of initially produced lactol) the crystalline ketal **17** was obtained in 92% yield. The structure of this compound followed from a single-crystal X-ray analysis (see Figure 2 and the Experimental Section), which revealed that the associated pyran and cyclohexane rings are fused in a *cis* fashion and with the angular methoxy group axially oriented as a result of the operation of the anomeric effect.

Extensive efforts were made to try and avoid the undesired reduction of the enone C=C bond observed during the course of the conversion of **5** (P = Bn)→**17** but all to no avail. Accordingly, efforts were directed toward "salvaging" matters by elaborating ketal **17** to a derivative that incorporated a propionic acid side chain to which the required polyfunctionalized aromatic residue could be attached. To such ends, compound **17** was treated with aqueous HCl in acetone, and the ensuing



Scheme 4. Synthesis of Yoshimitsu's intermediate **24**: a) H_2 (1 atm), 10% Pd on C, MeOH, 18 °C, 16 h, 94%; b) 1 M aq. HCl, acetone, 0.25 h, 18 °C; c) PCC, NaOAc, CH_2Cl_2, 18 °C, 2 h; d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH/water, 18 °C, 1 h, 45% over three steps; e) DOWEX-50 (acidified), MeOH/water, 65 °C, 48 h, 24% of **19** and 46% of **20**; f) 4-NHAc-TEMPO, *p*-TsOH·H_2O, CH_2Cl_2, 0 to 18 °C, 4 h, 88%; g) BzCl, DMAP, Et_3N, CH_2Cl_2, 0 to 18 °C, 16 h, 95%; h) SmI_2, THF, −78 °C, 0.25 h, 88%; and i) $Ph_3P{=}CH_2$, THF, 0 °C, 0.5 h, 63%.

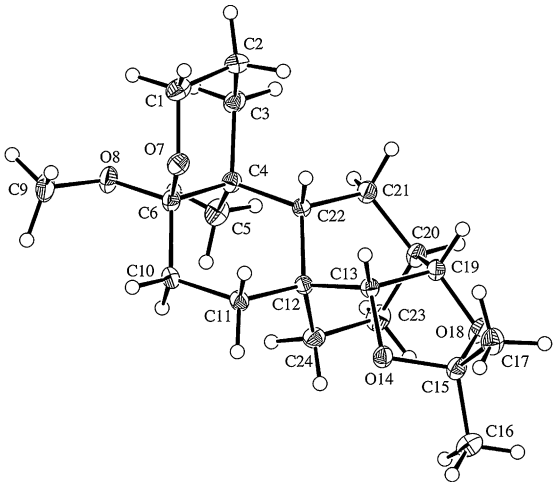


Figure 2. ORTEP diagram derived from the single-crystal X-ray analysis of compound **17**. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

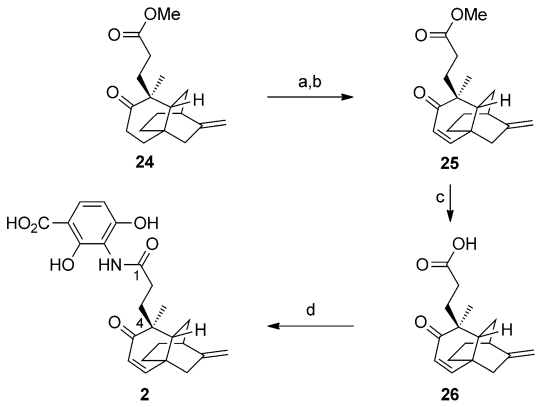
lactol immediately oxidized with pyridinium chlorochromate (PCC) in the presence of sodium acetate to give the corresponding keto-aldehyde. As a result of its instability, this last compound was immediately subjected to a Pinnick oxidation and thus afforded the desired carboxylic acid **18** in 45% yield over the three steps involved. Cleavage of the acetonide residue within the last compound proved rather difficult but could ultimately be achieved by treating a solution of the substrate in methanol/water with acidified Dowex-50 resin at 65 °C for 48 h. After workup, a chromatographically separable mixture of esters **19** (24%) and **20** (46%) was obtained. Subjecting the former product to the reaction conditions again gave additional quantities of the latter (57% at 82% conversion). The diol residue within compound **20** could be regioselectively monooxidized using the sterically demanding oxammonium salt derived from the acid-catalyzed disproportionation of 4-acetamido-TEMPO[24] (TEMPO = (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl) and thus afforded acyloin **21** in 82% yield. Esterification of the remaining hydroxyl group within compound **21** using benzoyl chloride in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) and triethylamine afforded benzoate **22** (95%) and this was subjected to a samarium iodide promoted reduction[25] and thereby generated the diketo ester **23** (88%). Finally, subjection of compound **23** to a Wittig olefination reaction using $Ph_3P{=}CH_2$ gave a chromatographically separable mixture of the desired alkene **24** (37%) and the corresponding twofold methylenation product (13%). The yield of the former product could be increased to 63% if the reaction was carried out at 0 °C for 0.5 h rather than between 0 and 18 °C for 16 h.

The racemic modification of olefin **24** has been described by Yoshimitsu et al.[12e] and served as a late-stage intermediate in their synthesis of (±)-platencin. As such, we were prompted to compare the spectral data sets they derived from their sample of racemic material with those obtained from our homochiral counterpart. These comparisons proved very favorable as evidenced by the closely matching chemical shifts observed in the relevant ^{13}C NMR spectra (Table 1).

Table 1. Comparison of the ^{13}C NMR spectroscopic data (δ_C) [ppm] recorded for compound **24** with those reported by Yoshimitsu and coworkers[12e] for the corresponding racemate.

Present work[a]	Yoshimitsu et al.[b]	$\Delta\delta$
215.9	216.0	−0.1
174.2	174.2	0
150.6	150.6	0
106.3	106.3	0
51.6	51.6	0
50.0	50.0	0
46.3	46.3	0
42.9	42.9	0
35.9	36.0	−0.1
35.4	35.4	0
35.2	35.2	0
32.8	32.8	0
31.3	31.3	0
29.4	29.4	0
28.3	28.3	0
28.2	28.2	0
26.6	26.6	0
20.3	20.3	0

[a] Data obtained from present work, recorded for samples in $CDCl_3$ at 100 MHz. [b] Data obtained from Ref. [12e], recorded for samples in $CDCl_3$ at 125 MHz.



Scheme 5. Completion of the synthesis of (−)-platencin (**2**): a) TMSCl, LiI, HMDS, CH_2Cl_2, 18 °C, 4 h; b) IBX, NMO, DMSO, 60 °C, 16 h, 53% over two steps; c) 1 M aq. NaOH, THF, 18 °C, 24 h, 88%; and d) 3-amino-β-resorcylic acid, DCC, Et_3N, DMAP, MeCN, DMF, 18 °C, 38 h, 44%.

Completion of the Synthesis of (−)-Platencin (2)

With the homochiral form, **24**, of a late-stage intermediate used in Yoshimitsu's synthesis of (±)-platencin[12e] in hand, it seemed most appropriate to deploy his method in establishing a synthesis of the natural product itself, namely, (−)-platencin (**2**). Accordingly, and as shown in Scheme 5, the first step was the conversion of ketone **24** into the corresponding silyl enol ether through treatment of the former compound with a mixture of trimethylsilyl chloride (TMSCl), lithium iodide, and hexamethyldisilazane (HMDS). The enol ether formed in this way was not isolated. Rather, it was immediately treated with 2-iodoxybenzoic acid (IBX) and 4-methylmorpholine 4-oxide (NMO)[26] so as to affect its oxidation to the corresponding enone **25** (57% over two steps). By such means the carbonyl-conjugated C=C moiety that had been unavoidably removed immediately after the IMDA reaction was now reinstated. Saponification of ester **25** by using aqueous sodium hydroxide in THF followed by an acid workup afforded the carboxylic acid **26** (97%). As was the case with compound **24**, the spectral data acquired on congeners **25** and **26** were in complete accord with the assigned structures and matched those data reported by Yoshimitsu et al.[12e] for their racemic counterparts.

The final step in the synthesis of (−)-platencin involved, as prescribed by Yoshimitsu, coupling of acid **26** with 3-amino-β-resorcylic acid[17] in the presence of dicyclohexylcarbodiimide (DCC), triethylamine, and DMAP. The purification of the (−)-platencin [(−)-**2**] formed in this way proved problematic because of the difficulties in separating this material from coproduced *N*,*N*′-dicyclohexylurea. After extensive chromatography, the target natural product was obtained in essentially pure form and 44% yield. The derived NMR spectroscopic, IR, and mass spectral data were in complete accord with the assigned struc-

ture and the set of ^{13}C NMR spectroscopic chemical shifts recorded for our material proved to be a good match (Table 2) with that derived from the material prepared by Mulzer et al.[27] This is especially so when one takes account of the capacity for variations in the chemical shifts of carbon atoms associated with acidic residues such as phenolic and carboxylate moieties.

Table 2. Comparison of the ^{13}C NMR data (δ_C) [ppm] recorded for compound **2** with those reported by Mulzer et al.[27]

Present work[a]	Mulzer et al.[b]	$\Delta\delta$
205.6	205.9	−0.3
174.1	174.1	0
172.7	172.5	+0.2
155.7	156.0	−0.3
155.6	155.4	+0.2
154.4	154.4	0
148.3	148.3	0
128.2	128.2	0
126.0	126.0	0
114.5	114.4	+0.1
111.4	111.3	+0.1
107.7	107.7	0
103.1	103.3	−0.2
47.7	47.7	0
44.5	44.4	+0.1
39.6	39.4	+0.2
36.3	36.3	0
35.8	35.8	0
32.4	32.3	+0.1
31.1	31.0	+0.1
28.1	28.0	+0.1
26.6	26.5	+0.1
25.8	25.7	+0.1
21.1	21.2	−0.1

[a] Data obtained from present work, recorded for samples in $CDCl_3$ at 200 MHz. [b] Data obtained from Ref. [27], recorded for samples in $CDCl_3$ at 150 MHz.

The specific rotation ($[\alpha]_D$) of our material, recorded at 18 °C, was −5.7 (c = 0.21, methanol) and this compares with a value of −15 (c = 0.24, methanol) recorded by Mulzer et al.[27] at 20 °C. Two factors might be contributing to these rather disparate values. First of all, it is clear from Mulzer and co-workers' studies[27] that the specific rotation of platencin varies to a reasonable degree as a function of temperature. Secondly, it is conceivable that variations in specific rotation will occur as a function of small variations in the pH because of the presence of acid residues attached to the aromatic core of (−)-platencin.

Conclusion

The present work has provided a new route to (−)-platencin (**2**) and serves to demonstrate the utility of IMDA reactions of the general form **6**→**5** as a means for the direct assembly of the tricarbocyclic framework associated with this important natural product. Although the reaction sequence reported here is too lengthy to be of any real value in generating useful quantities of compound **2** for further studies, it does, as will be reported elsewhere, allow for the production of small amounts of a range of analogues. Furthermore, variations to the structure of compound **8** that participates in the Stille cross-coupling reaction, and wherein, for example, the $BnOCH_2$ residue is replaced by a carboxamide group, should allow for a more convergent approach to biologically relevant systems. Similarly, variations in the nature of the iodinated cyclohexadiene (compound **7** in the present case) that engages in the Stille cross-coupling reaction could deliver further efficiencies. Such possibilities are currently under active investigation in our laboratories.

Experimental Section

Specific Synthetic Transformations

Compound 10

Following the procedure of Nordin and Thomas,[19] a magnetically stirred solution of aminodiol **9** (10.00 g, 59.8 mmol) in methanol (50 mL) was treated with methyl formate (4.00 mL, 68.67 mmol) and sodium methoxide (150 mg, 3 mmol). The ensuing mixture was stirred at 18 °C for 3.5 h then concentrated under reduced pressure to give brown crystals. This material was dissolved in dimethylformamide (DMF; 280 mL), and the resulting solution was treated with 2-methoxypropene (14.00 mL, 143 mmol), then *p*-TsOH·H_2O (*p*-TsOH = *p*-toluenesulfonic acid; 2.30 g, 12.04 mmol). The mixture thus obtained was stirred at 18 °C for 2 h before being quenched with $NaHCO_3$ (500 mL) and extracted with ethyl acetate (4×250 mL). The combined organic layers were washed with brine (1×50 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a viscous yellow oil. This was dissolved in hydrazine hydrate (50 mL of an 50–60% solution in water), and the ensuing mixture was heated under reflux conditions for 2 h before being cooled and then extracted with toluene (3×100 mL). The combined organic fractions were washed with water (2×50 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford compound **10**[18,19] (11.37 g, 89% yield) as an orange oil. $[\alpha]_D^{25} = +37.5$ (c = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.19 (complex m, 5H), 5.04 (d, J = 1.8 Hz, 1H), 4.23 (dd, J = 12.0, 2.4 Hz, 1H), 3.87 (dd, J = 12.0, 1.8 Hz, 1H), 2.75 (m, 1H), 1.80 (br s, 2H), 1.48 ppm (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.4 (C), 128.3 (CH), 127.3 (CH), 125.6 (CH), 99.1 (C), 73.6 (CH), 65.9 (CH_2), 49.5 (CH), 29.7 (CH_3), 18.5 ppm (CH_3); IR (KBr): $\tilde{\nu}_{max}$ = 2990, 2938, 2871, 1605, 1586, 1498, 1450, 1379, 1271, 1238, 1199, 1161, 1051, 944, 865, 739, 700 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 208 (13) $[M+H]^+$, 192 (29) $[M-{}^{\bullet}CH_3]^+$, 150 (24), 149 (40), 132 (100), 119 (68), 105 (66), 91 (94), 77 (92).

Compound 12

Following the procedure of Yamashita et al.,[18] a magnetically stirred solution of aldehyde **11** (405 μL, 4.2 mmol) in benzene (8.7 mL) maintained under nitrogen in a round-bottomed flask fitted with a Dean–Stark trap topped with a Liebig condenser was treated successively with compound **10** (870 mg, 4.2 mmol), then trifluoroacetic anhydride (15 μL). The ensuing mixture was heated at reflux for 5 h, then cooled to 18 °C, diluted with diethyl ether (15 mL) and dried (Na_2SO_4) before being filtered and concentrated under reduced pressure to afford compound **12**[18] (1.16 g, quant.) as a light brown solid. $[\alpha]_D^{25} = +70.8$ (c = 1.0, $CHCl_3$); ^1H NMR

(300 MHz, $CDCl_3$): $\delta = 7.42$ (s, 1H), 7.26–7.14 (complex m, 5H), 5.65 (m, 1H), 5.23 (d, $J = 2.7$ Hz, 1H), 4.35 (dd, $J = 12.0$, 2.7 Hz, 1H), 3.87 (dd, $J = 12.0$, 2.4 Hz, 1H), 3.30 (m, 1H), 1.71 (m, 6H), 1.61 (s, 3H), 1.59 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 166.1$ (CH), 139.2 (C), 137.3 (C), 135.7 (CH), 128.3 (CH), 127.6 (CH), 127.0 (CH), 99.4 (C), 74.3 (CH), 66.5 (CH), 65.2 (CH_2), 28.8 (CH_3), 19.8 (CH_3), 14.1 (CH_3), 11.1 ppm (CH_3); IR (KBr): $\tilde{\nu}_{max} = 2990$, 2938, 2862, 1648, 1629, 1451, 1378, 1267, 1238, 1196, 1168, 1127, 1097, 849, 745, 698 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 273 (1) [$M^{+\bullet}$], 258 (7), 109 (100), 108 (53), 94 (63), 82 (45); HRMS (EI, 70 eV): *m/z* calcd for $C_{17}H_{23}NO_2$: 273.1729 [$M^{+\bullet}$]; found: 273.1738 [$M^{+\bullet}$].

Compound 14

In a minor modification of the procedure described by Yamashita et al.,[18] a magnetically stirred solution of diisopropylamine (24.7 mL, 170 mmol) in THF (87 mL) maintained under nitrogen was cooled to $-15\,^{\circ}C$, then *n*BuLi (99.0 mL of a 1.6 M solution in hexane, 159 mmol) was added dropwise. The ensuing mixture was maintained at $-15\,^{\circ}C$ for 0.5 h before being cooled to $-78\,^{\circ}C$, and a solution of compound **12** (28.96 g, 106 mmol) in THF (87 mL) was then added. After 2 h, compound **13**[20] (43.9 g, 159 mmol) was also added, and the ensuing mixture was allowed to warm to $18\,^{\circ}C$ over 16 h before being quenched with water (670 mL), then treated with THF (1100 mL) and HCl (670 mL of a 2 M aqueous solution). After being stirred at $18\,^{\circ}C$ for 5 h, the reaction mixture was diluted with diethyl ether (500 mL) and the separated aqueous phase extracted with diethyl ether (1×500 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a dark brown oil. Subjection of this material to flash column chromatography (silica, 1:19 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions afforded three fractions: A, B, and C.

Concentration of fraction A ($R_f = 0.4$ in 1:9 v/v ethyl acetate/hexane) afforded the starting iodide **13** (15.0 g, 34% recovery) that was identical in all respects to an authentic sample.

Concentration of fraction B ($R_f = 0.4$ in 1:9 v/v ethyl acetate/hexane) afforded aldehyde **14** (12.0 g, 53%) as a light yellow oil. $[\alpha]_D^{25} = +20.2$ ($c = 1.0$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 9.37$ (s, 1H), 7.35–7.25 (complex m, 5H), 5.76 (dd, $J = 17.4$, 10.8 Hz, 1H), 5.26 (dd, $J = 10.8$, 0.6 Hz, 1H), 5.12 (d, $J = 17.4$, 0.6 Hz, 1H), 4.47 (s, 2H), 3.45 (t, $J = 6.0$ Hz, 2H), 1.60 (m, 2H), 1.53 (m, 2H), 1.16 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 202.6$, 138.5, 138.4, 128.3, 127.6, 127.5, 116.8, 72.8, 70.3, 52.4, 31.8, 24.3, 17.6 ppm; IR (KBr): $\tilde{\nu}_{max} = 2948$, 2858, 1726, 1632, 1454, 1368, 1102, 923, 736, 697 cm^{-1}; MS (ESI^+): *m/z* (%): 255 (100) [M+Na]$^+$, 125 (81); HRMS (ESI^+): *m/z* calcd for $C_{15}H_{20}O_2$: 255.1361 [M+Na]$^+$; found: 255.1362 [M+Na]$^+$.

Concentration of fraction C ($R_f = 0.5$ in 1:4 v/v ethyl acetate/hexane) afforded (*E*)-7-(benzyloxy)-2-methylhept-2-enal[28] (2.32 g, 9%) as a light yellow oil. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 9.39$ (s, 1H), 7.36–7.25 (complex m, 5H), 6.48 (m, 1H), 4.51 (s, 2H), 3.50 (m, 2H), 2.37 (m, 2H), 1.73 (s, 3H), 1.65–1.50 ppm (complex m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 195.2$, 154.4, 139.4, 138.4, 128.3, 127.5, 72.9, 69.7, 29.6, 29.4, 28.7, 25.1, 9.1 ppm; IR (KBr): $\tilde{\nu}_{max} = 2926$, 2854, 1686, 1454, 1102 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 232 (9) [$M^{+\bullet}$], 141 (72), 126 (58), 108 (38), 92 (100), 79 (40), 65 (50); HRMS (EI, 70 eV): *m/z* calcd for $C_{15}H_{20}O_2$ [$M^{+\bullet}$]: 232.1463; found: 232.1467 [$M^{+\bullet}$].

Compound (±)-14

Step 1: A magnetically stirred solution of (*E*)-2-methylbut-2-enal (1.00 g, 11.90 mmol) in benzene (4.8 mL) maintained under nitrogen in a round-bottomed flask fitted with a Dean–Stark trap topped with a Liebig condenser was treated with 1,1-dimethylhydrazine (1.1 mL, 14.28 mmol) and trifluoroacetic anhydride (5 μL) at $18\,^{\circ}C$. The resulting mixture was stirred under reflux conditions for 5 h, then cooled to room temperature and diluted with diethyl ether (20 mL) and water (5 mL). The separated organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the yellow residue thus obtained was subjected to column chromatography (silica, 1:19 v/v ethyl acetate/hexane elution). Concentration of the relevant fractions ($R_f = 0.5$ in 1:9 v/v ethyl acetate/hexane) afforded (*E*)-2-methylbut-2-enal *N*,*N*-dimethylhydrazone[29] (1.00 g, 66% yield) as a clear, colorless oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.04$ (s, 1H), 5.63 (m, 1H), 2.80 (s, 6H), 1.83 (s, 3H), 1.77 ppm (d, $J = 8.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 140.6$, 135.2, 127.3, 43.2, 13.8, 11.3 ppm; IR (KBr): $\tilde{\nu}_{max} = 3354$, 2952, 2918, 2854, 2787, 1590, 1120 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 127 (24) [M+H$^+$], 111 (26), 100 (34), 87 (63), 84 (100), 72 (52); HRMS (EI, 70 eV): *m/z* calcd for $C_7H_{14}N_2$: 127.1235 [M+H]$^+$; found: 127.1236 [M+H]$^+$

Step 2: A magnetically stirred solution of diisopropylamine (570 μL, 4.04 mmol) in THF (8 mL) maintained under a nitrogen atmosphere at $-5\,^{\circ}C$ was treated with *n*BuLi (2.5 mL of a 1.6 M solution in hexane, 4.08 mmol), and after another 0.5 h, a solution of (*E*)-2-methylbut-2-enal *N*,*N*-dimethylhydrazone (500 mg, 3.96 mmol) in THF (2 mL) was added to the reaction mixture. After another 1 h, iodide **13** (930 mg, 4.08 mmol) was added, and the resulting mixture was warmed to approximately $18\,^{\circ}C$, then stirred at this temperature for 20 h before being diluted with diethyl ether (10 mL) and water (10 mL). The separated organic layer was washed with brine (1×10 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow residue obtained in this way was subjected to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution), and concentration of the relevant fractions ($R_f = 0.2$) afforded the anticipated *C*-alkylation product (500 mg, 46%) as clear, colorless oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.34$–7.27 (complex m, 5H), 6.49 (s, 1H), 5.87 (dd, $J = 17.2$, 10.8 Hz, 1H), 4.96–5.04 (complex m, 2H), 4.49 (s, 2H), 3.45 (m, 2H), 2.71 (s, 6H), 1.59 (m, 4H), 1.16 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 144.9$, 143.4, 138.6, 128.3, 127.6, 127.4, 112.2, 72.8, 71.0, 43.3, 35.8, 24.7, 22.3 ppm; IR (KBr): $\tilde{\nu}_{max} = 3082$, 3029, 2950, 2852, 2783, 1634, 1602, 1495, 1468, 1454, 1410, 1362, 1249, 1204, 1137, 1101 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 274 (10) [$M^{+\bullet}$], 183 (66), 125 (100), 98 (35), 91 (91), 82 (36); HRMS (EI, 70 eV): *m/z* calcd for $C_{17}H_{26}N_2O$: 274.2045 [$M^{+\bullet}$]; found: 274.2042 [$M^{+\bullet}$].

Step 3: A magnetically stirred solution of $CuCl_2$ (59 mg, 0.40 mmol) in water (3.65 mL) maintained at $18\,^{\circ}C$ was treated with a solution of the product of step 2 (100 mg, 0.37 mmol) in THF (5.5 mL). The resulting mixture was stirred at this temperature for 4 h, then quenched with ammonia (5 mL of an 3 M aqueous solution) and extracted with ethyl acetate (3×10 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting brown residue was subjected to flash chromatography (silica, 1:19 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions ($R_f = 0.4$ in 1:9 v/v ethyl acetate/hexane), compound (±)-**14** (67 mg, 79%) as a clear, yellow oil. The spectral data recorded on this material were identical in all respects to those obtained from compound **14**.

Formation of the SAMP Hydrazones of Compounds 14 and (±)-14

A magnetically stirred solution of aldehyde **14** (20 mg, 0.09 mmol) in benzene (1 mL) maintained under a nitrogen atmosphere at

18 °C was treated with SAMP (22 mg, 0.17 mmol) and trifluoroacetic acid (2 μL). The ensuing mixture was heated under reflux conditions for 2 h, then cooled to 18 °C and diluted with diethyl ether (5 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow residue thus obtained was subjected to flash chromatography (silica, 1:20 v/v ethyl acetate/hexane elution), and concentration of the appropriate fractions (R_f = 0.3 in 1:4 v/v ethyl acetate/hexane) afforded the SAMP hydrazone of compound **14** (20 mg, 67% yield) as a light yellow oil in 92% *ee*. $[\alpha]_D^{20} = -63.6$ (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.26 (complex m, 5H), 6.49 (s, 1H), 5.87 (dd, J = 17.4, 10.8 Hz, 1H), 5.04–4.93 (complex m, 2H), 4.49 (s, 2H), 3.59 (dd, J = 9.0, 3.6 Hz, 1H), 3.47–3.27 (complex m, 5H), 3.37 (s, 3H), 2.70 (m, 1H), 1.99–1.74 (complex m, 4H), 1.67–1.52 (complex m, 4H), 1.15 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.1, 143.0, 138.6, 128.3, 127.6, 127.4, 112.0, 74.6, 72.8, 71.0, 63.4, 59.2, 49.9, 43.4, 35.8, 26.5, 24.7, 22.4, 21.9 ppm; IR (KBr): $\tilde{\nu}_{max}$ = 2925, 2854, 1596, 1453, 1361, 1197, 1114 cm^{-1}; MS (ESI$^+$): m/z (%): 367 (14) [M+Na]$^+$, 345 (100) [M+H]$^+$, 237 (35), 143 (68), 129 (24), 91 (50); HRMS (ESI$^+$): m/z calcd for $C_{21}H_{32}N_2O_2$: 367.2361 [M+Na]$^+$; found: 367.2364 [M+Na]$^+$.

Analogous treatment of the racemic modification (namely (±)-**14**) of aldehyde **14** afforded a light yellow oil on workup. Subjection of this material to flash chromatography (silica, 1:20 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.5 in 1:4 v/v ethyl acetate/hexane) afforded a 1:1 mixture of the diastereoisomeric forms of the SAMP hydrazones of compound (±)-**14** (22 mg, 73% yield) as a pale yellow oil. The ^{1}H and ^{13}C NMR spectroscopic as well as the IR and mass spectral data recorded on this mixture were essentially indistinguishable from those obtained from the SAMP hydrazone of compound **14** as detailed immediately above.

High-performance liquid chromatography (HPLC) analysis of the SAMP hydrazone of compound **14** on a Daicel Chiracel OD-H column eluted isocratically using 1% isopropanol in hexane elution at a flow rate of 1 mL min^{-1} revealed peaks at 12.4 and 13.3 min in a 96:4 ratio. The equivalent analysis of the SAMP hydrazones derived from compound (±)-**14** showed the same peaks in a 1:1 ratio.

Compound 15

A magnetically stirred solution of ethynylmagnesium bromide in THF (12.5 mL of a 0.5 M solution, 6.26 mmol) maintained at −10 °C was treated dropwise with aldehyde **14** (1.21 g, 5.22 mmol). The ensuing mixture was stirred at −10 °C for 1.5 h then quenched with NH_4Cl (50 mL of a saturated aqueous solution) and extracted with ethyl acetate (3×50 mL). The combined organic phases were washed with brine (2×10 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The light brown oil thus obtained was subjected to flash chromatography (silica, 3:20→5:20 v/v ethyl acetate/hexane gradient elution), and concentration of the relevant fractions (R_f = 0.5 in 1:4 v/v ethyl acetate/hexane) afforded compound **15** (1.31 g, 85%) as a light yellow oil and an approximately 1:1 mixture of diastereoisomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.20 (complex m, 5H), 5.76 (m, 1H), 5.18 (dd, J = 10.5, 1.2 Hz, 1H), 5.05 (ddd, J = 17.4, 3.0, 1.2 Hz, 1H), 4.43 (s, 2H), 4.08–4.00 (complex m, 1H), 3.38 (m, 2H), 2.45 (m, 0.5H), 2.04–2.02 (m, 1.5H), 1.51–1.45 (complex m, 4H), 1.03 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.0, 141.3, 138.4, 128.3, 127.6, 127.5, 116.4, 116.2, 82.8, 82.5, 74.4(2), 74.3(5), 72.8, 70.8, 69.2, 69.1, 44.9(0), 44.8(7), 33.0, 32.7, 24.3, 24.2, 18.2, 17.5 ppm (six signals obscured or overlapping); IR (KBr): $\tilde{\nu}_{max}$ = 3419, 3298, 2947, 2859, 1638, 1495, 1454, 1414, 1369, 1098 cm^{-1}; MS (EI, 70 eV): m/z (%): 258 (5) [$M^{+\bullet}$], 225 (10), 203 (68), 185 (45), 157 (28), 143 (53), 129 (40), 117 (40), 107 (60), 95 (87), 92 (100), 65 (78); HRMS (EI, 70 eV): m/z calcd for $C_{17}H_{22}O_2$: 258.1620 [$M^{+\bullet}$]; found: 258.1620 [$M^{+\bullet}$].

Compound 8 (*P* = *Bn*)

A solution of propargyl alcohol **15** (850 mg, 3.3 mmol) in hexane (15 mL) was poured into a flask that contained $Bu_2Sn(OTf)H$ (3.40 g, 8.47 mmol) prepared according to the method of Hosomi et al.[21] and maintained at 18 °C. The ensuing mixture was stirred at 18 °C for 16 h, then diluted with anhydrous diethyl ether (15 mL) and cooled to 0 °C before being treated with *n*BuLi (2.64 mL of a 2.5 M solution in hexane, 6.6 mmol). After 0.25 h, the reaction mixture was quenched with a mixture of NH_4Cl (20 mL of a saturated aqueous solution) and water (20 mL) before being filtered through Celite and the filtrate extracted with diethyl ether (3× 20 mL). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a clear, colorless oil that was subjected to flash chromatography (silica, 1:20 v/v ethyl acetate/hexane elution). Concentration of the relevant fractions (R_f = 0.6 in 1:9 v/v ethyl acetate/hexane) afforded compound **8** (P = Bn) (980 mg, 54% yield) as a clear, colorless oil and very unstable material that was immediately subjected to the next step of the reaction sequence.

Compound 16

A magnetically stirred solution of iodide **7** (1.10 g, 3.95 mmol) and alkenyl stannane **8** (P = Bn) (2.39 g, 4.35 mmol) in DMF (9.6 mL) maintained at 18 °C under a nitrogen atmosphere was treated with cesium fluoride (1.20 g, 7.9 mmol), [$Pd(PPh_3)_4$] (204 mg, 0.20 mmol), and CuI (75 mg, 0.40 mmol). The ensuing mixture was stirred at 18 °C for 16 h, then diluted with water (90 mL) and dichloromethane (225 mL) before being filtered through a pad Celite that was washed with ethyl acetate/dichloromethane (300 mL of a 1:1 v/v mixture). The separated organic phase derived from the filtrate was dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the resulting dark brown oil was subjected to flash chromatography (silica, 1:5 v/v ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.4(6) in 3:7 v/v ethyl acetate/hexane) afforded a single diastereoisomeric form of compound **16** (630 mg, 39%) as light brown oil. $[\alpha]_D^{25} = -11.1$ (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.26 (complex m, 5H), 6.10–6.07 (complex m, 2H), 5.92–5.89 (complex m, 1H), 5.80 (dd, J = 17.5, 10.5 Hz, 2H), 5.66 (dd, J = 12.5, 10.5 Hz, 1H), 5.16 (dd, J = 11.0, 1.5 Hz, 1H), 5.05 (dd, J = 17.5, 1.5 Hz, 1H), 4.91 (d, J = 9.0 Hz, 1H), 4.74 (dd, J = 9.0, 3.5 Hz, 1H), 4.48 (s, 2H), 4.34 (dd, J = 10.0, 5.0 Hz, 1H), 3.44 (m, 2H), 2.70 (d, J = 5.0 Hz, 1H), 1.60–1.34 (complex m, 3H), 1.43 (s, 3H), 1.38 (s, 3H), 1.08 (s, 3H), 0.92 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.5, 138.5, 133.2, 131.2, 131.0, 128.3, 127.6, 127.5, 124.8, 124.7, 124.6, 114.8, 105.5, 73.0, 72.8, 72.7, 71.3, 71.0, 43.7, 33.2, 26.7, 24.8, 24.3, 18.4 ppm; IR (KBr): $\tilde{\nu}_{max}$ = 3481, 2982, 2934, 2870, 1454, 1379, 1370, 1235, 1209, 1159, 1099, 1078, 1051, 1028, 1005, 913, 892, 867, 736, 698 cm^{-1}; MS (ESI$^+$): m/z (%): 433 (100) [M+Na]$^+$; HRMS (ESI$^+$): m/z calcd for $C_{26}H_{34}O_4$: 433.2355 [M+Na]$^+$; found: 433.2359 [M+Na]$^+$.

Concentration of fraction B (R_f = 0.4(3) in 3:7 v/v ethyl acetate/hexane) afforded the second diastereoisomeric form of compound **16** (660 g, 41%) as a light brown oil. $[\alpha]_D^{25} = +58.4$ (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.26 (complex m, 5H), 6.21 (d, J = 12.0 Hz, 1H), 6.08–6.01 (complex m, 2H), 5.89–5.81 (complex m, 2H), 5.64 (m, 1H), 5.22 (dd, J = 11.0, 1.5 Hz, 1H), 5.08 (dd, J = 17.5,

1.5 Hz, 1H), 4.78 (m, 1H), 4.69 (d, J=8.5 Hz, 1H), 4.48 (s, 2H), 4.40 (br d, J=10.0 Hz, 1H), 3.44 (m, 2H), 1.75–0.09 (complex m, 5H), 1.44 (s, 6H), 0.95 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=143.0, 138.6, 132.7, 132.3, 130.4, 128.3, 127.6, 127.5, 126.2, 124.8, 123.5, 115.5, 105.3, 72.9, 72.2, 72.1, 71.8, 71.0, 44.3, 33.8, 26.8, 25.0, 24.4, 17.1 ppm; IR (KBr): $\tilde{\nu}_{max}$=3435, 2981, 2931, 2856, 1454, 1380, 1370, 1235, 1210, 1098, 1050, 1028, 914, 736, 697 cm^{-1}; MS (ESI$^+$): m/z (%): 433 (100) $[M+Na]^+$; HRMS (ESI$^+$): m/z calcd for $C_{26}H_{34}O_4$: 433.2355 $[M+Na]^+$; found: 433.2357 $[M+Na]^+$.

Compound 6 (P=Bn)

A magnetically stirred solution of tetraene **16** (1.70 g of an 1:1 mixture of diastereoisomers, 4.14 mmol) in dichloromethane (83 mL) maintained at 0 °C under a nitrogen atmosphere was treated with pyridine (2.13 mL, 27.51 mmol), then the Dess–Martin periodinane (3.16 g, 7.46 mmol). The ensuing mixture was stirred at 0 °C for 0.75 h and then at 18 °C for an additional 0.5 h before being diluted with diethyl ether (80 mL). The mixture thus obtained was filtered through Celite, and the filtrate was concentrated under reduced pressure to give a clear, yellow oil. This was subjected to flash chromatography (silica, 1:5 v/v ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f=0.7 in 3:7 v/v ethyl acetate/hexane) afforded compound **6** (P=Bn) (900 mg, 69% yield at 77% conversion) as a light yellow oil. $[\alpha]_D^{25}=+91.5$ (c=1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.35–7.27 (complex m, 5H), 6.31–6.27 (m, 2H), 6.21 (d, J=13.0 Hz, 1H), 6.11 (dd, J=10.0, 6 Hz, 1H), 6.01 (m, 1H), 5.91 (dd, J=17.5, 10.5 Hz, 1H), 5.21–5.07 (complex m, 3H), 4.65 (dd, J=9.0, 4.5 Hz, 1H), 4.49 (s, 2H), 3.47 (t, J=7.0 Hz, 2H), 1.75 (t, J=8.5 Hz, 2H), 1.58–1.55 (complex m, 2H), 1.34 (s, 3H), 1.30 (s, 3H), 1.27 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=204.4, 141.9, 138.5, 137.7, 134.1, 128.7, 128.3, 127.5(8), 127.5(0), 127.5(6), 126.4, 124.9, 115.1, 105.4, 72.9, 70.9, 70.8, 70.7, 53.4, 33.6, 26.8, 25.0, 24.6, 19.7 ppm; IR (KBr): $\tilde{\nu}_{max}$=2982, 2934, 2858, 1683, 1630, 1591, 1454, 1407, 1235, 1207, 1159, 1100, 1056, 1027, 917, 871, 735, 697 cm^{-1}; MS (ESI$^+$): m/z (%): (100) $[M+Na]^+$; HRMS (ESI$^+$): m/z calcd for $C_{26}H_{32}O_4$: 431.2198 $[M+Na]^+$; found: 431.2197 $[M+Na]^+$.

Concentration of fraction B (R_f=0.5 in 3:7 v/v ethyl acetate/hexane) afforded an 1:1 mixture of the diastereoisomeric forms of the starting material **16** (391 mg, 23% recovery) that was identical in all respects with an authentic sample.

Compound 5 (P=Bn)

A magnetically stirred solution of tetraene **6** (1.03 g, 2.70 mmol) in toluene (1 L) was stirred under reflux conditions for 16 h then cooled and concentrated under reduced pressure. The resulting dark residue was subjected to flash chromatography (silica, 1:5 v/v ethyl acetate/hexane elution), and concentration of the appropriate fractions (R_f=0.5 in 3:7 v/v ethyl acetate/hexane) afforded compound **5** (P=Bn) (720 mg, 70%) as a white, crystalline solid. M.p. 54 °C; $[\alpha]_D^{25}=+61.0$ (c=1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.34–7.27 (complex m, 5H), 7.13 (d, J=10.0 Hz, 1H), 6.21 (m, 1H), 6.02 (d, J=10.0 Hz, 1H), 5.83 (br d, J=8.4 Hz, 1H), 4.48 (s, 2H), 4.26 (dd, J=6.8, 2.8 Hz, 1H), 3.86 (d, J=8.0 Hz, 1H), 3.51–3.36 (complex m, 2H), 2.92 (m, 1H), 1.94 (m, 1H), 1.84 (m, 1H), 1.63–1.40 (complex m, 3H), 1.35 (s, 3H), 1.27 (s, 3H), 1.26–1.15 (complex m, 2H), 0.81 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=203.6, 149.5, 138.6, 130.9, 130.7, 128.3, 128.1, 127.6, 127.5, 109.2, 82.5, 78.6, 72.8, 70.8, 47.8, 43.4, 37.4, 35.1, 31.1, 25.4, 25.1, 24.9, 23.8, 23.0 ppm; IR (KBr): $\tilde{\nu}_{max}$=2923, 2852, 1683, 1595, 1454, 1371, 1208, 1161, 1098, 1071, 918, 737, 698 cm^{-1}; MS (EI, 70 eV): m/z (%): 393 (16) $[M-{}^{\bullet}CH_3]^+$, 259 (52), 241 (33), 201 (66), 91 (100); HRMS (EI, 70 eV): m/z calcd for $C_{26}H_{32}O_4$: 393.2066 $[M-{}^{\bullet}CH_3]^+$; found: 393.2063 $[M-{}^{\bullet}CH_3]^+$.

Compound 17

A magnetically stirred solution of unsaturated ketone **5** (P=Bn) (640 mg, 1.57 mmol) in methanol was treated with 10% palladium on carbon (640 mg), and the resulting suspension was stirred at 18 °C under a hydrogen atmosphere for 16 h. The mixture thus obtained was filtered through a pad of Celite that was washed with ethyl acetate (150 mL). The combined filtrates were concentrated under reduced pressure to give the title compound **17** (495 mg, 94% yield) as a white, crystalline solid. M.p. 106 °C; $[\alpha]_D^{25}=-34.0$ (c=1.0, $CHCl_3$) (R_f=0.6 in 3:7 v/v ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.13 (dd, J=8.4, 4.0 Hz, 1H), 3.63 (dd, J=8.4, 2.0 Hz, 1H), 3.60–3.57 (complex m, 2H), 3.17 (s, 3H), 1.90–1.51 (complex m, 9H), 1.50–1.35 (complex m, 4H), 1.49 (s, 3H), 1.35 (s, 3H), 1.34–1.21 (complex m, 3H), 1.03 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=108.1, 100.8, 83.8, 76.3, 60.2, 47.1, 39.2, 34.6, 33.5, 30.4, 29.7, 28.9, 25.7, 24.5, 24.3, 24.2, 21.0, 19.7, 19.4, 19.0 ppm; IR (KBr): $\tilde{\nu}_{max}$=2980, 2938, 2873, 2823, 1471, 1381, 1368, 1260, 1201, 1164, 1119, 1107, 1093, 1071, 1035, 930, 901, 878, 819 cm^{-1}; MS (EI, 70 eV): m/z (%): 336 (2) $[M^{+\bullet}]$, 321 (85) $[M-{}^{\bullet}CH_3]^+$, 304 (100), 289 (58), 231 (58), 202 (39), 127 (36), 85 (51), 69 (59), 55 (70); HRMS (EI, 70 eV): m/z calcd for $C_{20}H_{32}O_4$: 321.2066 $[M-{}^{\bullet}CH_3]^+$; found: 321.2070 $[M-{}^{\bullet}CH_3]^+$.

Compound 18

A magnetically stirred solution of ketal **17** (930 mg, 2.77 mmol) in acetone (93 mL) was treated with HCl (93 mL of a 1 M aqueous solution), and the resulting mixture was stirred at 18 °C for 0.17 h, then extracted with ethyl acetate (3×100 mL). The combined organic phases were washed with brine (1×20 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a white solid presumed to be the lactol derived from the starting material. This solid was dissolved in dichloromethane (40 mL) and the resulting solution was stirred magnetically at 18 °C, and then treated with 4 Å molecular sieves (200 mg), sodium acetate (354 mg, 4.26 mmol), and PCC (2.29 g, 10.64 mmol). After 2 h, the reaction mixture was diluted with diethyl ether (100 mL), then filtered through a pad of Celite, and the solids thus retained were washed with diethyl ether (2×100 mL). The combined filtrates were concentrated under reduced pressure to afford a pale yellow oil presumed to contain the aldehydic precursor to acid **18**. A magnetically stirred solution of this oil in *t*BuOH (19.7 mL) maintained at 18 °C and that contained water (6.02 mL) was treated with 2-methyl-2-butene (1.50 mL), $NaH_2PO_4{\cdot}H_2O$ (338 mg, 2.45 mmol), and $NaClO_2$ (177 mg, 1.97 mmol). After 1 h, the reaction mixture was quenched with brine (50 mL) and extracted with ethyl acetate (4×50 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a light yellow oil that was subjected to column chromatography (60:40:05 v/v ethyl acetate/hexane/acetic acid elution). Concentration of the relevant fractions (R_f=0.2 in 2:3 v/v ethyl acetate/hexane) afforded carboxylic acid **18** (440 mg, 47% from **17**) as a clear, colorless oil. $[\alpha]_D^{25}=-1.2$ (c=1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.17 (m, 1H), 3.64 (d, J=7.6 Hz, 1H), 2.59 (m, 1H), 2.32 (m, 2H), 2.20 (td, J=14.4, 4.8 Hz, 1H), 1.99–1.50 (complex m, 15H), 1.52 (s, 3H), 1.36 (s, 3H), 1.25 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=215.5, 179.0, 108.7, 82.1, 75.8, 50.2, 40.6, 34.6, 33.9, 33.0, 31.2, 29.3, 29.1, 25.7, 24.2, 24.1, 20.4, 19.8, 19.1 ppm; IR (KBr): $\tilde{\nu}_{max}$= 2934, 1706, 1471, 1454, 1380, 1281, 1261, 1207, 1163, 1067, 1037,

974 cm^{-1}; MS (ESI^-): *m/z* (%): 335 (100) $[M-H^+]^-$; HRMS (ESI^-): *m/z* calcd for $C_{19}H_{28}O_5$: 335.1858 $[M-H^+]^-$; found: 335.1858 $[M-H^+]^-$.

Compounds 19 and 20

A magnetically stirred solution of carboxylic acid **18** (440 mg, 1.31 mmol) in methanol/water (12.3 mL of a 5:1 v/v mixture) was treated with DOWEX-50 resin (465 mg, acidified form). The ensuing mixture was heated at 65 °C for 48 h, then cooled. The resin was removed by filtration and washed with methanol (3×10 mL). The combined filtrates were concentrated under reduced pressure and the residue diluted with brine (5 mL), then extracted with ethyl acetate (3×25 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure and the light yellow oil thus obtained subjected to column chromatography (silica, 30:70 v/v ethyl acetate/hexane→80:20:0.5 v/v ethyl acetate/hexane/acetic acid gradient elution) to afford three fractions: A, B, and C.

Concentration of fraction A (R_f=0.4 in 3:7 v/v ethyl acetate/hexane) afforded methyl ester **19** (110 mg, 24%) as a clear, colorless oil. $[\alpha]_D^{25}=-1.3$ (*c*=1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ= 4.17 (dd, *J*=7.6, 3.2 Hz, 1H), 3.65 (s, 3H), 2.61–2.52 (complex m, 1H), 2.26 (t, *J*=7.6 Hz, 2H), 2.19 (dt, *J*=15.2, 4.8 Hz, 1H), 1.97–1.90 (complex m, 3H), 1.80–1.54 (complex m, 7H), 1.51 (s, 3H), 1.50–1.47 (complex m, 3H), 1.35 (s, 3H), 1.23 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=215.3, 174.1, 108.7, 82.0, 76.0, 51.6, 50.2, 40.4, 34.6, 33.9, 32.9, 31.5, 29.5, 29.1, 25.7, 24.2, 24.1, 20.5, 19.9, 19.1 ppm; IR (KBr): $\tilde{\nu}_{max}$=2935, 2879, 1738, 1706, 1437, 1380, 1296, 1261, 1207, 1165, 1067, 1038, 974, 876, 812, 731, 647, 517 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 350 (2) $[M^{+\bullet}]$, 335 (100) $[M-{}^{\bullet}CH_3]^+$, 303 (23), 263 (54), 243 (73), 215 (29), 205 (28), 91 (30), 55 (30); HRMS (EI, 70 eV): *m/z* calcd for $C_{20}H_{30}O_5$: 335.1858 $[M-{}^{\bullet}CH_3]^+$; found: 335.1858 $[M-{}^{\bullet}CH_3]^+$.

Concentration of fraction B (R_f=0.4 in 80:20:0.5:1.0:0.5 v/v ethyl acetate/hexane/water/methanol/acetic acid) afforded compound **20** (198 mg, 49%) as a clear, colorless oil. $[\alpha]_D^{25}=-0.9$ (*c*=0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ=3.98 (dm, *J*=8.4 Hz, 1H), 3.66 (s, 3H), 3.47 (br d, *J*=8.4 Hz, 1H), 2.51 (m, 1H), 2.27–2.20 (complex m, 2H), 2.00–1.30 (complex m, 15H) 1.21 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=215.7, 174.0, 73.6, 68.1, 51.6, 49.9, 39.5, 35.0, 34.9, 32.3, 31.4, 31.3, 29.4, 24.7, 20.8, 20.8, 19.0 ppm; IR (KBr): $\tilde{\nu}_{max}$= 3405, 2931, 2869, 1736, 1705, 1594, 1438, 1381, 1299, 1259, 1199, 1170, 1135, 1107, 1070, 1029, 987 cm^{-1}; MS (ESI^+): *m/z* (%): 310 (<1) $[M^{+\bullet}]$, 239 (100), 196 (60); HRMS (EI, 70 eV): *m/z* calcd for $C_{17}H_{26}O_5$: 310.1780 $[M^{+\bullet}]$; found: 310.1780 $[M^{+\bullet}]$.

Concentration of fraction C (R_f=0.1 in 80:20:0.5:1.0:0.5 v/v ethyl acetate/hexane/water/methanol/acetic acid) afforded the carboxylic acid derived from the hydrolysis of compound **20** (28 mg, 7%) as clear, colorless oil. $[\alpha]_D^{20}=-2.8$ (*c*=1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ=3.97 (d, *J*=6.4 Hz, 1H), 3.47 (d, *J*=6.4 Hz, 1H), 2.55–2.48 (complex m, 1H), 2.21 (m, 3H), 2.05–1.25 (complex m, 15H), 1.22 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=216.1, 178.0, 73.6, 68.0, 50.0, 39.6, 35.0, 32.1, 31.4, 31.0, 29.7, 29.3, 24.7, 20.8, 20.7, 19.0 ppm; IR (KBr): $\tilde{\nu}_{max}$=3304, 2918, 1705, 1399, 1384, 1070 cm^{-1}; MS (ESI^+): *m/z* (%): 319 (100) $[M+Na]^+$, 302 (17), 276 (24), 190 (11); HRMS (ESI^+): *m/z* calcd for $C_{16}H_{24}O_5$: 319.1521 $[M+Na]^+$; found: 319.1526 $[M+Na]^+$.

Resubjecting compound **19** to the above-mentioned reaction conditions provided further quantities of compound **20** (57% at 82% conversion).

Compound 21

A magnetically stirred mixture of *p*-TsOH·H_2O (412 mg, 2.215 mmol) and 4-acetamido-TEMPO (320 mg, 1.03 mmol) in dichloromethane (21 mL) was maintained at 18 °C for 0.5 h, and the resulting suspension was added, in portions, to a magnetically stirred solution of compound **20** (320 mg, 1.032 mmol) in dichloromethane (21 mL) maintained at 0 °C. Stirring was continued for a further 2.5 h, then the resulting mixture was quenched with $NaHCO_3$ (20 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (3×100 mL) and the combined organic fractions washed with water (1×10 mL) and brine (1×10 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography (silica, 2:3 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions (R_f=0.4), acyloin **21** (262 mg, 82%) as a clear, colorless oil. $[\alpha]_D^{25}=+15.1$ (*c*=1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ=3.65 (s, 3H), 3.43 (s, 1H), 2.93 (s, 1H), 2.63 (m, 1H), 2.50 (br s, 1H), 2.36–2.22 (complex m, 3H), 2.05–1.58 (complex m, 11H), 1.28 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=217.5, 214.1, 173.9, 81.0, 51.6, 50.4, 42.2, 41.1, 39.9, 34.7, 31.1, 31.0, 29.4, 26.4, 23.0, 20.3(4), 20.2(7) ppm; IR (KBr): $\tilde{\nu}_{max}$=3417, 2951, 2870, 1730, 1706, 1465, 1438, 1384, 1313, 1298, 1195, 1180, 1142, 1100, 1070 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 308 (21) $[M^{+\bullet}]$, 293 (19), 276 (90), 222 (73), 221 (80), 55 (100); HRMS (EI, 70 eV): *m/z* calcd for $C_{17}H_{24}O_5$: 308.1624 $[M^{+\bullet}]$; found: 308.1627 $[M^{+\bullet}]$.

Compound 22

A magnetically stirred solution of acyloin **21** (255 mg, 0.828 mmol) in dichloromethane (11.6 mL) maintained at 18 °C was treated, in portions and successively, with triethylamine (230 μL, 1.66 mmol), benzoyl chloride (370 μL, 3.15 mmol), and DMAP (17 mg, cat.). The ensuing mixture was stirred at 18 °C for 16 h, then quenched with $NaHCO_3$ (20 mL of a saturated aqueous solution). The resulting biphasic system was stirred for 0.5 h at 18 °C, then diluted with dichloromethane (20 mL). The separated aqueous phase was extracted with dichloromethane (3×20 mL), and the combined organic fractions were then washed with brine (1×5 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The light yellow oil thus obtained was subjected to flash chromatography (silica, 2:3 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions (R_f=0.7 in 3:2 v/v ethyl acetate/hexane), compound **22** (323 mg, 95%) as a clear, colorless oil. $[\alpha]_D^{25}=+95.5$ (*c*=1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ=8.03–8.01 (complex m, 2H), 7.59–7.55 (complex m, 1H), 7.45–7.42 (complex m, 2H), 5.16 (d, *J*=1.6 Hz, 1H), 3.64 (s, 3H), 2.62–2.54 (complex m, 2H), 2.33–1.60 (complex m, 14H), 1.28 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=213.4, 210.4, 173.7, 165.7, 133.4, 129.8, 129.1, 128.4, 79.1, 51.6, 50.1, 42.0, 41.0, 39.2, 34.4, 31.1, 30.1, 29.2, 25.0, 23.3, 21.8, 20.5 ppm; IR (KBr): $\tilde{\nu}_{max}$=2950, 2874, 1737, 1471, 1451, 1437, 1315, 1270, 1195, 1177, 1111, 1070, 1025, 991, 915, 853, 802, 731, 711 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 412 (<1) $[M^{+\bullet}]$, 174 (33), 146 (26), 105 (100), 77 (18); HRMS (EI, 70 eV): *m/z* calcd for $C_{24}H_{28}O_6$: 412.1886 $[M^{+\bullet}]$; found: 412.1889 $[M^{+\bullet}]$.

Compound 23

A magnetically stirred solution of benzoate **22** (67 mg, 0.16 mmol) in THF/methanol (3.6 mL of a 2:1 v/v mixture) was cooled to −78 °C then SmI_2 (approximately 3.5 mL of a 0.1 M solution in THF) was added dropwise until a blue color persisted. The ensuing mixture was stirred at −78 °C for a further 0.25 h then poured directly

into saturated K_2CO_3 (2 mL of a saturated aqueous solution), and the mixture thus formed was extracted with diethyl ether (4× 5 mL). The combined organic phases were washed with brine (1× 5 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting light yellow oil was subjected to column chromatography (silica, 2:3 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (R_f= 0.3), ketone **23** (42 mg, 88%) as clear, colorless oil. $[\alpha]_D^{25} = -26.9$ (c=0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.65 (s, 3H), 2.66 (m, 1H), 2.43–2.24 (complex m, 4H), 2.37–1.56 (complex m, 12H), 1.42 (m, 1H), 1.25 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=215.3, 214.3, 173.9, 54.5, 51.6, 50.1, 43.0, 42.5, 35.3, 34.9, 31.4, 29.3, 26.9, 25.1, 23.2, 20.0 ppm; IR (KBr): $\tilde{\nu}_{max}$=2948, 2871, 1728, 1706, 1438, 1383, 1296, 1261, 1172, 1100 cm^{-1}; MS (EI, 70 eV): m/z (%): 292 (5) [$M^{+\bullet}$], 277 (25), 245 (38), 206 (48), 205 (100); HRMS (EI, 70 eV): m/z calcd for $C_{17}H_{24}O_4$: 277.1440 [$M-{}^{\bullet}CH_3$]$^+$; found: 277.1437 [$M-{}^{\bullet}CH_3$]$^+$.

Compound 24

A magnetically stirred solution of Ph_3PCH_3Br (147 mg, 0.41 mmol) in THF (1 mL) maintained at 0 °C was treated with KO*t*Bu (43 mg, 0.38 mmol), and the resulting mixture was allowed to warm to 18 °C, stirred at this temperature for 1 h, then cooled again to 0 °C. A solution of compound **24** (27 mg, 0.09 mmol) in THF (1 mL) was then added dropwise to the now yellow reaction mixture. After the addition was complete, the reaction mixture was allowed to warm to 18 °C, then kept at this temperature for 16 h before being quenched with NH_4Cl (5 mL of a saturated aqueous solution) and extracted with diethyl ether (5×5 mL). The combined organic phases were washed with brine (1×5 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography (silica, 1:20 v/v ethyl acetate/hexane→1:10 v/v ethyl acetate/hexane gradient elution); two fractions, A and B, were obtained.

Concentration of fraction A (R_f=0.9 in 2:3 v/v ethyl acetate/hexane) afforded the twofold methylenation product (3.5 mg, 13%) as a clear, colorless oil. $[\alpha]_D^{25} = -46.0$ (c=0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.76 (s, 1H), 4.75 (m, 1H), 4.63 (s, 1H), 4.59 (m, 1H), 3.66 (s, 3H), 2.43–2.15 (complex m, 4H), 2.10–2.04 (complex m, 3H), 1.97–1.80 (complex m 2H), 1.74–1.56 (complex m, 5H), 1.49–1.33 (complex m, 3H), 1.25–1.14 (complex m, 1H), 1.11 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.8, 154.1, 152.0, 106.5, 105.2, 51.5, 47.4, 42.6, 42.1, 38.1, 36.4, 33.3, 32.9, 29.9, 29.1, 28.1, 27.0, 23.3 ppm (one signal obscured or overlapping); IR (KBr): $\tilde{\nu}_{max}$=2929, 2865, 1740, 1636, 1462, 1435, 1376, 1287, 1192, 1171, 877 cm^{-1}; MS (EI, 70 eV): m/z (%): 288 (17) [$M^{+\bullet}$], 273 (15), 207 (62), 201 (100), 173 (36), 145 (45), 13 (42), 91 (48); HRMS (EI, 70 eV): m/z calcd for $C_{19}H_{28}O_2$: 288.2089 [$M^{+\bullet}$]; found: 288.2079 [$M^{+\bullet}$].

Concentration of fraction B (R_f=0.7 in 2:3 v/v ethyl acetate/hexane) afforded compound **24**[12e] (10 mg, 37% yield) as a clear, colorless oil. $[\alpha]_D^{25} = -17.6$ (c=0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.82 (br s, 1H), 4.65 (br s, 1H), 3.65 (s, 3H), 2.59 (m, 1H), 2.35 (m, 1H), 2.04–2.26 (complex m, 5H), 1.92 (m, 1H), 1.75–1.47 (complex m, 8H), 1.33–1.23 (complex m, 2H), 1.18 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): see Table 1; IR (KBr): $\tilde{\nu}_{max}$=2918, 2867, 1738, 1706, 1649, 1436, 1378, 1292, 1260, 1194, 1172, 912, 732 cm^{-1}; MS (ESI$^+$): m/z (%): 313 (100) [M+Na]$^+$; HRMS (ESI$^+$): m/z calcd for $C_{18}H_{26}O_3$:, 313.1780 [M+Na]$^+$; found: 313.1779 [M+Na]$^+$.

The yield of compound **24** could be increased to 63% if the reaction was conducted at 0 °C for 0.5 h rather than between 0 and 18 °C for 16 h.

Compound 25

Following the procedure of Yoshimitsu et al.,[12e] a magnetically stirred solution of compound **24** (36 mg, 0.12 mmol) in dichloromethane (12 mL) maintained at 18 °C was treated with lithium iodide (164 mg, 1.24 mmol), hexamethyldisilazane (520 μL, 2.48 mmol), and trimethylsilyl chloride (160 μL, 1.24 mmol). The ensuing mixture was allowed to stir at 18 °C for 1 h, then treated with $NaHCO_3$ (5 mL of a saturated aqueous solution) before being extracted with diethyl ether (3×10 mL). The combined organic phases were washed with brine (2×5 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing light yellow oil was treated with freshly prepared IBX-NMO (500 μL of a 0.4 M solution in DMSO, 0.18 mmol), and the reaction mixture was stirred at 60 °C for 16 h before being cooled, then treated with $NaHCO_3$ (4 mL of a saturated aqueous solution) and extracted with diethyl ether (5×4 mL). The combined organic phases were washed with brine (2×2 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light yellow oil. Subjection of this material to flash chromatography (silica, 1:7 v/v ethyl acetate/hexane elution) afforded two fractions, A and B.

Concentration of fraction A (R_f=0.5(0) in 1:4 v/v ethyl acetate/hexane) afforded the starting ketone **24** (7 mg, 19% recovery), which was identical in all respects to an authentic sample.

Concentration of fraction B (R_f=0.4(7) in 1:4 v/v ethyl acetate/hexane) afforded enone **25**[12e] (19 mg, 53% at 81% conversion) as a clear, colorless oil. $[\alpha]_D^{25} = +9.7$ (c=1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.46 (d, J=10.4 Hz, 1H), 5.84 (d, J=10.4 Hz, 1H), 4.64 (m, 1H), 4.68 (m, 1H), 3.65 (s, 3H), 2.42 (m, 1H), 2.31 (dm, J= 16.0 Hz, 1H), 2.26–1.91 (complex m, 6H), 1.75–1.45 (complex m, 6H), 1.16 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.0, 174.1, 154.3, 148.8, 126.2, 107.3, 51.6, 47.2, 44.5, 39.5, 36.1, 35.9, 29.8, 29.3, 28.0, 26.6, 25.9, 21.2 ppm; IR (KBr): $\tilde{\nu}_{max}$=2924, 2862, 1739, 1674, 1451, 1436, 1383, 1357, 1288, 1262, 1228, 1172, 1122, 1092, 1077, 1019, 884, 826, 802 cm^{-1}; MS (ESI$^+$): m/z (%): 311 (100) [M+Na]$^+$; HRMS (ESI$^+$): m/z calcd for $C_{18}H_{24}O_3$: 311.1623 [M+Na]$^+$; found: 311.1624 [M+Na]$^+$.

Compound 26

Following the procedure of Yoshimitsu et al.,[12e] a magnetically stirred solution of compound **25** (37 mg, 0.13 mmol) in THF (1.5 mL) maintained at 18 °C was treated with sodium hydroxide (1.5 mL of a 1 M aqueous solution). After 48 h, the reaction mixture was diluted with water (4.0 mL) and brine (2.0 mL), then washed with diethyl ether (2×5 mL). The separated aqueous phase was acidified with HCl (approximately 1.5 mL of a 1.2 M aqueous solution) and extracted with diethyl ether (3×5 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give carboxylic acid **26**[12e] (31 mg, 88%) as a clear, colorless oil. $[\alpha]_D^{25} = +10.0$ (c=0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.47 (d, J=10.0 Hz, 1H), 5.84 (d, J=10.0 Hz, 1H), 4.85 (m, 1H), 4.69 (m, 1H), 2.43 (br s, 1H), 2.34–2.24 (complex m, 3H), 2.15–2.03 (complex m, 3H), 2.00–1.94 (complex m, 2H), 1.75–1.46 (complex m, 6H), 1.17 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.2, 178.3, 154.4, 148.7, 126.2, 107.4, 47.2, 44.5, 39.6, 36.1, 35.9, 29.5, 29.0, 28.0, 26.6, 25.8, 21.1 ppm; IR (KBr): $\tilde{\nu}_{max}$= 2932, 2867, 1708, 1674, 1455, 1293, 1181, 1124, 1093, 1078, 872, 827, 733 cm^{-1}; MS (ESI$^+$): m/z (%): 297 (100) [M+Na]$^+$; HRMS (ESI$^+$): m/z calcd for $C_{17}H_{22}O_3$: 297.1467 [M+Na]$^+$; found: 297.1468 [M+Na]$^+$.

This material was used directly in the next step of the reaction sequence.

Compound 2 ((−)-Platencin)

Following the procedure of Yoshimitsu et al.,[12e] a magnetically stirred solution of compound **26** (31 mg, 0.11 mmol) in acetonitrile (1.1 mL) maintained at 18 °C was treated with triethylamine (47 μL, 0.34 mmol), DMAP (28 mg, 0.23 mmol), and then DCC (150 μL of a 1.0 M solution in dichloromethane, 0.15 mmol). After 7.5 h, a solution of 3-amino-2,4-dihydroxybenzoic acid (38 mg, 0.23 mmol) in DMF (0.31 μL) was added to the reaction mixture, and stirring was then continued for another 70 h. The ensuing mixture was subjected, without concentration or workup, to flash chromatography (silica, 80:20:1:0.5:0.5 v/v ethyl acetate/hexane/methanol/acetic acid/water elution) to afford, after concentration of the relevant fractions ($R_f = 0.2$), platencin (**2**)[27] (20 mg, 42%) as a white, crystalline solid. $[\alpha]_D^{18} = -5.7$ ($c = 0.2$, CH_3OH) (lit.[27] $[\alpha]_D^{20} = -15.0$ ($c = 0.2$, CH_3OH)); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 11.57$ (br s, 1H), 11.24 (br s, 1H), 8.23 (s, 1H), 7.61 (d, $J = 9.2$ Hz, 1H), 6.57 (d, $J = 10.4$ Hz, 1H), 6.52 (d, $J = 9.2$ Hz, 1H), 5.92 (d, $J = 10.4$ Hz, 1H), 4.87 (s, 1H), 4.70 (s, 1H), 2.47–2.33 (complex m, 4H), 2.20–2.09 (complex m, 2H), 2.05–1.98 (complex m, 2H), 1.87–1.74 (complex m, 4H), 1.62–1.52 (complex m, 2H), 1.23 ppm (s, 3H) (signal due to one proton not observed); ^{13}C NMR (200 MHz, $CDCl_3$): see Table 2; IR (KBr): $\tilde{\nu}_{max} =$ 3296, 2923, 2861, 1651, 1596, 1533, 1377, 1289, 1237, 1180, 1151, 1057, 906, 880, 792, 730 cm^{-1}; MS (ESI^-): *m/z* (%): 424 (100) $[M-H]^-$; HRMS (ESI^-): *m/z* calcd for $C_{24}H_{27}NO_6$: 424.1760 $[M-H]^-$; found: 424.1760 $[M-H]^-$.

Crystallographic Studies

Crystallographic Data for Compound 5 (P = Bn)

Formula: $C_{26}H_{32}O_4$; $M_r = 408.54$; $T = 200$ K; orthorhombic, space group $P2_12_12$; $Z = 4$; $a = 9.5997(2)$, $b = 30.6320(6)$, $c = 7.6648(2)$ Å; $V = 2253.90(9)$ Å^3; $D_{calcd.} = 1.204$ g cm^{-3}; 2944 unique data ($2\theta_{max} = 55°$); $R = 0.031$ (for 2595 reflections with $I > 2\sigma(I)$), $wR = 0.074$ (all data), $S = 1.00$.

Crystallographic Data for Compound 17

Formula: $C_{20}H_{32}O_4$; $M_r = 336.47$; $T = 200$ K; orthorhombic, space group $P2_12_12_1$; $Z = 4$; $a = 7.8967(2)$, $b = 8.3168(3)$, $c = 27.2944(8)$ Å; $V = 1792.57(9)$ Å^3; $D_{calcd.} = 1.247$ g cm^{-3}; 2997 unique data ($2\theta_{max} = 60°$); $R = 0.031$ (for 2696 reflections with $I > 2.0\sigma(I)$), $wR = 0.079$ (all data), $S = 0.99$.

Structural Determination

Images were measured with a Nonius Kappa CCD diffractometer ($Mo_{K\alpha}$, graphite monochromator, $\lambda = 0.71073$ Å) and the data was extracted using the DENZO package.[30] Structure solution was carried out by direct methods (SIR92).[31] The structures of compounds **5** (P = Bn) and **17** were refined using the CRYSTALS program package.[32] Atomic coordinates, bond lengths, and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre.

CCDC-1021571 (**5** (P = Bn)) and -1021572 (**17**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Keywords: chirality · cross-coupling · cycloaddition · natural products · total synthesis

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FULL PAPER

Total Synthesis

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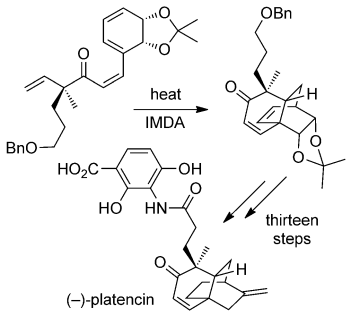
■■ – ■■

A Chemoenzymatic and Fully Stereocontrolled Total Synthesis of the Antibacterial Natural Product (−)-Platencin



Just apply enzymes, metals, and heat: A reaction sequence that involves enzymatic dihydroxylation, auxiliary-controlled alkylation, directed metalation, then Stille cross-coupling protocols provides a tetraene that engages in a thermally induced intramolecular Diels–Alder cycloaddition reaction (see scheme). The resulting adduct can be elaborated to the potent antibacterial agent (−)-platencin.