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Total Syntheses of (±)-Platencin and (−)-Platencin

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Abstract: The secondary metabolites platensimycin and platencin, isolated from the bacterial strain *Streptomyces platensis*, represent a novel class of natural products exhibiting unique and potent antibacterial activity. Platencin, though structurally similar to platensimycin, has been found to operate through a slightly different mechanism of action involving the dual inhibition of lipid elongation enzymes FabF and FabH. Both natural products exhibit strong, broad-spectrum, Gram-positive antibacterial activity to key antibiotic resistant strains, including methicillin-resistant *Staphylococcus aureus*, vancomycin-intermediate *S. aureus*, and vancomycin-resistant *Enterococcus faecium*. Described herein are our synthetic efforts toward platencin, culminating in both racemic and asymmetric preparation of the natural product. The syntheses demonstrate the power of the cobalt-catalyzed asymmetric Diels−Alder reaction and the one-pot reductive rearrangement of [3.2.1] bicyclic ketones to [2.2.2] bicyclic olefins.

Introduction

The initial euphoria associated with the discovery and development of penicillin was soon dampened by the realization that bacteria could evade its lethal activity through their ability to replicate and evolve rapidly into drug-resistant strains. The problems caused by bacterial drug resistance have been exacerbated by overuse and often misuse of antibiotics. Thus, in 1941, when penicillin was first introduced, virtually all strains of *Staphylococcus aureus* were susceptible to the novel antibiotic, but by 1944 many strains had developed resistance by evolving enzymes (e.g., β-lactamase) capable of destroying the drug before it could reach its biological target.[1] For a time, science and medicine were able to stay ahead of these menacing organisms by modifying existing antibiotics, but by the end of the 20th century humanity was faced with alarming challenges from drug-resistant bacteria. For example, a recent study estimated 94 360 cases of invasive methicillin-resistant *S. aureus* (MRSA) occurred in the United States in 2005, with 18 650 of them resulting in death.[2] Although the majority of such cases occur in hospital facilities, there has been a significant rise in the number of reported community-acquired infections. This concerning state of affairs led to a renewed surge in research activities to discover and develop new antibiotics to combat the increasing threat of bacterial resistance.

Fatty acid biosynthesis, an essential process for the survival and propagation of bacteria, is the primary means by which bacteria form fatty acids necessary for energy storage and cellular structure building blocks. This, along with the significant differences between the human and bacterial fatty acid biosynthetic machinery, makes the bacterial fatty acid synthase (FAS) pathway an attractive strategy in the fight against drug-resistant bacteria.[3,4] Taking advantage of modern biological techniques, a Merck team recently developed an antisense silencing RNA-based assay for identifying inhibitors of the type II fatty acid biosynthesis (FAS II) pathway present in bacterial cells.[3] The gene encoding the FabF and FabH condensing enzymes of FAS II was silenced, sensitizing the bacteria to inhibitors of these enzymes and allowing for a high-throughput, whole cell, target-based assay. Screening of 250 000 natural product extracts ultimately led to the discovery of the dual FabF/FabH inhibitor platencin (**1**) and its congener platencin A_1,[5] along with the selective FabF inhibitor platensimycin (**2**) (Figure 1).[6]

Platensimycin, isolated from *Streptomyces platensis* MA 7327, was discovered in a soil sample collected in Eastern Cape, South Africa, while platencin, isolated from *S. platensis* MA 7339, was found in a soil sample collected in Mallorca, Spain. The two antibiotics include in their structures the 3-amino-2,4-dihydroxybenzoic acid structural motif but differ in their more

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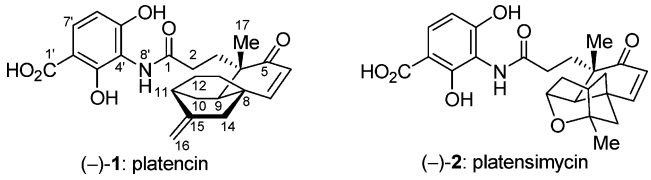

Figure 1. Molecular structures of platencin [(−)-**1**] and platensimycin [(−)-**2**].

hydrophobic ketolide portion. Platensimycin consists of a tetracyclic framework that contains a cyclic ether, whereas platencin features an exclusively carbocyclic framework with only three rings. Like its sibling, platencin exhibits potent and broad *in vitro* and *in vivo* antibiotic activity against Gram-positive bacteria, including activity against a variety of drug-resistant bacteria such as MRSA (1 μg/mL vs 0.5 μg/mL for platensimycin) and vancomycin-resistant *Enterococcus faecium* (VREF, <0.06 μg/mL vs 0.01 μg/mL for platensimycin). Platencin also exhibited comparable *in vivo* efficacy in a continuous infusion mouse model against *S. aureus* infection with no indication of toxicity. As might be expected from their close structural relationship, platencin and platensimycin operate through similar mechanisms of action. Each was shown to inhibit lipid biosynthesis in whole-cell labeling studies, but neither exhibited any activity against nucleic acid, protein biosynthesis, or cell wall construction. At a molecular level, platensimycin is a potent and selective inhibitor of FabF, the elongation condensing enzyme; however, platencin inhibits this enzyme with much lower potency. Platencin derives its overall potency from a dual inhibition mechanism involving moderate inhibition of both FabF and the initiation condensing enzyme FabH.[5] It should be noted that a recent report questioned the validity of the strategy to combat bacteria based on fatty acid biosynthesis since bacteria were found to sequester the needed fatty acids from their hosts.[4]

The structural novelty and potent activity of these antibiotics has attracted considerable attention, with a number of total syntheses of platensimycin[7] and platencin[8] reported to date. Several reports have also described the design and synthesis of related structures,[9] some of which are also potent antibiotics.[9a,b,d,e] In 2008, we published our preliminary results culminating in the first total synthesis of platencin (**1**) through an asymmetric route.[8a] Herein we present the full account of our work in this area that led to considerable improvements of the originally developed route.

Results and Discussion

Our total synthesis endeavors toward platencin, first as a racemate and then in its enantiomerically pure form, proceeded through a number of phases and evolved into a highly efficient and streamlined process. Below we describe these studies in approximately the chronological sequence they occurred.

Initial Retrosynthetic Analysis. Figure 2 shows our retrosynthetic analysis of **1**. Only a cursory inspection of the platencin molecule was needed to identify the first retrosynthetic disconnection, that of the amide bond, which revealed fragments **3** and **4** as potential precursors. Aniline derivative **3** was thought to be the ideal precursor for reasons of convenience and practicality, given the expected sensitivity of the exocyclic olefinic bond of the final product and the neutral conditions under which the TMSE group could be removed. Applying two consecutive retrosynthetic alkylations on tricyclic fragment **4** led to enone **5** as the required key intermediate for the ketolide domain of the molecule. The latter was envisioned to arise from a ketoaldehyde, derived from **6** (R = H or protecting group) through an aldol condensation. A radical pathway starting from xanthate **9a** or hydrazone **12**, and proceeding through species **8** (R = H or protecting group) and **7** (R = H or protecting group), was then traced on the basis of a homoallylic radical rearrangement.[10] Our initial analysis adopted xanthate **9a** as the potential precursor of the first radical species of the envisioned cascade and connected it to ketone **10**. Disconnection of the indicated carbon−carbon bonds within [3.2.1] bicyclic system **10** through a retro conjugate addition of an allyl group and a retro palladium-catalyzed cyclization revealed enol ether **11** as a potential precursor.[10a] The latter intermediate was then traced back to hydroxymethyl enone **15** as a starting material. Our alternative plan makes use of a hydrazone radical precursor of type **12**, which can be traced through ketone **13** by a similar retrosynthetic sequence, employing a gold(I)-catalyzed cyclization[11] of an enol ether such as **14** back to acetylenic hydroxymethyl enone **16**.

First-Generation Synthesis of Racemic Tricyclic Enone (±)-5. As part of our preliminary studies toward platencin (**1**), we explored the xanthate-based homoallylic rearrangement route to tricyclic ketone (±)-**5** using racemic materials (Scheme 1).

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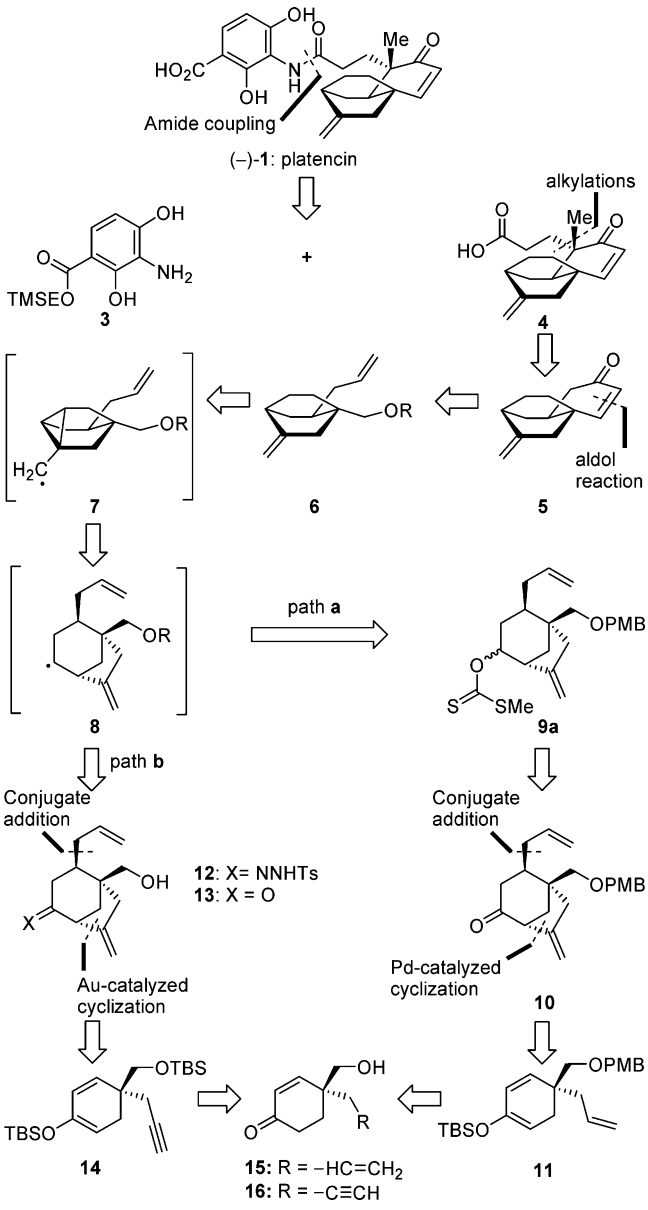
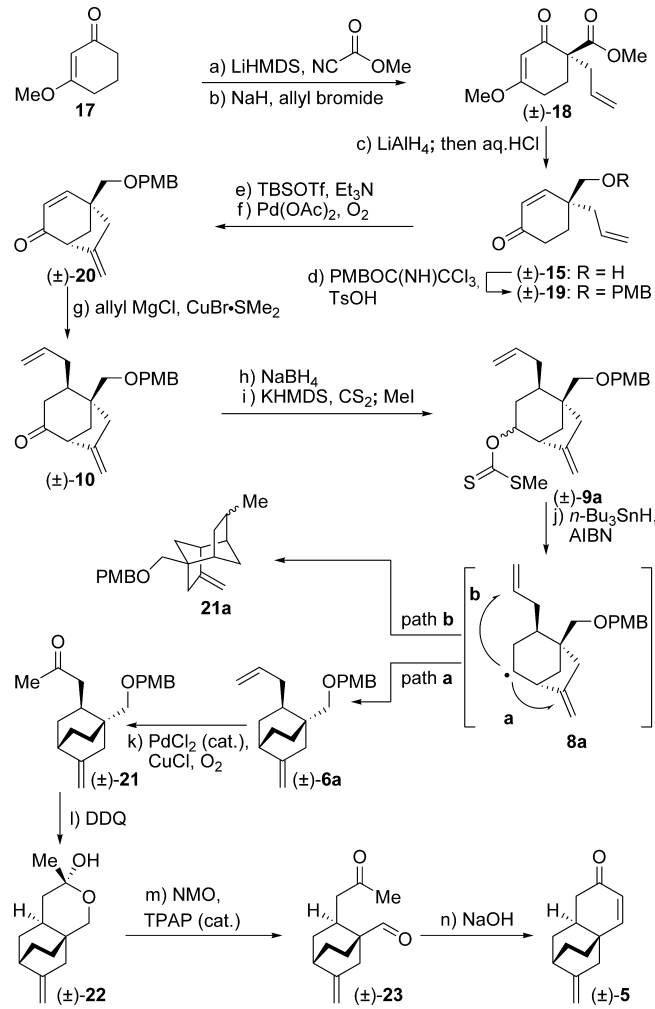


Figure 2. Retrosynthetic analysis of platencin [(−)-**1**].

Thus, treatment of enone **17** with LiHMDS in THF at −78 °C followed by addition of Mander's reagent (MeOCOCN)[12] gave the corresponding carboxymethylated product, which was allylated to afford compound (±)-**18** in 73% overall yield. Reduction of the latter with $LiAlH_4$ followed by acidic (aqueous HCl) workup led to enone (±)-**15** (82% yield), the free hydroxyl group of which was protected as a PMB ether to afford (±)-**19** (85% yield). Treatment of ketone (±)-**19** with TBSOTf in the presence of Et_3N led to the corresponding TBS enol ether (91% yield), which underwent smooth oxidative cycloalkenylation upon exposure to a catalytic amount of $Pd(OAc)_2$ under an atmosphere of O_2 to afford bicyclic system (±)-**20** in 85% yield, along with traces of the endocyclic olefinic byproduct. Copper-catalyzed conjugate addition of allyl magnesium chloride to (±)-**20** ($CuBr\cdot Me_2S$, −78 → −40 °C) gave ketone (±)-**10** in 86% yield as a single diastereoisomer. Sodium borohydride reduction of (±)-**10** gave a mixture of corresponding alcohols (97% yield, *ca.* 2:1 *dr*) that was converted to xanthates (±)-**9a** by the standard procedure.[13] Generation of the radical species from (±)-**9a** by treatment with *n*-Bu_3SnH-AIBN in toluene at 110 °C led to the desired [2.2.2] bicyclic product (±)-**6a** in excellent yield (92%), although the latter was contaminated with byproduct **21a** (*ca.* 4:1 ratio), arising from the alternative mode of cyclization (5-*exo*-trig, path b). The individual xanthate diastereomers obtained from the diasteroemerically pure alcohol precursors gave identical results, confirming that the stereochemistry of the radical precursor was inconsequential to the outcome of the reaction with regard to both yield and product distribution. The mixture of (±)-**6a** and **21a** was inseparable by chromatography, but Wacker oxidation[14] furnished ketone

Scheme 1. Synthesis of Racemic Tricyclic Enone [(±)-**5**][a]



[a] Reagents and conditions: (a) LiHMDS (1.0 M in THF, 1.2 equiv), methyl cyanoformate (1.2 equiv), THF, −78 → 0 °C, 2 h, 92%; (b) NaH (1.5 equiv), allyl bromide (1.5 equiv), THF, 0 → 25 °C, 2 h, 79%; (c) $LiAlH_4$ (1.0 M in THF, 1.2 equiv), Et_2O, 0 → 25 °C, 3 h; then HCl (2 M in MeOH, 6.0 equiv), 25 °C, 16 h, 82%; (d) $PMBOC(NH)CCl_3$ (2.0 equiv), TsOH (0.1 equiv), CH_2Cl_2, 0 → 25 °C, 2.5 h, 85%; (e) TBSOTf (2.5 equiv), Et_3N (4.0 equiv), THF, 0 °C, 1 h, 91%; (f) $Pd(OAc)_2$ (0.1 equiv), O_2 (balloon), DMSO, 45 °C, 12 h, 85%; (g) $CuBr\cdot Me_2S$ (2.0 equiv), allyl magnesium chloride (1.7 M in THF, 4.0 equiv), THF, −78 → −40 °C, 2 h, 86%; (h) $NaBH_4$ (2.5 equiv), MeOH, −5 → 25 °C, 30 min, 97%; (i) KHMDS (0.5 M in toluene, 5.0 equiv), CS_2 (10.0 equiv), MeI (10.0 equiv), THF, −78 → 25 °C, 2.5 h, 92%; (j) *n*-Bu_3SnH (2.0 equiv), AIBN (0.08 equiv), toluene, 110 °C, 8 h, 92%; (k) $PdCl_2$ (0.25 equiv), CuCl (1.5 equiv), O_2 (balloon), DMF/H_2O (6.6:1), 25 °C, 24 h, 81%; (l) DDQ (1.2 equiv), CH_2Cl_2/H_2O (20:1), 25 °C, 1 h, 53%; (m) TPAP (0.03 equiv), NMO (6.5 equiv), CH_2Cl_2, 25 °C, 4 h, 54%; (n) NaOH (6.0 equiv), EtOH, 25 °C, 8 h, 99%.

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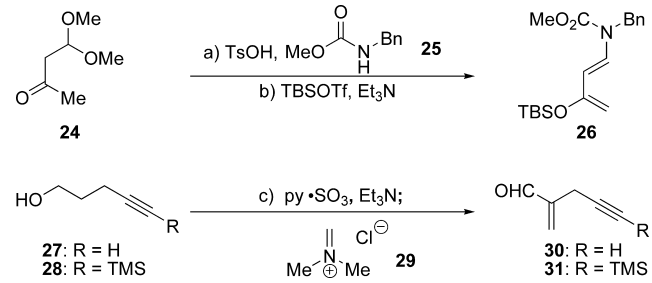
(±)-**21** (81% yield), which was easily separated from the unreactive byproduct **21a**. The product obtained by DDQ deprotection of PMB-protected intermediate (±)-**21** (53% yield) was found to exist in its lactol form [(±)-**22**], a fact that did not deter its oxidation to keto aldehyde (±)-**23** [NMO, TPAP (cat.), 54% yield].[15] Furthermore, the intended aldol condensation of (±)-**23** to racemic enone (±)-**5** proceeded under the influence of NaOH in ethanol in excellent yield, demonstrating the viability of this radical-based strategy for the synthesis of platencin. As additional intelligence, this initial study provided useful information regarding the stability of the PMB protecting group, the which, in a number of steps, particularly the Wacker oxidation, was less than stellar, prompting us to consider a more robust alternative for our first asymmetric approach to enone **5**.

Asymmetric Synthesis of Enone (+)-5. In contemplating an asymmetric version of the radical rearrangement approach to enone (±)-**5**, we sought to prepare an enone such as **15** or **16** (Figure 2) as single enantiomers, knowing that all the other centers could then be set through substrate control. One approach would be to effect an asymmetric variant of the alkylation reaction used to prepare ketoester (±)-**18** (Scheme 1). Palladium-catalyzed asymmetric allylation[16] reactions of similar ketoesters and their derivatives have been described in the literature;[17,18] however, factors including unsatisfactory *ee* in our system, lack of readily available catalysts (particularly for large scale use), and the fact that any such approach would be limited to the introduction of an allyl substituent led us to favor an asymmetric Diels–Alder reaction strategy.[19]

Rawal and co-workers have described the asymmetric Diels–Alder reaction of substituted 1-amino-3-silyloxybutadienes using the Jacobsen Cr(III)-salen catalyst.[20] This system appeared attractive for our purposes since it was reported to offer access to highly enantiomerically enriched 4,4-disubstituted cyclohexenones. The application of this reaction to the asymmetric synthesis of **16** (Figure 2) required diene **26** and dienophile **30**, the syntheses of which are summarized in Scheme 2.

Diene **26** was prepared from commercially available ketone **24** according to literature procedures,[21] while the rather volatile

Scheme 2. Construction of Diene **26** and Dienophiles **30** and **31**[a]



[a] Reagents and conditions: (a) **25** (1.0 equiv), **24** (2.0 equiv), TsOH (0.05 equiv), $CHCl_3$, 65 °C, 24 h, 89%; (b) TBSOTf (1.1 equiv), Et_3N (3.0 equiv), Et_2O, −78 → 0 °C, 1 h, 96%; (c) py•SO_3 (2.0 equiv), DMSO (5.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, 25 °C, 2 h; then CH_2NMe_2Cl (**29**) (1.5 equiv), 25 °C, 12 h, R = H, 53%, R = TMS, 92%.

dienophile **30** was synthesized from acetylenic alcohol **27** in one pot through a two-step process involving oxidation (py•SO_3, DMSO)[22] and addition of Eschenmoser's salt (**29**, 53% overall yield).[23] Reaction of diene **26** (excess) with dienophile **30** (Scheme 3) in the presence of catalyst **32** (see Figure 4) at −60 °C resulted in an impressive 92% yield of cyclohexene (−)-**33**, formed in 93% *ee* [determined by ^{1}H NMR spectroscopic analysis of the Mosher ester derived from downstream product (−)-**16**]. We subsequently realized that the enantioselectivity of this reaction ranged between 85 and 93% *ee*, presumably due to its sensitivity to temperature and the difficulties in maintaining a steady cryogenic temperature for the extended reaction time (60 h). This deficiency, coupled to the poor reproducibility of the results on larger scales, prompted subsequent studies that resulted in considerable improvements, as will be discussed later. Returning to Diels–Alder product (−)-**33**, it was found that its intended conversion to enone (−)-**16** (Scheme 3) could be achieved by reduction with $LiAlH_4$ followed by exposure of the resulting hydroxy carbamate (**34**) to aqueous acid (63% overall yield).

At this stage we selected the SEM group to protect the primary hydroxyl group in place of the PMB group used previously, by virtue of its robustness and linear shape, which we reasoned would not hinder any of the subsequently intended steps. Thus, treatment of (−)-**16** with SEMCl in the presence of Et_3N and 4-DMAP (cat.) furnished derivative (−)-**35** (94% yield), which was converted to TIPS diene (−)-**36** (TIPSOTf, Et_3N, 97% yield) in preparation for the crucial cycloalkenylation reaction. To this end, acetylenic enol ether (−)-**36** was exposed to the action of the cationic gold catalyst formed *in situ* from $AuCl(PPh_3)$ and $AgBF_4$, conditions that led, within 30 min at room temperature, to the desired bicyclic enone (+)-**37** in 94% yield.[11] Note that our initial study toward this type of [3.2.1] bicyclic system involved a palladium-catalyzed cycloalkenylation process of a similar substrate containing a terminal olefin rather than the terminal acetylene contained within (−)-**36** [i.e., (±)-**19** → (±)-**20**, Scheme 1]. In contrasting the two processes, one can easily recognize the advantage of the latter method in terms of catalyst loading (2% gold catalyst vs 10% palladium catalyst), reaction time (<30 min at 25 °C vs 12 h at 45 °C), and yield (94% vs 85%). Conjugate addition of an allyl group to enone (+)-**37** (allyl MgCl, CuBr•Me_2S) proceeded smoothly

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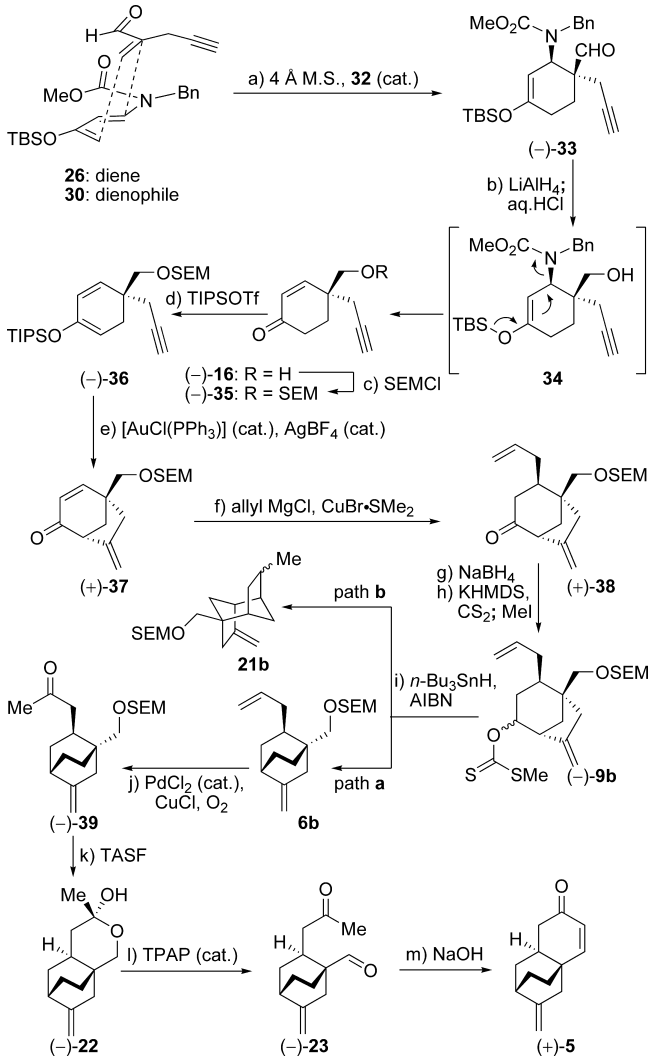
(23) (a) Kinast, G.; Tietze, L.-F. *Angew. Chem., Int. Ed.* **1976**, *15*, 239. This reagent is easily prepared on a large scale using a procedure previously reported; see: (b) Danishefsky, S.; Chackalamannil, S.; Harrison, P.; Silvestri, M. *J. Am. Chem. Soc.* **1985**, *107*, 2474.

Scheme 3. First-Generation Catalytic Asymmetric Synthesis of Tricyclic Enone (+)-**5**[a]



[a] Reagents and conditions: (a) **30** (1.0 equiv), **26** (1.7 equiv), **32** (0.05 equiv), 4 Å M.S., CH_2Cl_2, −60 °C, 60 h, 92%; (b) $LiAlH_4$ (1.0 M in THF, 1.5 equiv), Et_2O, −78 → −40 °C, 2 h; then HCl (2 M in MeOH, 10.0 equiv), 25 °C, 16 h, 63%; (c) SEMCl (1.2 equiv), Et_3N (4.0 equiv), 4-DMAP (0.1 equiv), THF, 70 °C, 16 h, 94%; (d) TIPSOTf (1.5 equiv), Et_3N (3.0 equiv), −78 → 0 °C, 1 h, 97%; (e) [AuCl(PPh$_3$)] (0.02 equiv), $AgBF_4$ (0.02 equiv), toluene/MeOH (10:1), 25 °C, 30 min, 94%; (f) allyl magnesium chloride (1.7 M in THF, 4.0 equiv), CuBr•Me_2S (2.0 equiv), THF, −78 °C, 1.5 h, 74%; (g) $NaBH_4$ (2.5 equiv), MeOH, −5 → 25 °C, 1 h, 97%; (h) CS_2 (10.0 equiv), KHMDS (0.5 M in toluene, 5.0 equiv), MeI (5.0 equiv), THF, −78 → 25 °C, 2.5 h, 100%; (i) *n*-Bu_3SnH (2.0 equiv), AIBN (0.08 equiv), toluene, 100 °C, 20 min, 92%; (j) $PdCl_2$ (0.25 equiv), CuCl (1.5 equiv), O_2 (balloon), DMF/H_2O (6.6:1), 25 °C, 24 h, 50% (two steps); (k) TASF (10.0 equiv), DMPU, 80 °C, 1.5 h, 63% (84% based on 25% recovered starting material); (l) TPAP (0.03 equiv), NMO (6.5 equiv), CH_2Cl_2, 25 °C, 4 h, 54%; (m) NaOH (6.0 equiv), EtOH, 25 °C, 8 h, 99%.

to afford ketone (+)-**38** as a single diastereomer in 74% yield. Ketone (+)-**38** was converted, as before, to a mixture of xanthates (−)-**9b** (*ca.* 2:1 *dr*) by the standard two-step sequence ($NaBH_4$; KHMDS, CS_2, MeI) in 97% overall yield. The radical rearrangement sequence of (−)-**9b** proceeded as before, giving a high yield of diene **6b** (92%) along with a minor quantity of byproduct **21b**.[24] Wacker oxidation also proceeded as expected to provide ketone (−)-**39** in 50% overall yield from (−)-**9b**; however, removal of the SEM group proved difficult. A systematic investigation of conditions identified nucleophilic fluoride sources as the only reagents capable of delivering the

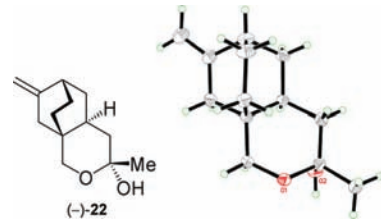


Figure 3. ORTEP of (−)-**22** derived from X-ray crystallographic analysis (non-hydrogen atoms are shown as 30% ellipsoids).

desired product, with TASF in DMPU being the optimum choice, giving up to 63% yield of lactol (−)-**22** along with *ca.* 25% recovered starting material (−)-**39**. Interestingly, lactol (−)-**22** was isolated as a single diastereoisomer regardless of which precursor was used. This compound crystallized from $CDCl_3$/CH_2Cl_2 as colorless needles (mp 115−117 °C), a circumstance that allowed its X-ray crystallographic analysis (see ORTEP2, Figure 3) and, thus, confirmed its structure as depicted in (−)-**22**.[25] The subsequent oxidation and aldol condensation steps proceeded well, as before, to afford enantiomerically enriched tricyclic enone (+)-**5**, as shown in Scheme 3.

Optimization of the Catalytic Asymmetric Synthesis of Enone (+)-5. The asymmetric synthesis of enone (+)-**5** described above proved a level of efficiency to allow us to complete the total synthesis of platencin [(−)-**1**] in a highly enantioenriched form (*vide infra*);[8a] however, we identified opportunities to improve the route at several steps while maintaining the overall strategy. These included the asymmetric Diels−Alder reaction, the radical rearrangement sequence, and the protecting group choice. We were able to optimize each of these processes, which, in turn, influenced the overall efficiency of the synthesis, leading to an effective and streamlined route.

A significant practical drawback in our original asymmetric route is the volatility of dienophile **30**. This enal was prepared in a highly efficient one-pot procedure that provided the product in excellent purity, but the isolated yield was only moderate, even when solvents were removed by careful distillation through a Vigreaux column. This issue was addressed by the simple inclusion of a TMS group on the alkyne. TMS-capped enal **31** was prepared from commercially available acetylene **28** using the same one-pot procedure and could be isolated by flash column chromatography or distillation in 92% yield, as shown in Scheme 2. We investigated the use of both dienophiles during optimization studies to improve the practicality of the asymmetric Diels−Alder reaction with the previously discussed Cr(III)-based catalyst (**32**) as well as a similar Co(III)-based system (**40**, Figure 4).

In these investigations, we were guided by the findings of the Rawal group in their development of asymmetric Diels−Alder reactions of aminosilyloxy dienes;[26] our results are summarized in Table 1.

We were able to optimize the reaction of our original dienophile (**30**) with diene **26** and chromium catalyst **32** (entries 1−3) to 92% yield and 93% *ee*, although, as mentioned above,

(24) Tricyclic byproduct **21b** was characterized by NMR spectroscopic analysis; structures of the corresponding byproduct, such as **21a** and **21c**−**e**, were assigned by analogy.

(25) CCDC-671740 contains the crystallographic data for compound (−)-**22**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

(26) Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 5950. (b) McGilvra, J. D.; Rawal, V. H. *Synlett* **2004**, *13*, 2440.

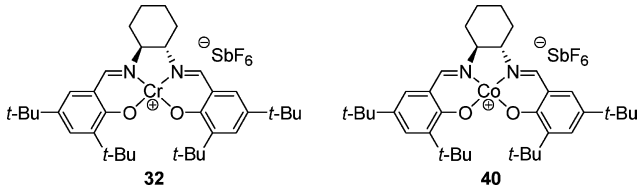
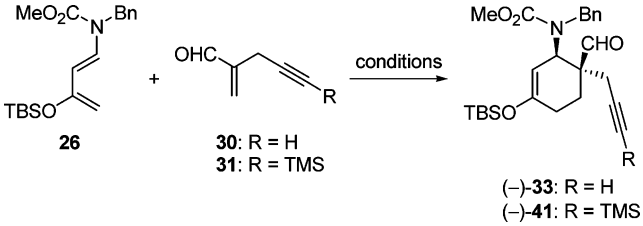


Figure 4. Molecular structures of Cr(III)- and Co(III)-salen catalysts **32** and **40**.

Table 1. Optimization of the Catalytic Asymmetric Diels–Alder Reaction[a]



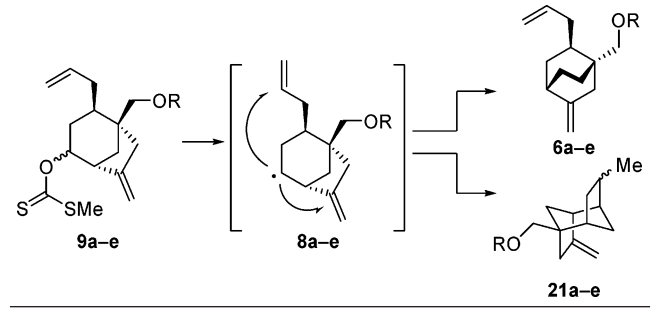
entry	dienophile	diene (equiv)	catalyst (mol %)	temp (°C)	time (h)	yield (%)	*ee* (%)
1	**30**	1.5	**32** (5)	25	60	85	75
2	**30**	1.5	**32** (5)	−40	60	87	85
3	**30**	2.0	**32** (5)	−60	60	92	93[b]
4	**30**	1.8	**40** (5)	0	2	79	76
5	**31**	1.8	**40** (5)	0	1.5	92	93
6	**31**	1.5	**40** (1)	0	0.5	93	94
7	**31**	1.1	**40** (0.1)	0	0.5	97	96
8	**31**	1.5	none	25	0.5	5	0

[a] Reactions were carried out on 0.1−1.0 mmol scale with 1.0 equiv of dienophile **30** or **31** in the presence of 4 Å M.S. in CH_2Cl_2. [b] Enantiomeric excess (*ee*) ranged from 86 to 93%.

the reaction was very slow and somewhat unreliable with respect to the *ee* of the product. The use of cobalt-salen catalyst **40** (entry 4) with dienophile **30** resulted in a much faster reaction at the expense of reduced *ee* and somewhat reduced yield; however, changing to dienophile **31** brought significant improvements. We tentatively ascribe this observation to the improved purity of the less volatile dieneophile. Further study of the cobalt-catalyzed reaction of **31** with **26** led to the optimized conditions (entry 7), which use only a slight excess of diene and give an almost quantitative yield of product (−)-**41** with excellent enantioselectivity (96% *ee*). Noteworthy features of the Diels–Alder reaction using catalyst **40** and dienophile **31** include the much increased reaction rate (0.5 h vs 60 h with catalyst **32**) and the improved selectivity at more convenient temperatures (0 °C vs −60 °C). We also observed that the Diels–Alder reaction between dienophile **31** and diene **26** proceeded to some extent at ambient temperature in the absence of any catalyst (entry 8).

We next turned our attention to the radical rearrangement reaction. This reaction performed as expected in our original route, but the three-step conversion of ketone (±)-**10** or (+)-**38** to (±)-**6a** (Scheme 1) or **6b** (Scheme 3) involved the use of toxic reagents in both the radical and xanthate formation steps and suffered from the formation of small but significant quantities of the 5-*exo*-trig byproduct. At this time, we were also investigating the optimum protecting group for the primary alcohol, which led to an interesting observation. When testing the radical sequence using substrates with various protecting groups, we noted that the pathway of the radical process was dependent on the nature of the protecting group used (Table 2). When smaller, linear protecting groups were used, such as

Table 2. Effect of Protecting Group on the Radical Deoxygenation Reaction[a]



entry	R (compd)	yield (%)	product ratio **6**:**21**[b]
1	MOM (**9c**)	93	5.4:1 (**6c**)
2	SEM (**9b**)	92	5.5:1 (**6b**)
3	PMB (**9a**)	92	4:1 (**6a**)
4	Ac (**9d**)	71	1:1.5 (**6d**)
5	Piv (**9e**)	65	1:2 (**6e**)

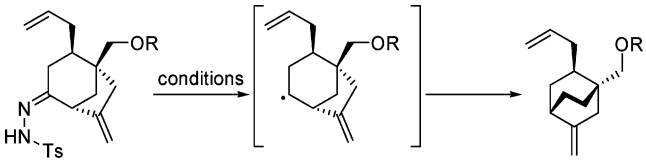
[a] Reactions were carried out on 0.01 mmol scale with 2.0 equiv of n-Bu_3SnH and 0.08 equiv of AIBN in toluene at 100 °C. [b] Ratios were determined by ^1H NMR (500 MHz) spectroscopic analysis.

MOM or SEM, the radical sequence proceeded to give the desired [2.2.2] bicyclic products (**6a**–**e**) with good selectivity over the 5-*exo*-trig byproduct (entries 1 and 2); the PMB ether gave similar selectivity, affording an approximately 4:1 mixture (entry 3). However, both acetate and pivalate esters yielded significantly lower selectivities, affording an approximately 1:2 mixture of the two products (entries 4 and 5), indicating the finely balanced nature of the selectivity between the two competing reaction manifolds. Presumably, steric interactions of the ester groups position the olefinic moiety of the allyl group in such a way as to favor the 5-*exo*-trig pathway, leading to the undesired byproduct **21a**–**e**.

In an effort to streamline the overall conversion of the ketone intermediate to the radical rearrangement product, we explored the Wolff–Kishner-type conditions for radical generation from carbonyl compounds reported by Toyota et al.[27] Table 3 summarizes our optimization studies using several hydrazone intermediates prepared from the corresponding ketones [$TsNHNH_2$, TsOH (cat.), CH_2Cl_2, 70 °C]. Our initial attempts to apply the reported $NaBH_3CN/ZnCl_2$ conditions[10b] to hydrazones **12a**–**c** (entries 1–3) failed to furnish any of the desired products, leading only to decomposition. Reasoning that the Lewis acid conditions employed were responsible for the observed outcome, we attempted the reaction with the SEM-protected hydrazone **12d** employing $NaBH_4$ in THF (entry 4), but again we observed only decomposition. Use of the milder reductant $NaBH(OAc)_3$ was also unsuccessful, this time leading to recovery of the starting material (entry 5). Further studies led us to return to $NaBH_4$ as a potential reductant in a variety of solvents. Our efforts were rewarded when we employed hydrazone **12d** and $NaBH_4$ in refluxing CH_2Cl_2/MeOH (1:1), conditions that led to 50% yield of the desired product (−)-**6b** (entry 6). These conditions were then optimized (entries 8–11) to a satisfactory level (entry 11), which required portionwise addition of $NaBH_4$ to a refluxing solution of hydrazone **12d** in CH_2Cl_2/MeOH [20:1, 70% yield of (−)-**6b**]. Furthermore, by

(27) (a) Taber, D. F.; Wang, Y.; Stachel, S. J. *Tetrahedron Lett.* **1993**, *34*, 6209. (b) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662. (c) Zard, S. Z.; Miranda, L. D. *Chem. Commun.* **2001**, 1068. (d) Taber, D. E.; Wang, Y.; Pahutski, T. F., Jr. *J. Org. Chem.* **2000**, *65*, 3861.

Table 3. Optimization of the Radical-Based Conversion of Hydrazones **12** to [2.2.2] Bicyclo Systems **6**[a]



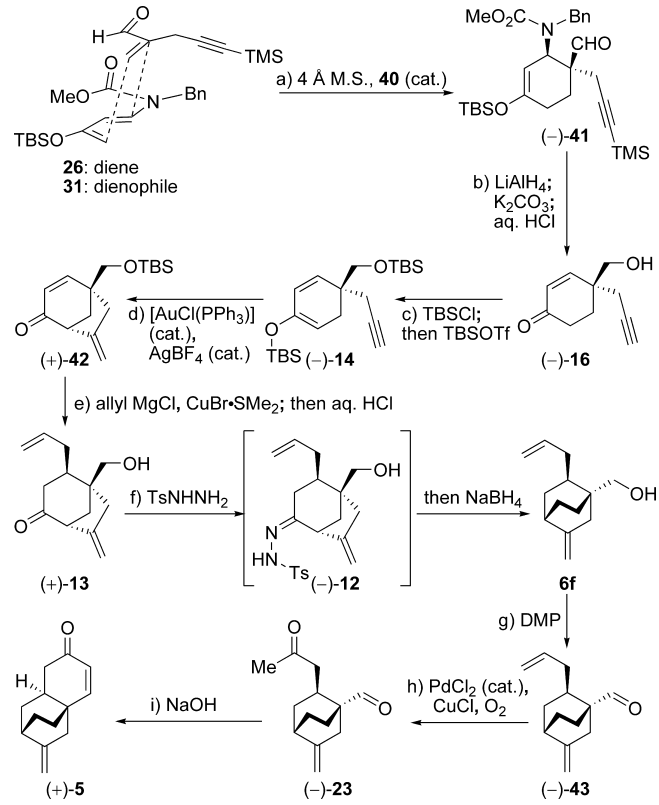
entry	R (compd)	reductant (equiv)	solvent	temp (°C)	yield (%)
1	MOM (**12a**)	$NaBH_3CN$ (3.8)[b]	THF	80	0[c]
2	PMB (**12b**)	$NaBH_3CN$ (3.8)[b]	THF	80	0[c]
3	Piv (**12c**)	$NaBH_3CN$ (3.8)[b]	THF	80	0[c]
4	SEM (**12d**)	$NaBH_4$ (1.4)	THF	90	0[c]
5	SEM (**12d**)	$NaBH(OAc)_3$ (4.0)	DCE/AcOH (9:1)	100	0[d]
6	SEM (**12d**)	$NaBH_4$ (8.0)	CH_2Cl_2/MeOH (1:1)	45	50
7	SEM (**12d**)	$NaBH_4$ (8.0)	THF/MeOH (1:1)	70	47
8	SEM (**12d**)	$NaBH_4$ (8.0)	CH_2Cl_2/MeOH (1:1)	25	0[c]
9	SEM (**12d**)	$NaBH_4$ (8.0)	CH_2Cl_2/MeOH (20:1)	45	55
10	SEM (**12d**)	$NaBH_4$ (8.0)	CH_2Cl_2/EtOH (20:1)	45	60
11	SEM (**12d**)	$NaBH_4$ (2.0 × 3)	CH_2Cl_2/MeOH (20:1)	45	70
12	H (**12**)	$NaBH_4$ (2.0 × 4)	CH_2Cl_2/MeOH (20:1)	45	74 (**6f**)

[a] Reactions were carried out on 0.1−1.0 mmol scale. [b] With 3.8 equiv of $ZnCl_2$. [c] Only decomposition observed. [d] No reaction observed.

avoiding the need for a xanthate formation step, we were able to employ the hydroxy hydrazone **12** (R = H) to produce rearranged product **6f** (R = H) under the same optimized conditions in 74% yield (Table 3, entry 12).

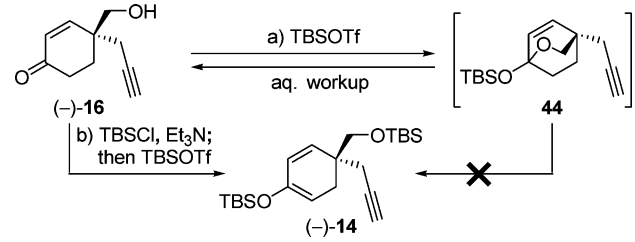
Our optimized Diels−Alder and radical rearrangement steps were then combined to furnish our second-generation asymmetric synthesis of key enone intermediate (+)-**5** (Scheme 4). Thus, following the asymmetric Diels−Alder reaction of **26** with **31**, product (−)-**41** was converted to hydroxy enone (−)-**16** in a one-pot procedure involving reduction of the aldehyde ($LiAlH_4$, Et_2O/THF), cleavage of the acetylenic TMS group by addition of MeOH and K_2CO_3, and, finally, elimination of the carbamate group by acidification with methanolic HCl. Hydroxy enone (−)-**16** was obtained in 89% overall yield and 96% *ee*. A single recrystallization of the product from hexanes/EtOAc (mp 100−102 °C) increased the *ee* to >98%. In preparation for the gold-catalyzed cyclization, we attemped to generate the bis-TBS derivative (−)-**14** from hydroxyl enone (−)-**16** by exposure of the latter to TBSOTf and Et_3N. Although a smooth reaction under these conditions was observed by TLC, upon workup only starting material was recovered. Closer monitoring and NMR spectroscopic analysis of the reaction mixture in CD_2Cl_2 revealed the formation of bicyclic ketal **44** (see Scheme 5), which apparently is stable under the reaction conditions but immediately reverts back to starting material [(−)-**16**] upon workup. To circumvent this troublesome circumstance, we employed a one-pot protocol involving sequential treatment of hydroxy enone (−)-**16**, first with TBSCl in the presence of Et_3N and 4-DMAP (capping the hydroxyl group) followed by TBSOTf (forming the TBS enol ether), conditions that led to generation of the desired bis-TBS derivative (−)-**14** in 97% yield. This material was then subjected to the gold-catalyzed ring closure conditions [2 mol % $AuCl(PPh_3)$, 2 mol % $AgBF_4$] to produce bicyclic enone (+)-**42** in 95% yield (Scheme 4). Exposure of enone (+)-**42** to allylmagnesium bromide in the presence of $CuBr\cdot SMe_2$ at −78 → −40 °C, followed by acidic workup (aqueous HCl), led to intermediate (+)-**13** in 85% overall yield, thus avoiding either specific protection or deprotection steps.

Scheme 4. Second-Generation Catalytic Asymmetric Synthesis of Tricyclic Enone (+)-**5**[a]



[a] Reagents and conditions: (a) **31** (1.0 equiv), **26** (1.05 equiv), **40** (0.1 mol %), 4 Å M.S., CH_2Cl_2, 0 °C, 97%; (b) $LiAlH_4$ (1.0 M in THF, 1.5 equiv), Et_2O, −78 → −40 °C, 2 h; then K_2CO_3 (5.0 equiv), MeOH (50 equiv), 25 °C, 5 h; then HCl (4 M in MeOH, 20.0 equiv), 25 °C, 16 h, 92%; (c) TBSCl (1.5 equiv), Et_3N (4.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 45 °C, 16 h; then TBSOTf (1.5 equiv), 0 °C, 4 h, 97%; (d) $[AuCl(PPh_3)]$ (0.02 equiv), $AgBF_4$ (0.02 equiv), toluene/MeOH (10:1), 25 °C, 30 min, 95%; (e) $CuBr\cdot Me_2S$ (2.0 equiv), allyl magnesium chloride (1.7 M in THF, 4.0 equiv), THF, −78 → −40 °C, 1.5 h; then 2 M aq HCl (10.0 equiv), 25 °C, 4 h, 85%; (f) $TsNHNH_2$ (1.2 equiv), TsOH (0.1 mol %), CH_2Cl_2, 45 °C, 1 h; then $NaBH_4$ (2.0 equiv), MeOH (7.0 equiv), 45 °C, 74%; (g) DMP (2.0 equiv), pyridine (0.1 equiv), CH_2Cl_2, 25 °C, 1.5 h, 90%; (h) $PdCl_2$ (0.25 equiv), CuCl (1.5 equiv), O_2 (balloon), DMF/H_2O (6.6:1), 25 °C, 24 h, 90%; (i) NaOH (6.0 equiv), EtOH, 25 °C, 8 h, 99%.

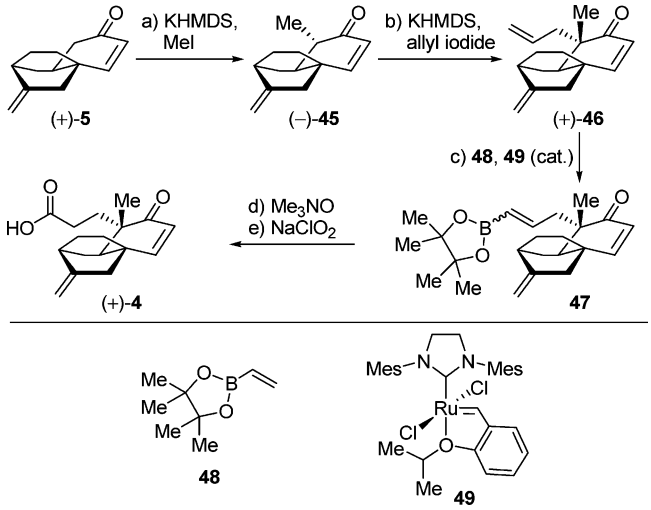
Scheme 5. Bis-silylation of Hydroxy Enone (−)-**16**[a]



[a] Reagents and conditions: (a) TBSOTf (2.5 equiv), Et_3N (5.0 equiv), CH_2Cl_2, −78 → 0 °C, 1 h; (b) TBSCl (1.5 equiv), Et_3N (4.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 45 °C, 16 h; then TBSOTf (1.5 equiv), 0 °C, 4 h, 97%.

Conversion of keto alcohol (+)-**13** to bicyclo[2.2.2]octane system (−)-**6** was easily achieved without the need to isolate intermediate hydrazone (−)-**12** (Scheme 4). Thus, formation of the hydrazone in CH_2Cl_2 with $TsNHNH_2$ and 0.1 mol % TsOH, followed by addition of MeOH and reduction as previously described, furnished (−)-**6** in 74% overall yield. The alcohol was then oxidized to aldehyde (−)-**43** with DMP, and the latter

Scheme 6. Alkylation of Tricyclic Enone (+)-**5** and Construction of Carboxylic Acid (+)-**4**[a]



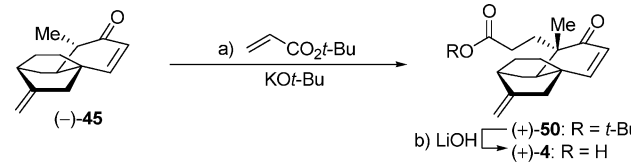
[a] Reagents and conditions: (a) KHMDS (0.5 M in toluene, 1.1 equiv), MeI (8.0 equiv), THF/HMPA (4:1), −78 → 0 °C, 2 h, 90%; (b) KHMDS (0.5 M in toluene, 4.0 equiv), allyl iodide (8.0 equiv), THF/HMPA (4:1), −78 → 0 °C, 3 h, 86%; (c) **48** (5.0 equiv), Hoveyda−Grubbs II cat. **49** (0.1 equiv), benzoquinone (0.1 equiv), benzene, 70 °C, 1 h, 75%; (d) Me_3NO (5.0 equiv), THF, 70 °C, 1 h, 63%; (e) $NaClO_2$ (3.0 equiv), NaH_2PO_4 (5.0 equiv), 2-methyl-2-butene (10.0 equiv), *t*-BuOH/H_2O (1:1), 25 °C, 20 min, 82%.

compound was subjected to Wacker oxidation [$PdCl_2$ (cat.), CuCl, O_2] to afford keto aldehyde (−)-**23** in 90% yield, thus obviating the troublesome SEM deprotection and avoiding the intermediacy of lactol (−)-**22**. Finally, exposure of (−)-**23** to NaOH in EtOH as before furnished tricyclic enone (+)-**5** in 99% yield.

Synthesis of Carboxylic Acid Coupling Partner (+)-4. Having developed a streamlined and practical catalytic asymmetric route to the platencin core (+)-**5**, we turned our attention to the introduction of the appendages required for the carboxylic acid coupling partner (+)-**4**. We initially applied our sequence originally used for the corresponding platensimycin carboxylic acid, involving sequential alkylations and metathesis as shown in Scheme 6.[7a] Thus, enone (+)-**5** was methylated [KHMDS, MeI, THF/HMPA (4:1), −78 → 0 °C, 90% yield] to afford methyl enone (−)-**45** (*ca.* 10:1 *dr*), which was subjected to a second alkylation with allyl iodide (KHMDS, allyl iodide, THF/HMPA (4:1), −78 → 0 °C, 86% yield, single diastereomer) to give triene (+)-**46**. The latter compound was converted to the desired carboxylic acid (+)-**4** through a three-step procedure involving cross-metathesis with boronate **48**[28] in the presence of Hoveyda−Grubbs catalyst **49**[29] and benzoquinone,[30] oxidation of the resulting vinyl boronate with Me_3NO to the corresponding aldehyde, and Pinnick oxidation of the latter in 39% overall yield.[31]

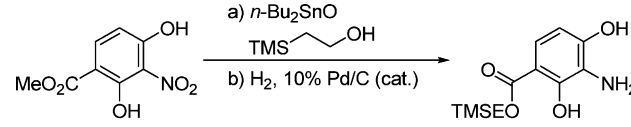
In a separate attempt to access the carboxylic acid (+)-**4** from methylated enone (−)-**45**, and inspired by Corey's platensimycin

Scheme 7. Synthesis of Carboxylic Acid (+)-**4** *via* Conjugate Addition[a]



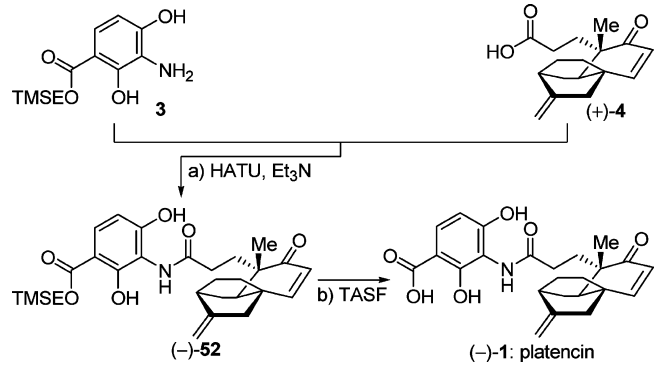
[a] Reagents and conditions: (a) *tert*-butyl acrylate (2.0 equiv), KO*t*-Bu (1.0 M in *t*-BuOH, 2.0 equiv), THF, 25 °C, 30 min, 92% (*ca.* 2:1 *dr*); (b) LiOH (1 N aqueous)/MeOH (1:1), 50 °C, 6 h, 97%.

Scheme 8. Preparation of Aniline Derivative **3**[a]



[a] Reagents and conditions: (a) TMSEOH (14.8 equiv), *n*-Bu_2SnO (1.5 equiv), 70 °C, 3 h, 61%; (b) H_2 (balloon), 10% Pd/C (0.05 equiv), AcOH (1.0 equiv), EtOAc/MeOH (5:1), 25 °C, 15 h, 100%.

Scheme 9. Completion of the Total Synthesis of Platencin [(−)-**1**][a]



[a] Reagents and conditions: (a) **3** (3.2 equiv), HATU (3.2 equiv), Et_3N (4.2 equiv), DMF, 25 °C, 14 h, 61%; b) TASF (2.0 equiv), DMF, 40 °C, 40 min, 93%.

analogue work,[9d] we subjected this compound to enolate formation (KO*t*-Bu) in the presence of methyl acrylate. However, we were disappointed to observe modest yield of the desired methyl ester product and a number of undesired byproducts (−10 → 0 °C). We then resorted to the use of *tert*-butyl acrylate (less prone to polymerization than its methyl counterpart under the reaction conditions) at ambient temperature and realized a 92% yield of the targeted product [(+)-**50**, Scheme 7], albeit in *ca.* 2:1 *dr* favoring the desired stereoisomer, which was chromatographically separated and fully characterized. The required cleavage of the *tert*-butyl ester within the latter compound demanded basic conditions [LiOH (1 N aqueous)/MeOH (1:1), 50 °C, 97% yield], as the exocyclic double bond was prone to isomerization and further destructive side reactions under acidic conditions (i.e., TFA).

Preparation of Aniline Coupling Partner and Completion of the Total Synthesis of (−)-Platencin. The susceptibility of the core structural motif of platencin to acidic conditions dictated modification of the sequence originally employed in our total synthesis of platensimycin.[7a] Thus, aniline partner **3** (Scheme 8), equipped with a TMSE group, was designed as a suitable coupling partner for carboxylic acid (+)-**4** due to the mild conditions under which we expected to carry our the final deprotection (−TMSE).

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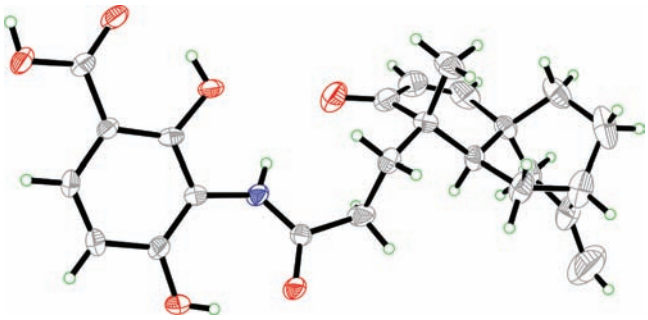

Figure 5. ORTEP of (−)-**1** derived from X-ray crystallographic analysis (non-hydrogen atoms are shown as 30% ellipsoids).

The preparation of this partner proceeded from the readily available nitro methyl ester (**51**) through ester exchange (*n*-Bu_2SnO, $TMSCH_2CH_2OH$, 70 °C, 61% yield)[32] and reduction (H_2, 10% Pd/C, quantitative) of the resulting product, as shown in Scheme 8. The coupling of carboxylic acid (+)-**4** with aniline derivative **3** proceeded under the influence of HATU and Et_3N in DMF at ambient temperature to give protected platencin (−)-**52** in 61% yield, from which the TMSE group was removed through the action of TASF (40 °C, 93% yield), as shown in Scheme 9. Synthetic (−)-platencin [(−)-**1**] crystallized from acetone/hexanes in cubic colorless crystals (mp 194−197 °C dec) upon prolonged standing. Its X-ray crystallographic analysis (see ORTEP, Figure 5)[33] unambiguously confirmed its structure and, therefore, that of the natural substance, whose X-ray crystallographic analysis has not been previously reported.

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Conclusion

The described chemistry provides a streamlined asymmetric approach to the newly reported antibiotic platencin and its analogues. The developed synthetic strategies delivered both the racemic [(±)-**1**] and naturally occurring [(−)-**1**] forms of the natural product and allowed for the first X-ray crystallographic analysis of this antibiotic. Demonstrated by this synthesis are the power of the cobalt-catalyzed asymmetric Diels−Alder reaction[26] and the one-pot reductive rearrangement of [3.2.1] bicyclic ketones to [2.2.2] bicyclic olefins through their hydrazones.[27] Further applications of these synthetic technologies in chemical synthesis are foreseen.

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Supporting Information Available: Complete refs 2, 3b,5a, and 6a, experimental procedures, and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(33) CCDC-740150 contains the supplementary crystallographic data for compound (−)-**1**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.