Published in final edited form as:
J Am Chem Soc. 2009 November 25; 131(46): 16905–16918. doi:10.1021/ja9068003.

Total Synthesis of Platensimycin and Related Natural Products

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Abstract

Platensimycin (**1**) is the flagship member of a new and growing class of antibiotics with promising antibacterial properties against drug resistant bacteria. The total syntheses of platensimycin and its congeners, platensimycins B_1 (**7**) and B_3 (**9**), platensic acid (**2**), methyl platensinoate (**3**), platensimide A (**4**), homoplatensimide A (**5**), and homoplatensimide A methyl ester (**6**) (Figure 1) are described. The convergent strategy developed toward these target molecules involved construction of their cage-like core followed by attachment of the various side chains through amide bond formation. In addition to a racemic synthesis, two asymmetric routes to the core structure are described: one exploiting a rhodium-catalyzed asymmetric cycloisomerization, and another employing a hypervalent iodine-mediated dearomatizing cyclization of an enantiopure substrate. The final two bonds of the core structure were forged through a samarium diiodide-mediated ketyl radical cyclization and an acid-catalyzed etherification. The rhodium-catalyzed asymmetric reaction involving a terminal acetylene was developed as a general method for the asymmetric cycloisomerization of terminal enynes.

Introduction

The discovery of new antibiotics is an urgent medical priority due to the continuous emergence of drug resistant strains of pathogenic bacteria. As evolution drives the inevitable development of bacterial resistance to existing drugs, so the search for new treatments of bacteria-induced infections must continue.[1,2] Natural antibiotics are produced by microorganisms as chemical defenses in their fight for scarce resources. Such molecules have been at the forefront of antibiotic research since the seminal discovery of penicillin.[3,4] The screening of compounds for antibacterial activity is fraught with difficulty, however, due to two conflicting sets of problematic circumstances.[5] Firstly, high throughput whole-cell assays of naturally occurring molecules struggle to distinguish specific antibiotic action from non-specific toxicity and can lead to the re-isolation of known compounds. Any hit must then be individually identified and its mechanism of action determined, requiring a significant investment of effort and resources. On the other hand, the use of target-based assays, while ensuring the hits are active against a known cellular target, has proven troublesome due to difficulties in realizing such activity in whole-cell settings. A team led by Wang and Singh at Merck recently addressed these problems by developing an antisense RNA assay for antibiotic activity.[5] Briefly, they screened natural product isolates against a strain of *Staphylococcus aureus* in which the expression of the FabH and FabF condensing enzymes of the fatty acid biosynthesis pathway (FAS II) was inhibited by the presence of antisense RNA corresponding to the genes encoding both proteins. The strain is thus sensitized to fatty acid biosynthesis inhibitors. By screening samples against this

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Supporting Information Available: Complete refs [5b, 6a] and [11a], experimental procedures, and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

strain and one expressing these enzymes normally in parallel, samples containing compounds that act through inhibition of FAS II could be identified by their differential effects on the two strains.[5]

Using this technique, Wang, Soisson, Singh, and coworkers identified several potent FAS II inhibitors, including platensimycin (**1**, Figure 1), which was isolated from a strain of *Streptomyces platensis* from a soil sample collected in South Africa.[6] They determined the complex polycyclic structure of platensimycin and demonstrated that it acts through highly potent and selective inhibition of the elongation condensing enzyme FabF. As this mechanism of action is not shared by any clinically used antibiotic, platensimycin showed no cross-resistance and was found to be active against a broad range of pathogenic Gram-positive bacterial species. Platensimycin was also shown to be effective *in vivo*, clearing a model *S. aureus* infection in mice, although only at relatively high, continuously administered doses. Interestingly, the fatty acid inhibition strategy to combat bacteria has recently been challenged on the basis of experiments that showed their survival does not depend crucially on their own production of fatty acids since they can tap on the reserves of their hosts for such essential ingredients.[7]

Singh and coworkers also disclosed biosynthetic studies on platensimycin (**1**), indicating the terpenoid nature of the tetracyclic carboxylate "right-hand" portion,[8] as well as preliminary chemical studies[9] and the structures of several related natural products (Figure 1).[10] Platensic acid (**2**) and its methyl ester (**3**) were isolated as natural products in their own right,[10a] as might be expected from the biosynthetic pathway, and were found to have virtually none of the antibiotic activity of platensimycin (**1**). The naturally occurring aliphatic amide platensimide A (**4**),[10a] which retains the right hand structural motif of platensimycin (**1**), was also found to be inactive, as was homoplatensimide A (**5**).[10b] The relative stereochemistry of the 2,4-diaminobutyrate unit of platensimide A (**4**) was verified by the semisynthesis of **4** from **2**.[10a] Homoplatensimide A (**5**) and its methyl ester, homoplatensimide A methyl ester (**6**), contain a carboxylate moiety with the complete C_{20} skeleton of a diterpene, in keeping with the biosynthetic proposal for these compounds, bound through an amide linkage to glutamide.[10b] Platensimycins B_1–B_3 (**7**–**9**, Figure 1), three other natural congeners of platensimycin (**1**) with modest changes in the benzoic acid domain of the molecule, also show poor activity due to the lack of a free carboxylic acid moiety.[10c] Platencin (**10**, Figure 1) was also isolated from a strain of *S. platensis*.[11] Although it shows an overall structural similarity with platensimycin (**1**), particularly in the common aromatic portion, the latter compound has a less-oxygenated ketolide domain. Platencin (**10**) possesses a similar biological profile to platensimycin (**1**), but, surprisingly, a slightly different mechanism of action.[11]

The novel and intricate chemical structure and vitally important biological activity of platensimycin (**1**) made it an attractive target for total synthesis, and a number of groups have reported their synthetic studies toward this end. Following our initial reports on the total synthesis of (±)-platensimycin [(±)-**1**][12a] and, later, of the natural (−)-enantiomer [(−)-**1**],[12b] several groups reported alternative elegant approaches.[12c–k] Additionally, our research group and those of others have prepared a number of biologically active analogues of platensimycin.[13] We present here an improved synthesis of platensimycin (**1**) and a full account of our studies on the total synthesis of this fascinating target as well as the related compounds (**2**–**7**, **9**) sharing its tetracyclic enone structural motif. Our studies on the total synthesis of platencin (**10**) are reported elsewhere.[14]

Results and Discussion

Retrosynthetic Analysis

We began our studies by pondering a retrosynthetic analysis of the platensimycin molecule (**1**). The final route developed is depicted in retrosynthetic format in Figure 2. Our analysis began with the straightforward amide disconnection to generate aromatic amine **11** and platensic acid (**2**) as potential precursors. From here, a double disconnection of the propionate and methyl α-substituents revealed the tetracyclic ketolide **12** as the primary synthetic subtarget. The inherent structural bias of cage-like intermediate **12** was expected to impart stereocontrol in the construction of the C4 quaternary center. We considered a variety of disconnection strategies at this stage. We hypothesized that disconnection of the ether ring, as shown, was likely to be productive since it not only simplified the target significantly, but also offered the chance to control the C15 stereocenter as a result of geometric constraints, and complete the cage-like structure by way of well-understood chemistry. The most straightforward etherification substrate, tricyclic enone **13**, contains a 4-hydroxyketone structural motif. Disconnection of the C9–C10 bond by way of a retro 1,4-addition was an intriguing prospect. This disconnection resulted in a spirocyclic 4,5-cyclohexadienone bearing a single stereogenic center (i.e. **14**, Figure 2). Although the success of the 1,4-addition reaction was by no means assured and the preparation of a suitable substrate might prove challenging to prepare, we were attracted to this strategy by the possibility of exploiting the local symmetry of the dienone unit to set the all-carbon quaternary center at the heart of this subtarget. Inspection of the three-dimensional structure of substrates such as **14** indicated that if a successful 1,4-addition reaction could be achieved, the stereochemistry at C8 and C9 would follow as a matter of course. Additionally, several reactions could be used to effect the desired intramolecular 1,4-addition to the enone, including radical and Stetter-type processes, giving the approach some flexibility. Aldehyde **14** could act as a substrate (or suitable precursor for such a substrate) for several of these reactions. Setting the absolute stereochemistry of the single stereocenter of **14** (C12) would be the key to realizing an asymmetric synthesis of platensimycin, a challenge for which we envisioned two separate possible solutions. The first (a, Figure 2) involved forging the C12 stereocenter and the spirocyclic cyclopentyl ring in a single cycloisomerization step from a symmetrical, achiral 1,6-enyne precursor (**15**). This intermediate, in turn, could be traced back, through Stork–Danheiser alkylation chemistry, to enone **16**. This route offered the advantages of a direct and potentially catalytic asymmetric synthesis, but faced the challenge of realizing an asymmetric cycloisomerization reaction of terminal alkyne substrates, which at the time was an unsolved problem. Our second strategy (b, Figure 2) involved separating the tasks of forming the spirocyclic system and the stereocenter. The former would result from a dearomatizing cyclization of a 4-substituted phenol such as **18**. Our interest in the chemistry of hypervalent iodine reagents led us to propose an oxidative cyclization using an allylsilane as an internal nucleophile. The substrate for this reaction (**18**) was easily envisioned to derive from a ketone such as **19**, which was expected to be available in enantiopure form *via* the alkylation of pseudoephedrine amide **20**. In this case, the advantages lay in the likely ease of substrate preparation employing Myers' alkylation technology using readily available starting materials. Within this route, a dearth of precedent for the dearomatization reaction gave us some concern. In the end, we would investigate both asymmetric approaches; initially, however, we focused on securing the relatively late key step, which was perceived to be the most challenging aspect of the proposed synthesis: the conversion of aldehyde **14** to cage structure **12**, using racemic material.

Construction of Racemic Aldehyde (±)-14

Our urgent desire to investigate reactions of aldehyde **14** led us to prepare this compound in racemic form in the first instance. This endeavor also served as a preliminary investigation for the first asymmetric route to platensimycin [(−)-**1**]. Our optimized route to (±)-**14** is shown in

Scheme 1. Starting from ketone **17**, we carried out sequential alkylation reactions using the established protocol of kinetic enolate generation with LDA. This allowed the installation of what would eventually become the quaternary center at C8 and all the carbon atoms needed for the lower region of the platensimycin enone domain to afford intermediate **16** in excellent overall yield. Reduction of enone **16** with DIBAL-H followed by treatment with aqueous HCl led to enone **22** in good yield.[15] Short reaction time and maintaining the mixture at 0 °C prevented significant loss of the silyl ether. Treatment of enyne **22** with ruthenium catalyst ($[CpRu(MeCN)_3]PF_6$) in acetone resulted in a smooth and efficient cycloisomerization reaction,[16] furnishing spirocycle **23** as an inconsequential 1:1 mixture of diastereoisomers. Formation of the TMS enol ether of enone **23** and oxidation gave dienone **24**, which was converted into aldehyde (±)-**14** by acidic hydrolysis of the TBS enol ether. The oxidation reaction could be carried out using stoichiometric amount of $Pd(OAc)_2$, as reported previously, 17a but was accomplished most efficiently using the mild catalytic system of $Pd_2(dba)_3$•$CHCl_3$ in combination with diallyl carbonate.[17b] In either case, excellent selectivity was observed for oxidizing the TMS enol ether to afford **24**.

Catalytic Asymmetric Synthesis of Aldehyde (−)-14

We also investigated an asymmetric version of the above route to aldehyde **14**. No asymmetric variant of the ruthenium-catalyzed cycloisomerization reaction[16] had been reported at the time; however, Zhang and coworkers had described an equivalent transformation catalyzed by chiral rhodium(I) diphosphine complexes.[18] While, in general, excellent substrate scope and enantiomeric excesses were noted in these reports, examples incorporating terminal alkyne partners were conspicuously absent. In order to investigate the possibility of an asymmetric cycloisomerization, the synthesis had to be slightly modified to incorporate the second olefin in the enone ring so as to produce achiral substrate **15** (Scheme 2). We also prepared related substrates with the alkyne moiety capped with various functional groups as shown in Scheme 2. Thus, activation of the ketone group of **22** gave trimethylsilyl enol ether **25**, which served as a common intermediate for all required substrates (Scheme 2). Oxidation of **25** with IBX•MPO[19] led to dienone **26**, with deprotection of the TBS ether giving parent prochiral substrate **15**. Alternatively, the oxidation of cyclohexenone **22** could be achieved in a one-pot procedure through the introduction of a phenylselenide group followed by selenoxide formation and syn elimination as summarized in Scheme 2. Two further substrate analogues were prepared by taking advantage of the temporary masking of the ketone group as enol ether **25**. Lithiation of the terminal alkyne followed by quenching with TMSCl or Mander's reagent gave enol ethers **27** and **28**, respectively (Scheme 2). In each case, oxidation with IBX•MPO (to afford **29** and **30**, respectively) and acid-induced desilylation proceeded smoothly, giving prochiral substrates **31** and **32**, respectively, as shown in Scheme 2.

As we expected from the lack of literature examples, our initial investigations into the asymmetric cycloisomerization of terminal enyne **15** proved disappointing. Exposure of this terminal alkyne to a mixture of $[Rh(cod)Cl]_2$, (*S*)-BINAP, and $AgSbF_6$, as reported by Zhang and coworkers,18c–g resulted in sluggish conversion and significant decomposition of the starting material upon prolonged reaction times, and, thus, only a very low yield of product aldehyde (−)-**14** and poor recovery of substrate alcohol **15** (Scheme 3). Increasing the catalyst loading did not improve the yield of (−)-**14**, but accelerated the decomposition of **15**. However, we were encouraged by the observation that aldehyde (−)-**14**, obtained in low yield (15%) under these conditions, was formed with excellent enantiomeric enrichment (95% ee). We made recourse to the 'capped' alkynes described above in an effort to improve the chemical yield of the reaction, and subjected alkynyl silane **31** to the same catalyst system (Scheme 3). Unfortunately, the expected spirocyclic aldehyde **33** was not detected in this case, presumably due to the steric hindrance of the TMS group.[20]

Fortunately, the ester-bearing substrate **32** proved amenable to cycloisomerization under asymmetric conditions, as shown in Scheme 4. Exposure of **32** to the standard rhodium catalyst system ($[Rh(cod)Cl]_2$, (*S*)-BINAP, $AgSbF_6$) rapidly gave spirocyclic ester (−)-**34** in excellent yield. HPLC analysis using a chiral stationary phase indicated that (−)-**34** was formed in greater than 95% ee.[21] The sense of asymmetric induction using the rhodium(I)-BINAP system appeared to be uniformly consistent throughout the published examples,[18] which span a variety of substrate types. We were, therefore, confident that (*S*)-BINAP would provide the correct absolute configuration required for our synthesis of (−)-platensimycin [(−)-**1**]. This expectation was borne out by comparison of optical rotations at a later stage (*vide infra*). The use of **32** in the successful asymmetric cycloisomerization reaction, however, came at the cost of removing the superfluous carboxylate moiety from product (−)-**34**. This was achieved by conversion of the potentially sensitive aldehyde group to the corresponding ethylene glycol acetal (−)-**35**, followed by saponification of the methyl ester to give carboxylic acid (+)-**36**, during which the exocyclic double bond had migrated to the endocyclic position, presumably to release some strain. Formation of the Barton ester (reaction with reagent **37** and EDC•HCl, Scheme 4) followed by photolysis in the presence of *t*-BuSH gave deacarboxylated compound (+)-**38**.[22] Finally, hydrolysis of the acetal group within (+)-**38** led to the corresponding aldehyde (+)-**39** as shown in Scheme 4.

The asymmetric synthesis of aldehyde (+)-**39** allowed us to demonstrate a formal asymmetric synthesis of (−)-platensimycin (−)-**1**;[12b] however, the requirement for a multi-step decarboxylation sequence amounted to an unsatisfactory overall efficiency. Obviously, the realization of an effective asymmetric cycloisomerization of enyne **15** would provide the most direct means to access the key intermediate aldehyde (−)-**14**.

At this point, we decided to embark on the development of an asymmetric enyne cycloisomerization reaction using terminal alkynes as substrates.[23] Employing 1,6-enyne **40** as a substrate, we examined a number of Rh-based complexes in order to find the optimum catalytic system; our results are summarized in Table 1. Thus, while the performance of $[Rh(cod)(MeCN)_2]BF_4$ in the presence of (*S*)-BINAP was rather modest (36% yield of product **40a**, after 12 h at 23 °C), the product was obtained with significant enantiomeric enrichment (90% ee, Table 1, entry 1). The complex generated *in situ* by mixing $[Rh(cod)Cl]_2$ and AgOTf in the presence of (*S*)-BINAP led to a 60% yield and a comparable ee (91% ee, Table 1, entry 2), whereas the combination of $[Rh(cod)Cl]_2$, $AgSbF_6$, and (*S*)-BINAP employed by Zhang et al. with internal alkynes [18c–g] gave **40a** in 65% yield and 95% ee (Table 1, entry 3). Finally, it was found that the preformed rhodium catalyst $[Rh((S)\text{-BINAP})]SbF_6$24 gave the best results, furnishing product **40a** in 86% yield and > 99% ee (Table 1, entry 4). The absolute configuration of product **40a** was determined by X-ray crystallographic analysis (see ORTEP drawing, Figure 3) of its *p*-bromophenyl carbamate derivative[25] (**40b**, m.p. 99–101 °C, EtOAc/hexanes 1:1, prepared as shown in Scheme 5).

The generality and scope of this new asymmetric reaction was examined and the results are summarized in Tables 2 and 3. As seen from entries 2–10 (Table 2), the process tolerates well all *cis* allylic alcohols tested as substrates (**42**–**50**, Table 2), leading to good to excellent yields and enantiomeric excesses of the cycloisomerized products (**42a**–**50a**, Table 2). The reaction, however, performed only modestly in the case of *trans* allylic alcohol **41** (Table 2, entry 1), giving aldehyde **40a** (the same product obtained from the *cis* allylic alcohol **40**, Table 1) in 45% yield and 29% ee. The reaction performed well with substrates containing a wide range of structural motifs, linking the two reactive ends of the molecule, namely sulfonamides (Table 2, entry 2), amides (Table 2, entries 3 and 4), 1,1-diesters (Table 2, entries 5 and 6), 1,1-sulfones (Table 2, entry 7), bis-aromatic moieties (Table 2, entry 8), and ether linkages (Table 2. entry 9). It was also demonstrated that amide carbonyl groups in conjugation with either the olefin or alkyne reactive moieties are tolerated in this process (Table 2, entries 3 and 4, respectively).

Most notable is the success of this asymmetric reaction with the bromoacetylenic substrate **50** (Table 2, entry 10), leading to vinyl bromide **50a**, a product that could be utilized in a variety of further transformations, thus expanding considerably the scope of the method.

Table 3 depicts a number of experiments undertaken in order to explore further aspects of the asymmetric cycloisomerization. Thus, TBS ether **51** and allylic acetate **52** (Table 3, entries 1 and 2, respectively) entered the reaction successfully to afford enol ether **51a** and vinyl acetate **52a**, respectively, in high yield and ee, whereas entries 3 (substrate **53**) and 4 (substrate **54**) demonstrate that the reaction tolerates sulfur and nitrogen substituents, respectively, on the ene side chain. Finally, it was shown that a heteroatom is not necessary in the ene side chain for the success of the reaction as demonstrated with substrate **55** (Table 3, entry 5).

Much to our delight, substrate **15**, the precursor to platensimycin [(−)-**1**], entered the asymmetric cycloisomerization with 5 mol % catalyst ([Rh((*S*)-BINAP)]SbF_6) to afford the desired spiro dienone aldehyde (−)-**14** in 86% yield and > 99% ee, as shown in Scheme 6. As mentioned above, application of Zhang's protocol[18c–g] to substrate **15** led to inferior yield (15%) and lower ee (95%) (see Scheme 3). Although we cannot pinpoint precisely the reasons for the observed difference between the two catalyst system at the present time, we can, however, speculate that the observed results may have their origins in the fact that our catalyst[24] is more well-defined than the various species that must be present in the previously employed catalyst system.[18c–g]

Asymmetric Synthesis of Aldehyde (−)-14 Through a Dearomatizing Cyclization

Alongside our efforts to develop an asymmetric cycloisomerization route to aldehyde (−)-**14**, we also investigated the alternative approach outlined retrosynthetically in Figure 2 (route b). In this approach, we planned to forge the spirocyclic ring system through a dearomatizing cyclization. Such processes commonly employ the combination of a phenol with a strong electrophile, such as a protonated diazoketone or allyl halide.[12f,g,26] The oxidation of phenols in the presence of a suitable nucleophile has been used to achieve a similar transformation, particularly using heteroatom or aromatic nucleophiles,[27] although examples with carbon-based nucleophiles, aside from aromatic systems, are rare.[28,29] We favored the use of an allyl silane nucleophile under oxidative conditions due to an interest in exploring the feasibility of such a transformation and the potential ease with which a suitable substrate might be prepared, although misgivings remained as to the success of the key step. Allylsilane nucleophiles had been employed only rarely in oxidative additions to phenols. Quideau and coworkers have reported the intermolecular addition of allyl trimethylsilane to naphthols mediated by iodine (III) reagents; however, they observed that good yields were obtained only when the phenolic partner was pre-treated with the oxidant followed by addition of the silane, suggesting an incompatibility between allylsilanes and iodine(III) oxidants.[28b]

As indicated in Figure 2, we adopted a plan which called for the installation of the stereogenic center found within key aldehyde **14** prior to the dearomatizing cyclization. As expected, the substrate for the cyclization was prepared in a straightforward manner using Myers' asymmetric alkylation protocol (Scheme 7). Thus, known carboxylic acid **56**[30] was coupled with (*S*,*S*)-pseudoephedrine **57** to give amide (−)-**20** in quantitive yield. Alkylation according to Myers' procedure[31] with benzylic bromide **58**[32] gave amide (−)-**59** in excellent yield, albeit with rather low selectivity (crude *de* ~85%) when compared with literature examples. However, a single recrystallization of the crude product provided (−)-**59** as a single diastereoisomer in 75% yield. Cleavage of the auxiliary group from (−)-**59** with methyllithium then provided methyl ketone (−)-**19** in excellent yield with enantiomeric excess of > 98%.[33] Treatment of ketone (−)-**19** with KHMDS and Comins reagent (**60**) gave enol triflate (−)-**61** in excellent yield, although the efficiency of this reaction was highly dependent on the quality of the Comins' reagent used. Kumada coupling of (−)-**61** with (trimethylsilyl)methyl Grignard

reagent [2.5 mol % $Pd(PPh_3)_4$, LiCl] and selective desilylation of the phenol under basic conditions (NaOH) furnished dearomatization substrate (−)-**18** in excellent overall yield.

A wide range of conditions were screened for the proposed oxidative cyclization reaction of (−)-**18**, some of which are summarized in Table 4. Iodine(III) reagents were quickly determined to be the most effective promoters, with $PhI(OAc)_2$, $PhI(O_2CCF_3)_2$, and PhIO all giving the desired spirocyclic product (−)-**62** in low to moderate yield under a variety of solvent and temperature conditions. Non-nucleophilic polar solvents proved the most effective media for this reaction, as might be expected for this type of transformation.[34] The combinations of the milder reagent $PhI(OAc)_2$ and either 2,2,2-trifluoroethanol (TFE) or 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) were equally effective, with the former solvent favored on the basis of cost (entry 4, Table 4). Under the optimized conditions, phenolic allylsilane (−)-**18** was converted to (−)-**62** in 68% yield as shown in Scheme 7. Removal of the acetal protecting group from this intermediate revealed aldehyde (−)-**14** in high yield.

The dearomatization reaction is presumed to proceed through an initial interaction of the iodine reagent with the phenol, followed by oxidation of the aromatic ring and either concomitant or step-wise addition of the nucleophile. Such a mechanism is in accordance with accepted reactivity of phenols with iodine(III) reagents[27] and with the results of Quideau mentioned above.[28b,c] Although we have not identified and characterized any of the by-products formed from the reactions of (−)-**18**, we observed that when the TBS ether of (−)-**18** was treated with $PhI(OAc)_2$ in TFE it underwent rapid proto-desilylation. This result, while not involving an oxidation reaction, indicates that the allylsilane group is indeed reactive under the reaction conditions. Based on this observation, we assume that at least some of the by-products generated under the dearomatization conditions employed may come through this parallel pathway.

The dearomatization reaction of phenolic allylsilanes was investigated further using several simpler substrates (Scheme 8). In each case, treatment of the phenol with the iodine(III) reagent led to cyclization to give the products shown, suggesting considerable generality of this process for the formation of spirocyclic systems. As shown, both branched and linear allylsilanes participated in this process satisfactorily. Canesi and coworkers have recently reported similar reactivity involving both allylsilane and enol ether nucleophiles in iodine(III)-mediated reactions of phenols to generate a variety of products, including (±)-aspidospermidine.[35]

Completion of the Synthesis of Platensimycin Core Structure (−)-12

Having secured access to aldehyde **14**, both in its racemic and enantioenriched forms, we began exploring the possibility of converting it to the next intermediate, such as tricyclic species **13**, through formation of the C9–C10 bond (see Scheme 9). Our initial investigations focused on ionic processes such as the nucleophilic carbene-catalyzed Stetter reaction. However, treatment of (−)-**14** with several hetereocyclic carbene species reported to promote the Stetter reaction[36] gave no tricyclic products. We attributed this failure to the strain involved in forming the norbornane motif of the targeted tricyclic structure. In an alternative approach from these laboratories,[12d] it proved possible to forge the C9–C10 bond using a Stetter reaction[36] to form a decalin system lacking the bridging ring, which was installed later. In an effort to increase the reactivity of substrates along similar lines, we prepared the TMS cyanohydrin of (−)-**14** (structure not shown) and attempted to induce cyclization through treatment with a strong base. Again, the results were disappointing and recourse was made to the ethoxyethyl (EE) protected cyanohydrin (−)-**66**, prepared in excellent yield from (−)-**14** through standard chemistry, as shown in Scheme 9. In this case, treatment of (−)-**66** with KHMDS at 0 °C led to rapid cyclization to form tricyclic product (−)-**67** in high yield (86%). The stereocenters at C9 and C10 were both formed as shown with complete control, although the product remained a mixture of two diastereoisomers due to the stereocenter within the EE group. The cyanohydrin

moiety could be removed in one step by sequential treatment with aqueous acid and base to give diketone (+)-**68** in 89% yield. The stereochemistry at C9, predicted based on geometric considerations in the 1,4-addition reaction, was confirmed at this stage by nOe studies. Reduction of (+)-**68** with DIBAL-H gave a diol, which could be oxidized selectively with MnO_2 to furnish alcohols **13a** and **13b** as a mixture of inseparable diastereoisomers (**13a: 13b** ca. 1:5). Unfortunately, the major isomer (**13b**) was found to be the undesired compound, as determined by the ability of only the minor isomer (**13a**) to engage its exocyclic olefin in a ring forming reaction (*vide infra*). Despite screening a range of reductants, we were not able to improve the ratio of these products. Additionally, alcohol **13b** was found to be resistant to inversion, with Mitsonobu conditions giving no reaction, and displacement of the corresponding mesylate or triflate proving fruitless.

In parallel with the studies outlined above, we also investigated the potential of a samarium diiodide-mediated ketyl radical cyclization as a means to convert (±)-**14** to (±)-**13a/13b**. Such a process has the advantage of giving (±)-**13a/13b** directly in a single step.[37] Additionally, the inherent stereochemical bias of these processes would be expected to favor the selective formation of the desired stereoisomer (±)-**13a**. Initial attempts to cyclize (±)-**14** were uniformly unsuccessful, despite a range of conditions being applied (Table 5). Optimization efforts were hampered by a lack of identifiable by-products. Small quantities of (±)-**13a/13b** (ca. 2:1 ratio) were isolated from a reaction employing HMPA and MeOH at low temperature (entry 4). This reaction was further optimized to provide a 2.2:1 mixture of (±)-**13a** and (±)-**13b** in up to 51% yield (entry 5). In this case, the major component in the reaction mixture was the desired isomer (±)-**13a**. Notably, the best results were obtained when the samarium reagent was added very rapidly, suggesting that the mixing rate is important. The mixing rate was especially crucial in preparative scale experiments. This result, although to some extent disappointing, allowed for the preparation of sufficient quantities of **13a** for further studies [the samarium diiodide-induced ring closure (entry 5, Table 5) was also carried out with (−)-**14** to afford (−)-**13a/** (+)-**13b**[38]]. Other reagents for the preparation of ketyl radical intermediates,[39] for example, titanium(III) species, AIBN/*n*-Bu_3SnH and Et_3B/O_2/*n*-Bu_3SnH, were investigated for this transformation (**14** → **13a/13b**) without success.

The final bond construction required to complete the platensimycin cage-like structural motif was etherification between the alcohol group at C10 (i.e. O16) and C15 (see Scheme 10). Treatment of a mixture of (−)-**13a** and (+)-**13b** [obtained from samarium diiodide-mediated cyclization with (−)-**14**] with PhSeCl in the presence of $K_2CO_3$40 at low temperature resulted in the smooth and rapid etherification of the major component (−)-**13a**, confirming its stereochemistry and providing C17-selenated platensimycin cage structure (+)-**69**, which underwent AIBN-induced radical reduction to give deselenated compound (−)-**12**. We were encouraged by the ease with which the proposed etherification reaction occurred, and subsequently discovered that exposure of the mixture of (−)-**13a** and (+)-**13b** to either TFA (excess) at 0 °C, or triflic acid (1.5 eq.) at −78 °C was sufficient to induce cyclization, forming cage structure (−)-**12** in excellent yield (based on the proportion of (−)-**13a** in the mixture of diastereomers, Scheme 10). This finding made our two-step selenation-based route to (−)-**12** unnecessary. Interestingly, alcohol (+)-**13b** was recovered unchanged from the reactions with PhSeCl and TFA, while upon the treatment with triflic acid its exocyclic double bond partially migrated to the endocyclic position (structure not shown). A sample of (−)-**12** crystallized from $CDCl_3/CH_2Cl_2$ to give colorless needles (m.p. 65–67 °C) suitable for X-ray crystallographic analysis.[41] The X-ray derived ORTEP drawing of (−)-**12** is shown in Figure 4.

Endocyclic aldehyde (+)-**39** was also investigated as a substrate for the samarium(II)-mediated cyclization/acid induced-etherification sequence. The successful cyclization of this substrate was essential to our early asymmetric synthesis efforts, to ensure that the cycloisomerization of ester-capped alkyne **32** would lead to a total synthesis of platensimycin [(−)-**1**]. As shown

in Scheme 11, aldehyde (+)-**39** proved to be a viable substrate for the ketyl olefin cyclization reaction, leading to alcohol **70** as a single diastereoisomer (^{1}H NMR spectroscopic analysis). Treatment of **70** with TFA resulted in clean conversion (36% yield for two steps) to cage-structure (−)-**12**, confirming the stereochemistry of **70** and completing the formal asymmetric total synthesis of platensimycin [(−)-**1**]. The dependency of the stereochemical outcome of the samarium(II)-mediated cyclizations on subtle differences in substrate structure is intriguing, and points to the sensitivity of the reaction to the precise structure and conformation of the spirocyclic substrate.

The configuration at C10 of cyanohydrin cyclization product (−)-**67** is correct with respect to the orientation of the masked hydroxyl group, and we sought to exploit this in an alternative route to the platensimycin cage structure [(−)-**12**]. Thus, hydrolysis of the ethoxyethyl ethyl (EE) group with aqueous acid followed by etherification of the resulting product with TFA (0 °C) gave C10-cyano cage compound (+)-**71** in high yield (81% for two steps) as shown in Scheme 12. Attempts to cleave the undesired carbon-carbon bond by treatment of the lithium anion of (+)-**71** with LDBB[42] failed to provide (−)-**12** (Scheme 12). Although the cyanohydrin addition route did not provide an efficient means to access the cage structure of platensimycin, it did provide access to the bioactive analogue carbaplatensimycin,[13b,c] and may potentially lead to other analogues with chemical modification on the cage such as C10-cyano platensimycin.

Completion of the Total Syntheses of Platensimycin and Related Natural Products

With a viable route to the core structure (**12**) of platensimycin in hand, we turned our attention to the installation of the side chain and completion of the total synthesis. Enone **12** could be methylated in excellent yield by exposure to KHMDS followed by addition of MeI in a THF-HMPA mixture (Scheme 13). The methyl group was introduced with almost complete stereoselectivity, giving **72** as essentially a single diastereoisomer, as judged by ^{1}H NMR spectroscopic analysis. A second alkylation was then investigated using various electrophiles. As might be expected, the enolate of **72** was found to be rather unreactive, and all attempts to install a side chain using 3-oxygenated propyl iodides (e.g. **73** or **74**) failed. Treatment of the potassium enolate of **72** with bromide **75** rapidly transferred the ester group to the enolate oxygen of the substrate to form the corresponding enol carbonate. However, this enolate did react with allyl bromide to provide the desired allylated compound **76** along with significant quantities of the *O*-allylated product. Recourse to allyl iodide overcame this complication, giving **76** in good yield (83%) and, again, essentially as a single diastereoisomer, verifying our retrosynthetic hypothesis. The conversion of **76** into platensic acid (**2**) was also problematic at first. The allyl side chain was not reactive toward bulky hydroboration reagents; treatment with BH_3•THF led to hydroboration of the allyl group with concomitant reduction of the enone carbonyl moiety, allowing isolation of diol **77** in low yield, along with several by-products. Oxidation of **77** with DMP then furnished aldehyde **78** in low overall yield from **76** (steps a and b were carried out with both racemic and enantiopure materials; steps c and d were carried out only with racemic compounds).

Fortunately, the allyl side chain of **76** was amenable to selective cross metathesis, and this provided a mild method for the required oxidation (Scheme 14). Thus, cross metathesis of **76** with vinyl pinacol boronate (**79**)[43] using Grubbs' second generation initiator **80**[44] (25 mol %) gave olefinic boronate **82** in good yield (81%) as an inconsequential mixture of isomers (*E:Z* ca. 6:1). The use of the Hoveyda–Grubbs second generation initiator **81**[45] gave similar results (81% yield) with much lower catalyst loading (10 mol %). Oxidation of the olefinic boronate **82** was accomplished by heating with trimethylamine-*N*-oxide,[46] to give aldehyde **78** in much higher overall yield than the hydroboration route described above. This two-step conversion of allyl groups to aldehydes was first employed by Danishefsky et al. in connection

with their work on epothilone analogues,[47] and has subsequently proved applicable to a range of platensimycin analogues.[13a–c] Further oxidation of **78** gave platensic acid [(±)-**2** and (−)-**2**] in high yield,[48] treatment of which with TMS-diazomethane gave methyl platensinoate [(±)-**3** and (−)-**3**] in quantitative yield as shown in Scheme 14. The latter compound is also naturally occurring.[10a]

Recently, Corey and Yeung reported the synthesis of a platensimycin analogue in which the propionate side chain was installed using the more direct method of 1,4-addition to methyl acrylate.[13d] Although we had investigated such a reaction initially with little success, these recent results prompted us to reinvestigate this transformation. Under Corey's conditions (methyl acrylate, *t*-BuOK, THF/*t*-BuOH) we found that methylated cage intermediate (−)-**72** was transformed into methyl platensinoate (**3**) directly; however, the yield of this transformation was modest and the desired compound was isolated, along with several by-products. This situation was improved by switching to *t*-butyl acrylate (Scheme 15), which allowed direct formation of *t*-butyl platensinoate (−)-**83** in high yield (84%). *t*-Butyl ester (−)-**83** could be cleaved quantitatively by treatment with TFA to give platensic acid [(−)-**2**]. This is now the preferred method for the conversion of (−)-**72** to (−)-**2**.

For the completion of platensimycin (**1**) from platensic acid (**2**), we required a suitably substituted aniline coupling partner. We chose to prepare aniline derivative **84** in the first instance, in which the carboxylic acid is protected as the methyl ester and the phenols are masked as MOM ethers. The choice of protecting groups was influenced by their ease of removal and by synthetic considerations. We prepared **84** from 2-nitroresorcinol (**85**, Scheme 16), a convenient and inexpensive starting material that incorporates three of the necessary substituents. MOM ether formation (MOMCl, *i*-Pr_2NEt) followed by hydrogenation of the nitro group (Pd/C, H_2) gave aniline derivative **86** in excellent yield, which later served as a coupling partner for the synthesis of platensimycin B_3 [(−)-**9**]. Boc protection of **86** (Boc_2O, neat) gave the corresponding carbamate in quantitative yield. Generation of the dilithio species by treatment with 2.2 equiv of *n*-BuLi, followed by addition of Mander's reagent [MeOC(O)CN], did give the desired product (**87**), however, yields were low due in part to incomplete *ortho*-lithiation even at 5 °C, resulting in the generation of *N*-acylated by-products. This problem was overcome by *in situ* protection of the carbamate anion with one equivalent of TMSCl, followed by addition of a second equivalent of *n*-BuLi to effect *ortho*-lithiation. Addition of Mander's reagent followed by mildly acidic workup then gave the desired ester **87** in good yield. Removal of the Boc protecting group was also problematic, with even 0.1% TFA in CH_2Cl_2 causing rapid decomposition of **87**. Fortunately, thermolysis of the Boc group was clean; heating **87** in 1,2-dichlorobenzene at 205 °C for 7 min gave aniline **84** in 83% yield. Shortly after us, Giannis et al. reported another efficient synthesis of **84**, employing ester **88** as a key intermediate.[49] Taking advantage of **88**, we readily prepared aniline **89**, a coupling partner required for the platensimycin B_1 synthesis, through ammonolysis with aqueous ammonium hydroxide, followed by hydrogenation of the nitro group as described above (see Scheme 16).

The coupling of platensic acid (**2**) with aniline derivative **84** was carried out by treatment with HATU and Et_3N in DMF, providing amide **90** in 86% yield (Scheme 17). Deprotection of **90** was achieved through a one-pot procedure involving methyl ester hydrolysis (aq. LiOH in THF, 45 °C) followed by MOM cleavage (addition of aq. HCl and continued heating at 45 °C), providing platensimycin (**1**) in high overall yield. Both racemic and enantioenriched platensimycins were prepared starting with (±)-**14** and enantioenriched (−)-**14**. Enantioenriched platensimycin [(−)-**1**] was identical in every respect to a reference sample of the natural material.[6]

Furthermore, platensimycins B_1 [(−)-**7**] and B_3 [(−)-**9**] were efficiently synthesized in a similar manner from platensic acid [(−)-**2**] and anilines **89** and **86**, respectively, as shown in Scheme 18. Notably, aniline **89** with two free hydroxyl groups showed good reactivity and stability under these amide forming coupling conditions, ensuring that platensimycin B_1 [(−)-**7**] could be formed directly in one step. However, the protecting group-free version of aniline **86** was not stable enough for handling, presumably due to the lack of an electron-withdrawing functional group on the aromatic ring. A two-step sequence was, therefore, necessary to synthesize platensimycin B_3 [(−)-**9**] as shown in Scheme 18. Thus, coupling of bis-MOM protected aniline **86** with platensic acid [(−)-**2**] under the HATU-Et_3N conditions, followed by removal of the MOM groups from the resulting product under acidic conditions, led to platensimycin B_3 [(−)-**9**] in 85% overall yield. The physical properties of both synthetic platensimycins B_1 [(−)-**7**] and B_3 [(−)-**9**] matched those reported in the literature for the naturally derived materials.[10c]

Naturally occurring platensimide A [(−)-**4**] consists of platensic acid [(−)-**2**] coupled to (*S*)-N^4-acetyl-2,4-diaminobutyrate in place of the aniline component of platensimycin. Singh et al. accomplished a semisynthesis of platensimide A [(−)-**4**] from naturally occurring platensic acid [(−)-**2**] as part of their isolation studies.[10a] They coupled platensic acid with mono-Boc-protected methyl diaminobutyrate, and subsequently installed the acetamide group. Within the context of a total synthesis (i.e. using synthetic platensic acid), we hoped to complete a more convergent route in which the acetamide was already in place. To this end, we prepared amine (+)-**91** from Cbz-glutamine *t*-butyl ester **92** (Scheme 19). Hoffmann degradation of **92** was carried out according to the literature procedure [$PhI(O_2CCF_3)_2$],50 however, rather than isolating the amine product, the latter was converted *in situ* to its acetamide derivative (−)-**93** with Ac_2O (70% overall yield), which served the dual role of saving one step and facilitating isolation. Hydrogenolysis of the Cbz group from (−)-**93** then gave amine (+)-**91** in 92% yield (Scheme 19). Coupling of (+)-**91** with the activated ester generated from platensic acid [(−)-**2**] and HOBt under the conditions of EDC•HCl furnished platensimide A *t*-butyl ester (−)-**94** in 94% yield. Hydrolysis of the latter with TFA then yielded synthetic platensimide A [(−)-**4**] in high yield (99%), whose physical properties were consistent with those of the naturally occurring product.[10a]

A similar strategy was employed for the total synthesis of the also naturally occurring homoplatensimide A [(−)-**5**, Scheme 20]. In this case, extension of the side chain of the platensimycin core was required. This was achieved through the highly selective Wittig reaction between stabilized ylide **95** and core aldehyde (−)-**78**, which gave unsaturated ester (−)-**96** in excellent yield (88%) as a single geometrical isomer (Scheme 20). Hydrolysis to the corresponding carboxylic acid (**97**, 94% yield) and coupling of the crude product with glutamine *t*-butyl ester [(+)-**98**, obtained by hydrogenolysis of its Cbz derivative **92**] under the HOBt/EDC•HCl conditions gave homoplatensimide A *t*-butyl ester [(−)-**99**] in 82% yield. Ester hydrolysis of the latter compound with TFA was again successful in revealing homoplatensimide A [(−)-**5**], which displayed physical properties in accord with those reported for the natural material.[10b] Homoplatensimide A methyl ester [(−)-**6**] was also prepared and fully characterized by treatment of (−)-**5** with $TMSCHN_2$ (98% yield) as shown in Scheme 20. Its physical data matched those reported for the natural product.[10b]

Conclusion

In conclusion, we developed several effective synthetic strategies for the total synthesis of platensimycin (**1**), a newly discovered antibiotic possessing a novel mechanism of action. In addition to a racemic synthesis, two complementary asymmetric approaches to a key synthetic intermediate [i.e. (−)-**14**] were devised. The first strategy was based on well known asymmetric alkylation technologies and a novel dearomatizing cyclization reaction of a phenolic

allylsilane. The reaction was developed as a viable and general method for the oxidative cyclization of phenolic allyl silanes to spiro hemiquinones. The second strategy featured a rhodium-catalyzed asymmetric cycloisomerization reaction especially developed for this total synthesis, which, however, turned out to be of general applicability and scope, accommodating a wide range of terminal enyne substrates. The developed convergent total synthesis of platensimycin proceeded through enone **9**, representing the cage core of the molecule, and which has been employed by all other syntheses reported to date[12a–l] of this natural product. Efficient strategies to install the side chain were also developed to ensure reliable syntheses of platensimycin and related compounds. In addition to providing access to synthetic platensimycin, this work has facilitated the total syntheses of a number of designed platensimycin analogues[13a–c] and its naturally occurring congeners, platensimide A [(−)-**4**], homoplatensimide A [(−)-**5**], homoplatensimide A methyl ester [(−)-**6**], and platensimycins B_1 [(−)-**7**] and B_3 [(−)-**9**]. The latter accomplishments represent the first total syntheses of these natural products. The reported synthetic strategies and methods are expected to facilitate the construction of further designed analogues of platensimycin and to find further applications in chemical synthesis.

Supplementary Material

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Acknowledgments

We thank Drs. D. H. Huang, R. Chadha, and G. Siuzdak for NMR spectroscopic, X-ray crystallographic, and mass spectrometric assistance, respectively. We also gratefully acknowledge A. Nold and Dr. H. Zhang for assistance with chiral HPLC, and Profs. X. Zhang, A. Lei, D. Crich, Drs. P. G. Bulger, L. A. McAllister, and J. S. Chen for helpful discussions. We are especially grateful to Dr. S. B. Singh for providing an authentic sample of natural platensimycin and NMR spectra of homoplatensimide A, and verification of the optical rotation of platensimide A. Financial support was provided by grants from the National Institutes of Health (USA), National Science Foundation (CHE-0603217) and Skaggs Institute for Research, graduate fellowships from Bristol-Myers Squibb and Eli Lilly (both to A.L.) and Novartis (to S.P.E.), and a postdoctoral fellowship from Merck Sharp & Dohme (to D.J.E).

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33. HPLC conditions: Chiralpak AD, hexane/*i*-PrOH 98:2, 0.1 mLmin^{-1}, $R_{t(minor)}$ = 22.05 min, $R_{t(major)}$ = 24.55 min; a pseudoracemate of 18 was obtained through the same sequence of reactions using a 1:1 mixture of (*RR,*)- and (*S*,*S*)-pseudoephedrine in the acylation step.
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35. (a) Bérard D, Alexandre J, Canesi S. Tetrahedron Lett 2007;48:8238–8241. (b) Bérard D, Racicot L, Sabot C, Canesi S. Synlett 2008:1076–1080. (c) Bérard D, Giroux MA, Racicot L, Sabot C, Canesi S. Tetrahedron 2008;64:7537–7544. (d) Sabot C, Commare B, Duceppe MA, Nahi S, Guérard KC, Canesi S. Synlett 2008:3226–3230. (e) Sabot C, Guérard KC, Canesi S. Chem Commun 2009:2941–2943.
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37. For selected reviews of the use of SmI_2 in organic synthesis, see: (a) Molander GA. Chem Rev 1992;92:29–68. (b) Molander GA. Org React 1994;46:211–367. (c) Molander GA, Harris CR. Chem Rev 1996;96:307–338. [PubMed: 11848755] (d) Molander GA, Harris CR. Tetrahedron 1998;54:3321–3354.(e) Kagan, HB.; Namy, J-L. Lanthanides: Chemistry and Use in Organic Synthesis. Kobayashi, S., editor. Springer; Berlin: 1999. p. 155-198. (f) Kagan HB. Tetrahedron 2003;59:10351–10372. (g) Edmonds DJ, Johnston D, Procter DJ. Chem Rev 2004;104:3372–3404.
38. Pure tricyclic hydroxy olefin (−)-13a was obtained through reaction of the (−)-13a:(+)-13b mixture with TBSCl and imidazole in DMF which led to selective silylation of the undesired diastereomer [(+)-13b] due to the steric reasons. See SI for further details.
39. For a review of radical conjugate additions, see: Srikanth GSC, Castle SL. Tetrahedron 2005;61:10377–10441.

40. (a) Nicolaou KC, Lysenko Z. J Am Chem Soc 1977;99:3185–3187. (b) Nicolaou KC, Lysenko Z. Tetrahedron Lett 1977;18:1257–1260.

41. CCDC-739776 contains the supplementary crystallographic data for (−)-12 and is available free of charge from The Cambridge Crystallographic Data Centre *via*. www.ccdc.cam.ac.uk/data_request/cif

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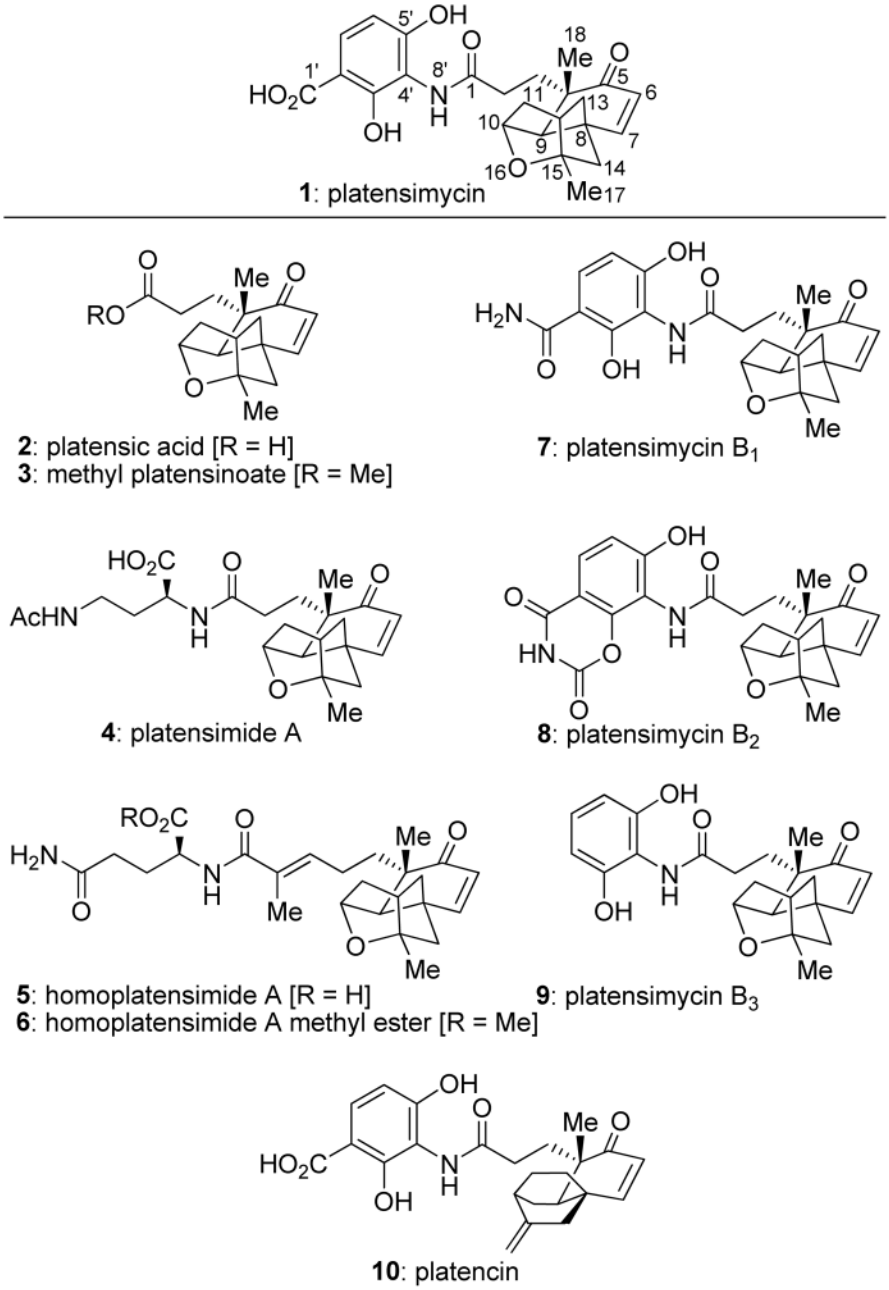


Figure 1.
Molecular structures of platensimycin (**1**) and related natural products (**2**–**10**).

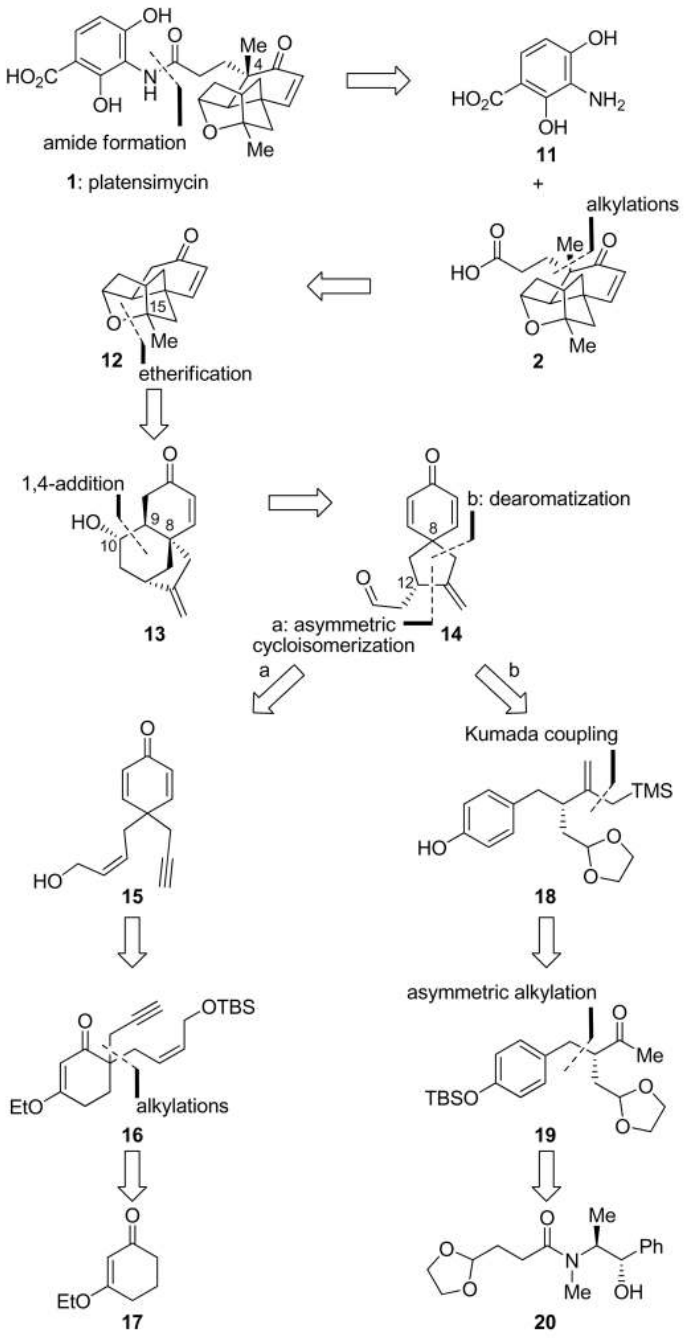


Figure 2.
Retrosynthetic analysis of platensimycin (**1**).

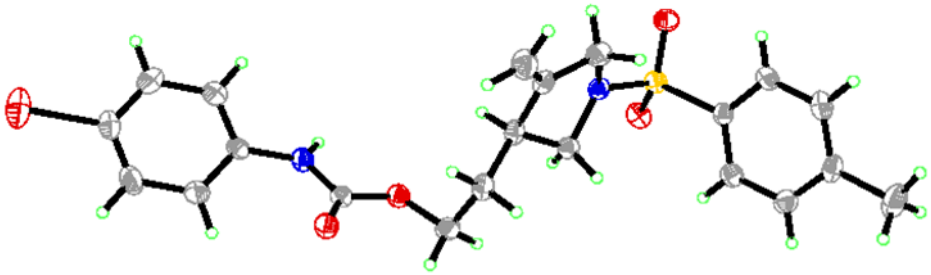


Figure 3.
X-Ray derived ORTEP drawing of *p*-bromophenyl carbamate **40b**. Non-hydrogen atoms are shown as 30% ellipsoids.

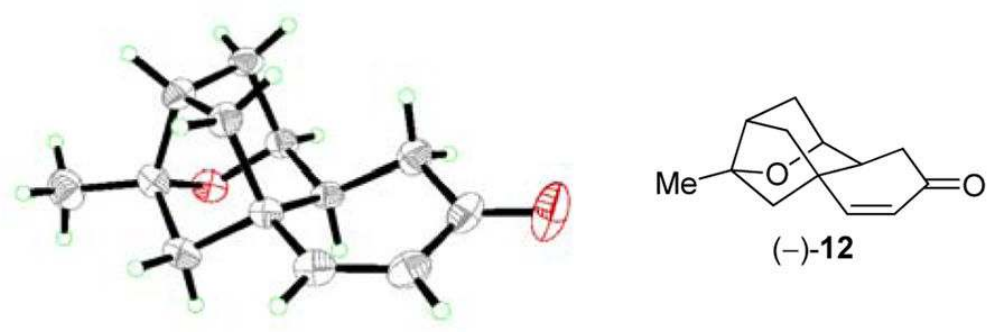
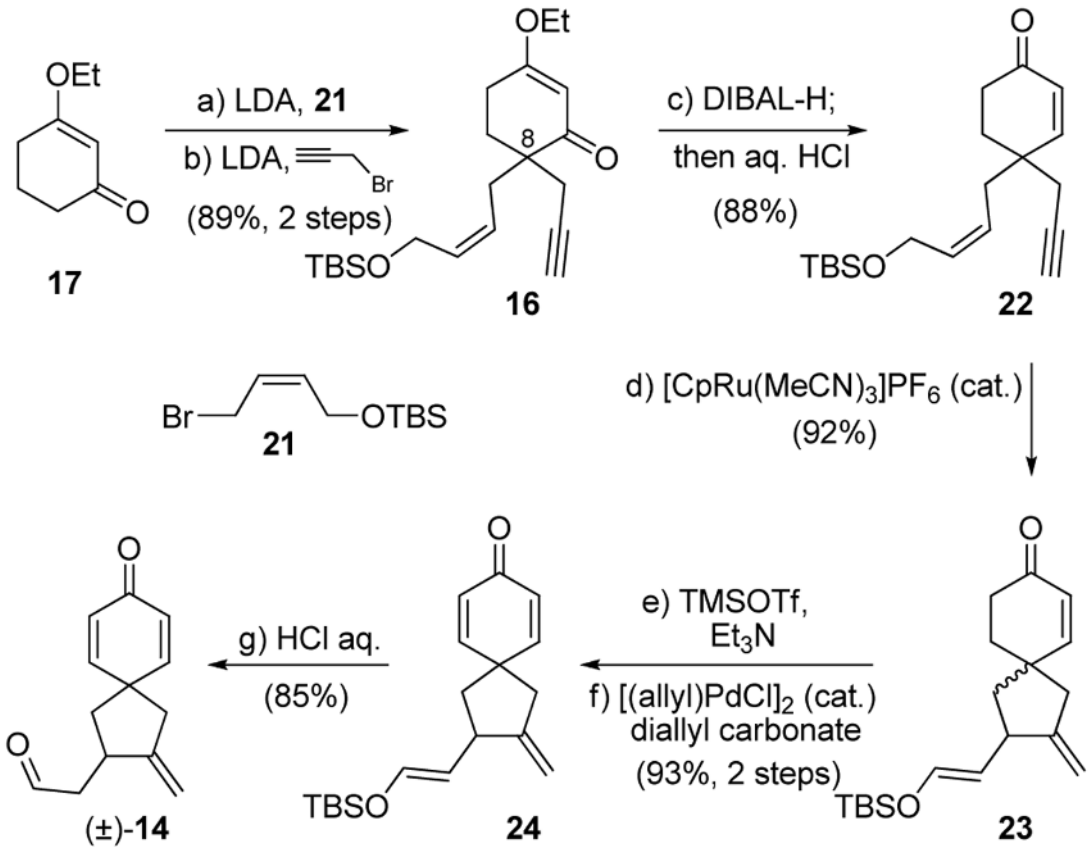
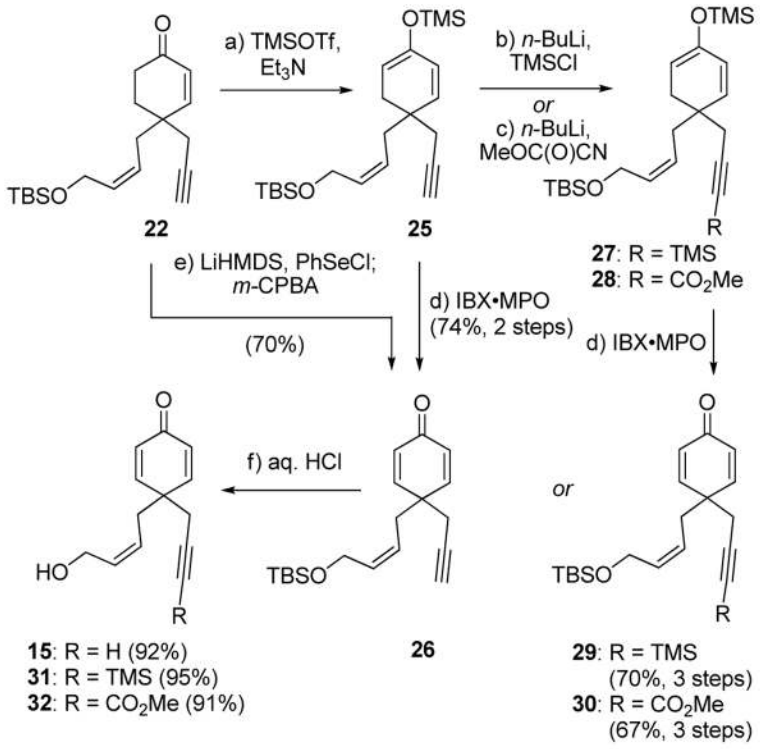


Figure 4.
X-Ray derived ORTEP drawing of (−)**-12**. Non-hydrogen atoms are shown as 30% ellipsoids.



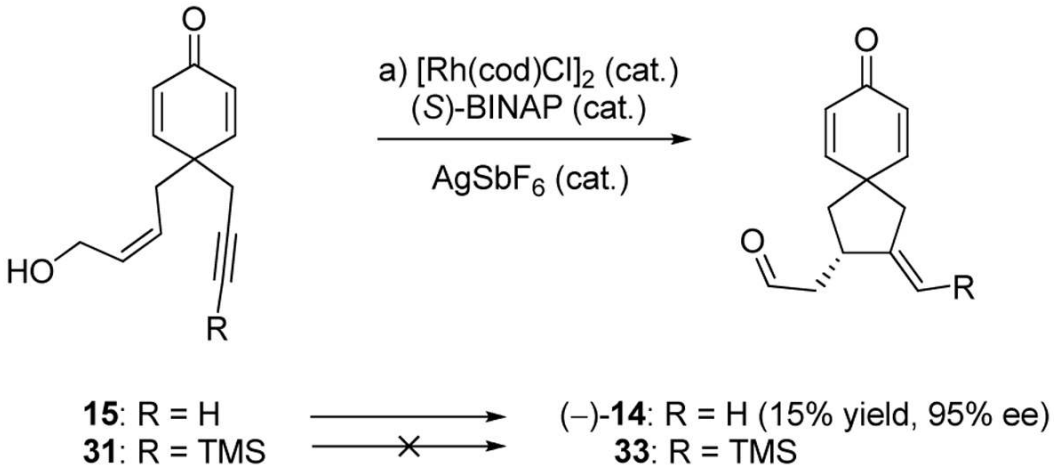
Scheme 1. Optimized Synthesis of Aldehyde (±)-14[a]

[a] Reagents and conditions: a) LDA (1.2 equiv), **21** (1.5 equiv), THF, −78 → 22 °C, 6 h, 92%; b) LDA (1.4 equiv), propargyl bromide (3.0 equiv), THF, −78 → 22 °C, 13 h, 97%; c) DIBAL-H (1.0 M in hexanes, 1.2 equiv), THF, −78 → −20 °C, 1 h; then 1 N aq. HCl, 0 °C, 30 min, 88%; d) $[CpRu(MeCN)_3]PF_6$ (0.02 equiv), acetone, 22 °C, 1.5 h, 92%, ca. 1:1 diastereomeric mixture; e) TMSOTf (1.2 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 0 °C, 30 min; f) $Pd_2(dba)_3$•$CHCl_3$ (0.05 equiv), diallyl carbonate (2.0 equiv), CH_3CN, 22 °C, 12 h, 93% (2 steps); g) 1 N aq. HCl/THF (1:1), 22 °C, 2 h, 85%.



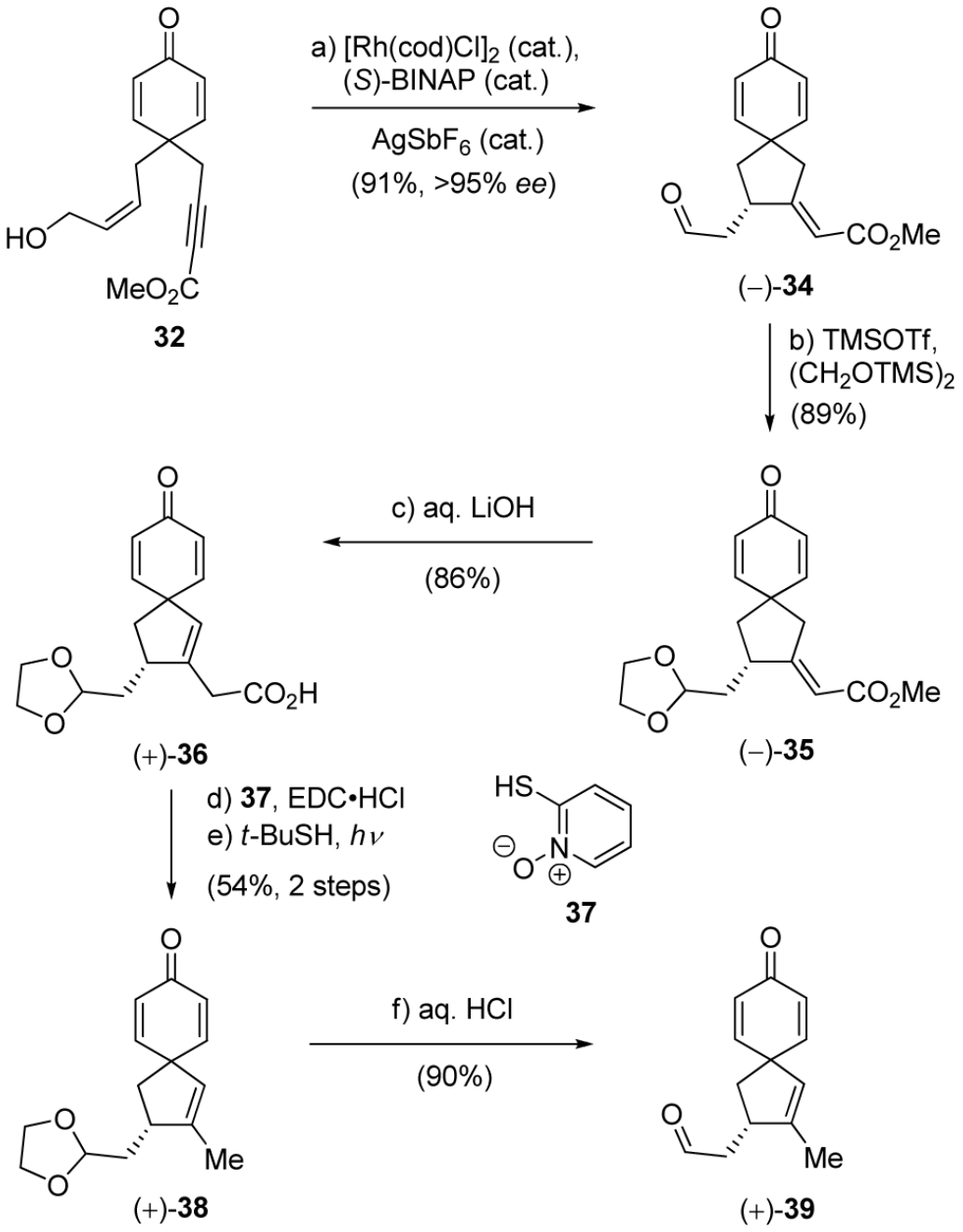
Scheme 2. Synthesis of Cycloisomerization Substrates 15, 31, and 32[a]

[a] Reagents and conditions: a) TMSOTf (1.2 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 0 °C, 30 min; b) *n*-BuLi (1.2 equiv), TMSCl (1.5 equiv), THF, −78 → −40 °C, 30 min; c) *n*-BuLi (1.2 equiv), MeOC(O)CN (1.5 equiv), THF, −78 → −40 °C, 30 min; d) IBX (1.2 equiv), MPO (1.2 equiv), DMSO, 22 °C, 3 h, 74% for **26** (2 steps), 70% for **29** (3 steps), 67% for **30** (3 steps); e) LiHMDS (1.05 equiv), PhSeCl (1.05 equiv), THF, −78 °C, 10 min; then *m*-CPBA (1.2 equiv), −78 → −40 °C, 30 min, 70%; f) 1 N aq. HCl, THF, 0 °C, 1 h, 92% for **15**, 95% for **31**, 91% for **32**.



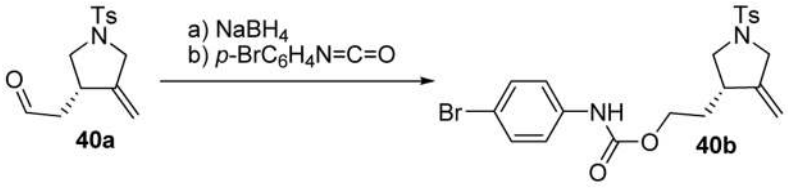
Scheme 3. Preliminary Asymmetric Cycloisomerization Reactions with Enynes 15 and 31[a]

[a] Reagents and conditions: a) $[Rh(cod)Cl]_2$ (0.05 equiv), (*S*)-BINAP (0.11 equiv), $AgSbF_6$ (0.20 equiv), DCE, 22 °C, 8 h.



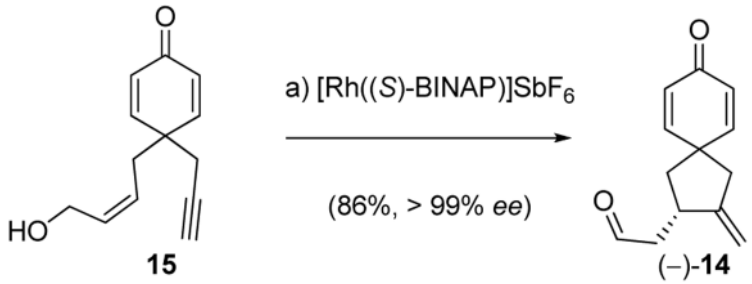
Scheme 4. Cycloisomerization of Ester Enyne 32 and Subsequent Decarboxylation of the Product[a]

[a] Reagents and conditions: a) $[Rh(cod)Cl]_2$ (0.05 equiv), (*S*)-BINAP (0.11 equiv), $AgSbF_6$ (0.20 equiv), DCE, 22 °C, 1 h, 91%; b) $(CH_2OTMS)_2$ (2.0 equiv), TMSOTf (1.0 equiv), −78 °C, 1 h, 89%; c) 0.6 N aq. LiOH (4.0 equiv), THF, 0 °C, 2 h, 86%; d) EDC•HCl (1.1 equiv), **37** (1.1 equiv), CH_2Cl_2, 22 °C, 2 h; e) visible light, 65 W lamp, *t*-BuSH (3.0 equiv), THF/benzene, 22 °C, 54% (2 steps); f) 1 N aq. HCl/THF (1:1), 40 °C, 20 min, 90%.



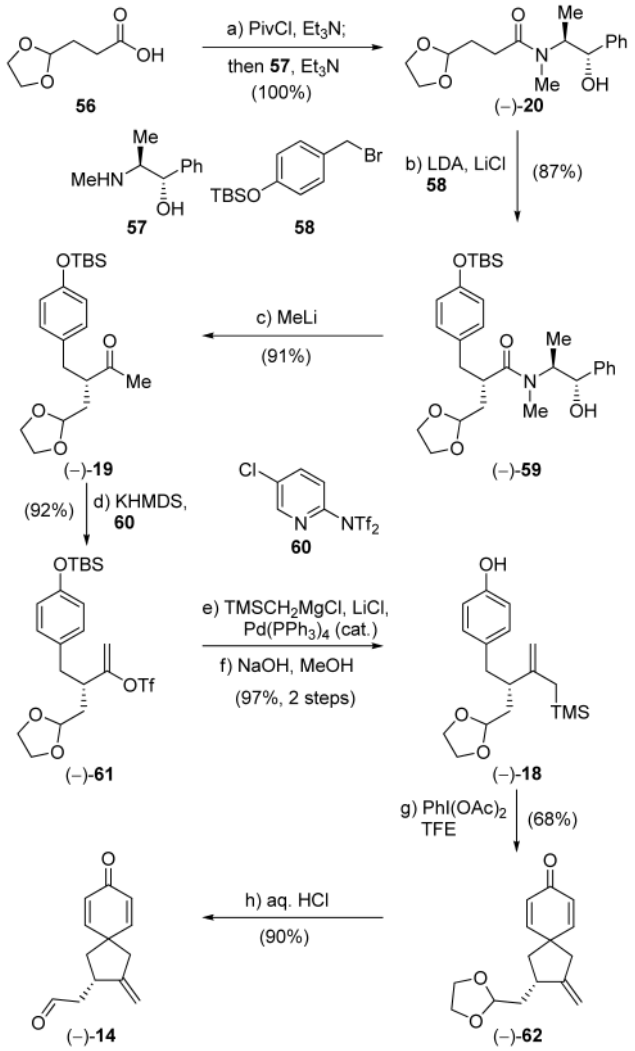
Scheme 5. Preparation of Crystalline *p*-Bromophenyl Carbamate 40b[a]

[a]Reagents and conditions: a) $NaBH_4$ (1.5 equiv), EtOH, 0 °C, 15 min; b) *p*-bromophenyl isocyanate Reagents and conditions: a) $NaBH_4$ (1.05 equiv), Et_3N (1.05 equiv), 0 °C, 1 h, 72% over 2 steps.



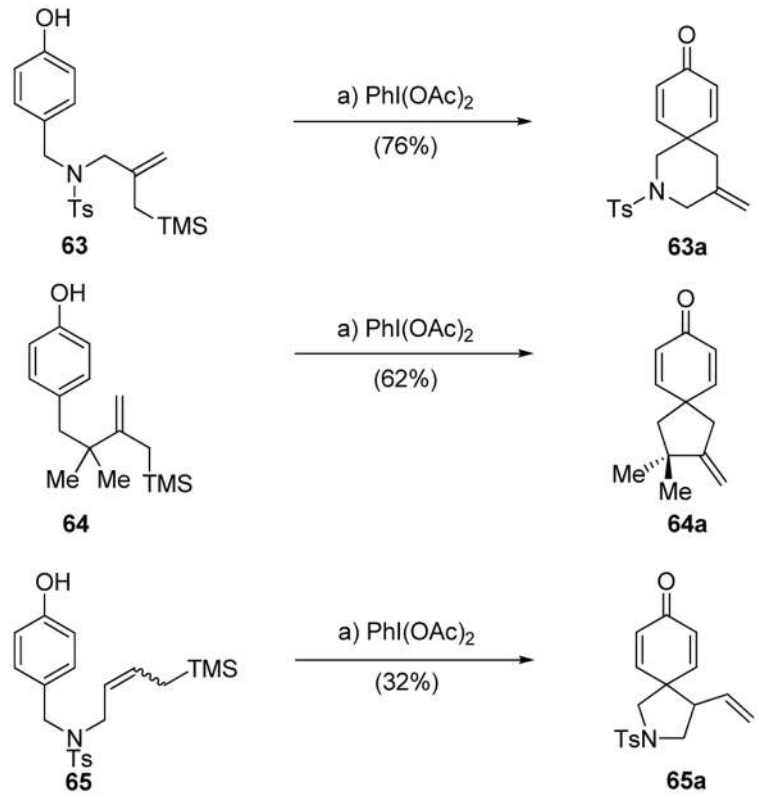
Scheme 6. Asymmetric Cycloisomerization of Enyne 15 to Aldehyde (−)-14[a]

[a] Reagents and conditions: a) [Rh((*S*)-BINAP)]SbF_6 (0.05 equiv), DCE, 23 °C, 12 h, 86% yield, > 99% ee.



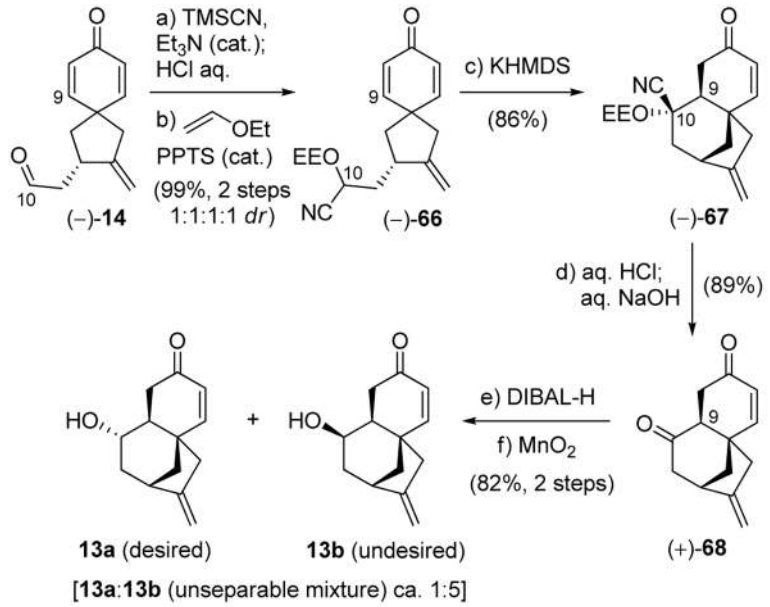
Scheme 7. Synthesis of Aldehyde (−)-14 Through Oxidative Dearomatization[a]

[a] Reagents and conditions: a) **56** (1.3 equiv), PivCl (1.3 equiv), Et_3N (3.0 equiv), MeCN, 0 °C, 1 h; then **57** (1.0 equiv), Et_3N (1.0 equiv), THF, 30 min, 100%; b) LDA (2.1 equiv), LiCl (7.0 equiv), **58** (1.3 equiv), −78 → 0 °C, 1.5 h, 87%; c) MeLi (1.36 M in Et_2O, 4.0 equiv), THF, −78 → −22 °C, 40 min, 91%; d) KHMDS (0.5 M in toluene, 2.5 equiv), **60** (2.5 equiv), THF, −78 → 0 °C, 1 h, 92%; e) $TMSCH_2MgCl$ (1.1 M in THF, 3.0 equiv), LiCl (3.0 equiv), $Pd(PPh_3)_4$ (2.5 mol %), THF, 22 °C, 30 min, 97%; f) NaOH (2.5 % w/v in MeOH), 0 → 22 °C, 2 h, 100%; g) $PhI(OAc)_2$ (1.2 equiv), TFE, −10 °C, 20 min, 68%; h) 1 N aq. HCl/THF (1:1), 40 °C, 3 h, 90%.



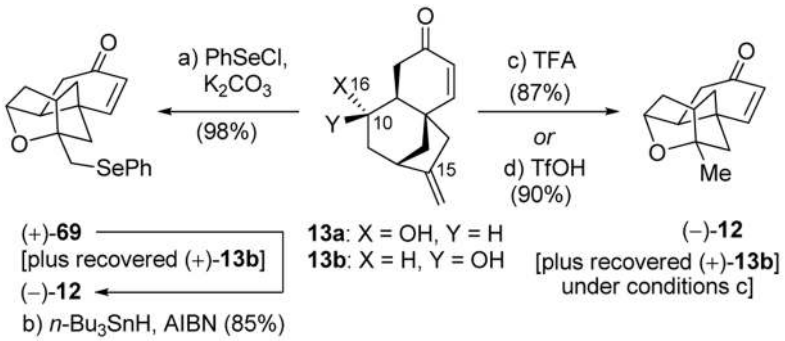
Scheme 8. Further Oxidative Cyclizations of Phenolic Allylsilanes to Spirosystems[a]

[a] Reagents and conditions: a) $PhI(OAc)_2$ (1.2 equiv), TFE, −10 °C, 20 min.



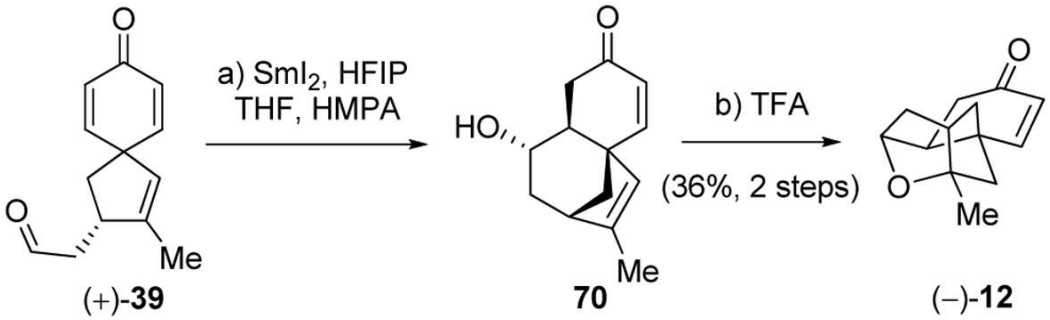
Scheme 9. Cyclization of Aldehyde (−)-14 *via* Cyanohydrin Formation[a]

[a] Reagents and conditions: a) TMSCN (1.2 equiv), Et_3N (0.2 equiv), CH_2Cl_2, 22 °C, 1 h; 1 N aq. HCl, 22 °C, 3 h; b) ethyl vinyl ether/CH_2Cl_2 (1:3), PPTS (0.1 equiv), 0 °C, 5 h, 99% (2 steps, mixture of 4 diastereoisomers, ca. 1:1:1:1); c) KHMDS (0.5 M in toluene, 1.5 equiv), THF, 0 °C, 10 min, 86% (ca. 1:1 mixture of diastereoisomers); d) 1 N aq. HCl/THF (1:1), 0 °C, 30 min; 2 N aq. NaOH, 0 °C, 30 min, 89%; e) DIBAL-H (1.0 M in hexanes, 2.4 equiv, −78 °C, 1 h; f) MnO_2 (5.0 equiv), EtOAc, 8 h, 82% (2 steps, **13a:13b** ca. 1:5).



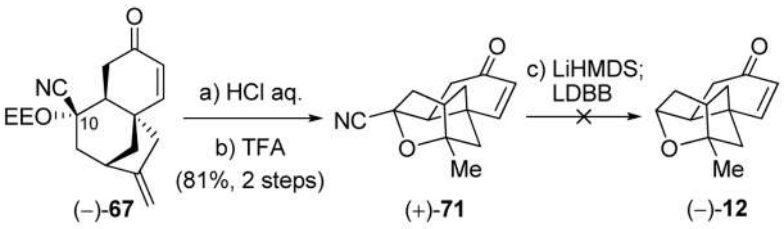
Scheme 10. Etherification Reactions of Hydroxy Olefin 13a/13b[a]

[a] Reagents and conditions: a) PhSeCl (1.5 equiv), K_2CO_3 (5.0 equiv), CH_2Cl_2, −78 °C, 15 min, 98% [plus recovered (+)-**13b**]; b) AIBN (0.2 equiv), *n*-Bu_3SnH (5.0 equiv), tolunene, 100 °C, 2 h, 85%; c) TFA/CH_2Cl_2 (2:1), 0 °C, 1.5 h, 87% [plus recovered (+)-**13b**]; d) TfOH (1.5 equiv), CH_2Cl_2, −78 °C, 1 h, 90% [plus recovered (+)-**13b** and iso-**13b** with endocyclic olefin bond]. Yields of steps a, c, and d are based on **13a** contained within the mixture of **13a:13b** (ca. 2.2:1).



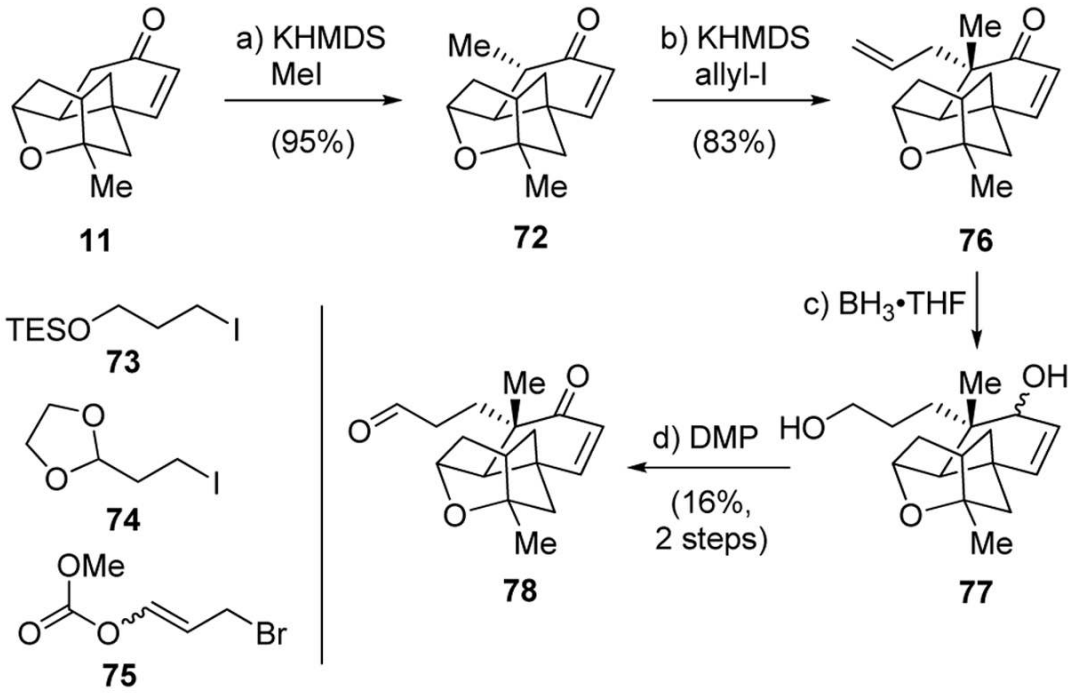
Scheme 11. Conversion of Endocyclic Aldehyde (+)-39 to Cage Compound (−)-12[a]

[a] Reagents and conditions: a) SmI_2 (0.1 M in THF, 2.2 equiv), HFIP (1.5 equiv), THF/HMPA (10:1), −78 °C, 1 min; b) TFA/CH_2Cl_2 (2:1), 0 °C, 1.5 h, 36% (2 steps).



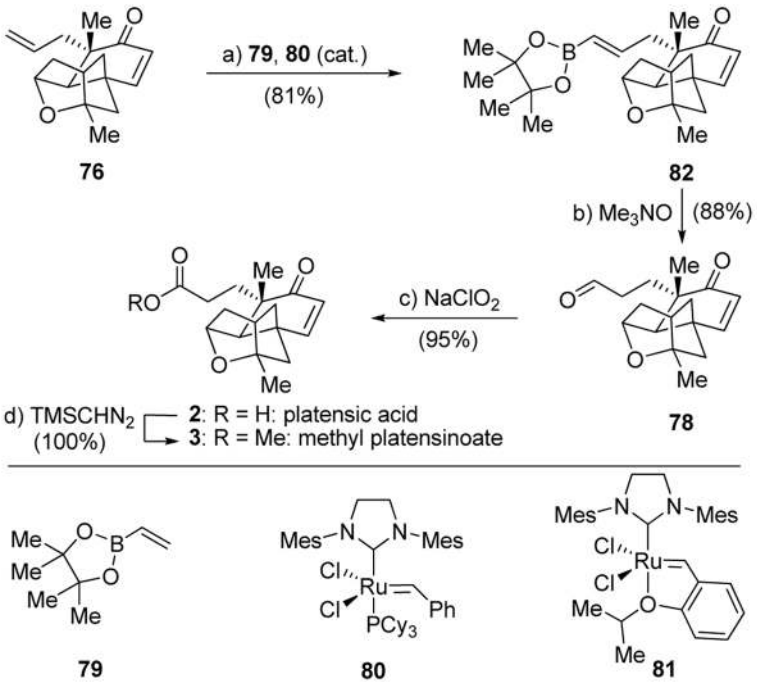
Scheme 12. Attempted Formation of (−)-12 *via* Cyano-Cage Compound (+)-71[a]

[a] Reagents and conditions: a) 1 N aq. HCl/THF (1:1), 0 °C, 30 min; b) TFA, 0 → 22 °C, 2 h, 81% (2 steps); c) LiHMDS (1.0 M in THF, 1.1 equiv), −78 °C, 15 min; LDBB (1.0 M in THF, 5 equiv), −78 °C, 2 h.



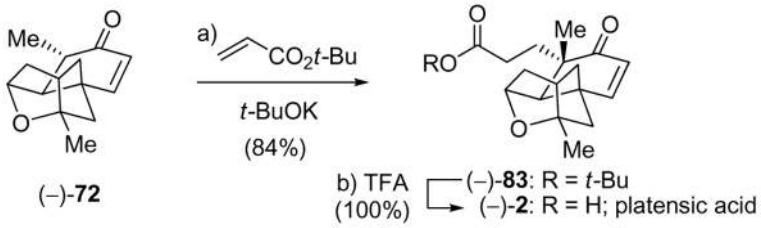
Scheme 13. Installation and Initial Manipulation of the Side Chain[a]

[a] Reagents and conditions: a) KHMDS (0.5 M in toluene, 1.5 equiv), MeI (4.0 equiv), THF/HMPA (5:1), −78 → −10 °C, 2 h, 95%; b) KHMDS (0.5 M in toluene, 2.0 equiv), allyl iodide (4.0 equiv), THF/HMPA (5:1), −78 → −10 °C, 2 h, 83%; c) BH_3•THF (1.0 M in THF, 2.5 equiv), THF, −78 °C, 20 min; d) Dess–Martin periodinane (4.0 equiv), CH_2Cl_2, 22 °C, 1 h, 16% (2 steps).



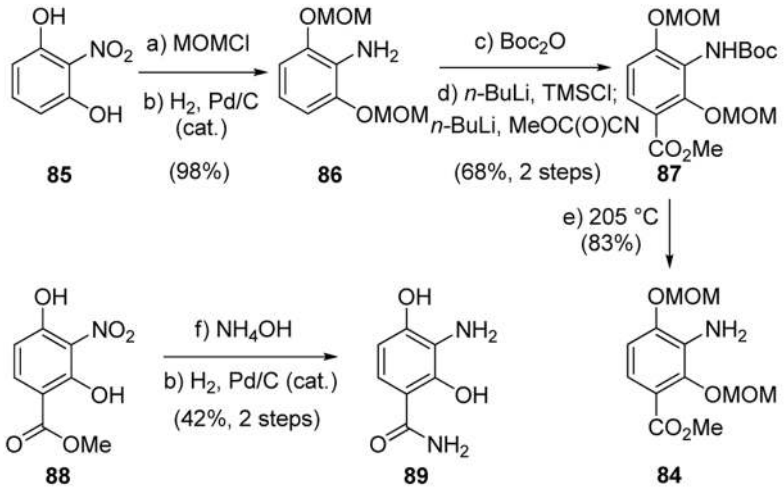
Scheme 14. Synthesis of Platensic Acid [(±)-2 and (−)-2] and Methyl Platensinoate [(±)-3 and (−)-3] *via* Cross Metathesis[a]

[a] Reagents and conditions: a) **79** (6.0 equiv), **80** (25 mol %) or **81** (10 mol %), CH_2Cl_2, 40 °C, 6 h, 81%, ca. 6:1 *E:Z*; b) Me_3NO (5.0 equiv), THF, 70 °C, 2 h, 88%; c) $NaClO_2$ (3.0 equiv), 2-methyl-2-butene (10 equiv), NaH_2PO_4 (5.0 equiv), *t*-BuOH:H_2O (1:1), 22 °C, 15 min, 95%; d) $TMSCHN_2$ (2.0 M in hexanes, 5.0 equiv), MeOH, 0 °C, 30 min, 100%.



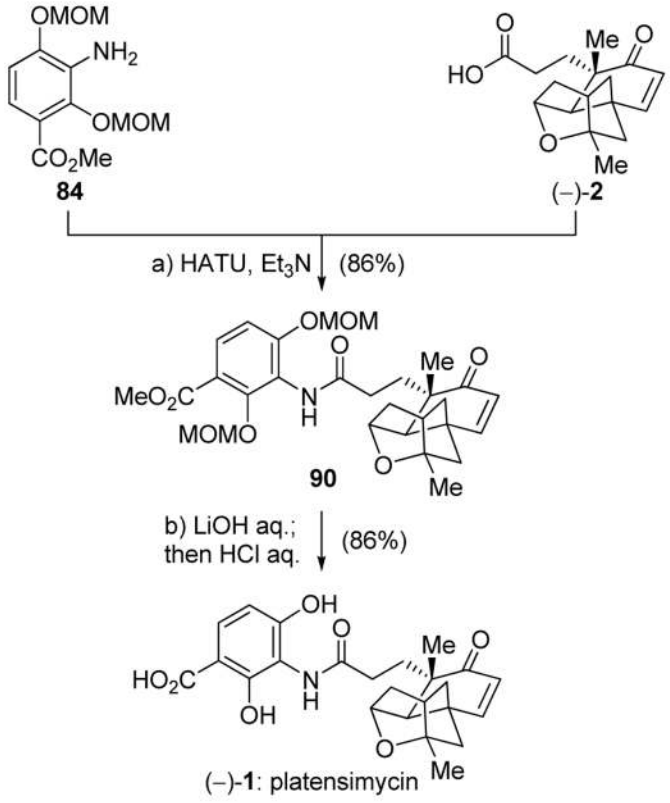
Scheme 15. Synthesis of Platensic Acid [(−)-2] *via* Michael Addition[a]

[a] Reagents and conditions: a) *tert*-butyl acrylate (3.0 equiv), *t*-BuOK (1.0 M in *t*-BuOH, 2.0 equiv), THF, −10 °C, 1 h, 84%; b) TFA/CH_2Cl_2 (1:1), 0 °C, 12 h, 100%.



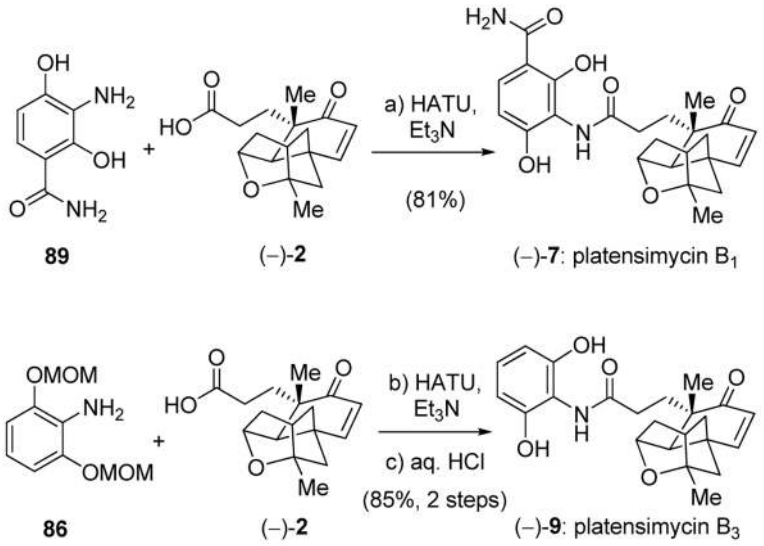
Scheme 16. Preparation of Aniline Derivatives 84, 86, and 89[a]

[a] Reagents and conditions: a) MOMCl (2.2 equiv), *i*-Pr_2NEt (3.0 equiv), DMF, 0 → 22 °C, 1.5 h, 98%; b) H_2 (balloon), 10% Pd/C (0.1 equiv), EtOAc, 22 °C, 1 h, 99% for **86**, 99% for **89**; c) Boc_2O (3.0 equiv), 40 °C, 4 h, 100%; d) *n*-BuLi (2.2 M in pentane, 1.0 equiv), TMSCl (1.0 equiv), −78 °C, 15 min; then *n*-BuLi (2.2 M in pentane, 1.2 equiv), methyl cyanoformate (1.2 equiv), THF, −78 °C, 30 min; then 1 N aq. HCl, 22 °C, 30 min, 68%; e) 1,2-dichlorobenzene, 205 °C, microwaves, 7 min, 83%; f) 28% aq. NH_4OH, 50 °C, 12 h, 42% (2 steps).



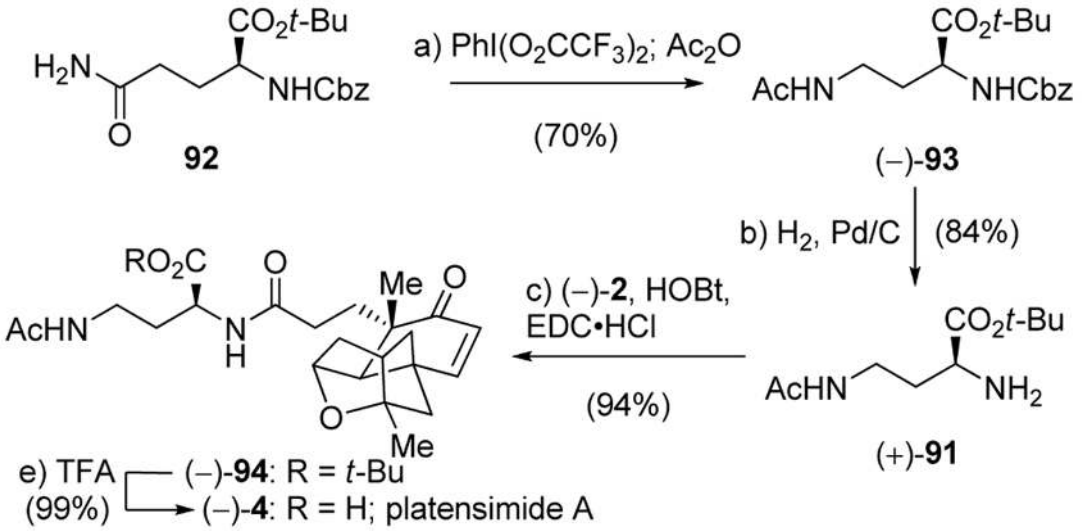
Scheme 17. Completion of the Asymmetric Total Synthesis of Platensimycin [(−)-1][a]

[a] Reagents and conditions: a) (−)-**2** (1.0 equiv), **84** (4.0 equiv), HATU (2.0 equiv), Et_3N (4.0 equiv), DMF, 22 °C, 12 h, 86%; b) 2.0 M aq. LiOH:THF(1:1), 45 °C, 2 h; then 2.0 M aq. HCl, 45 °C, 10 h, 86%.



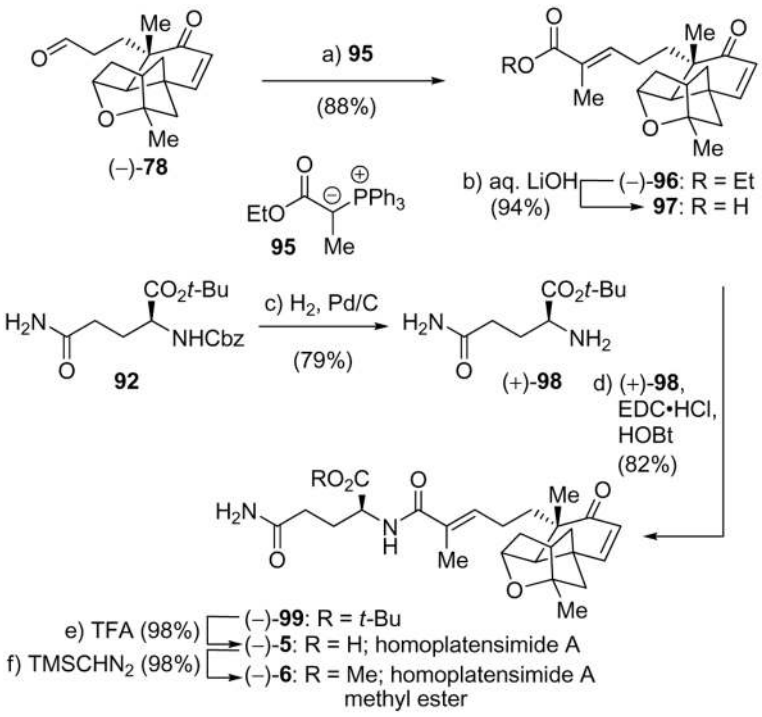
Scheme 18. Total Syntheses of Platensimycins B_1 [(−)-7] and B_3 [(−)-9][a]

[a] Reagents and conditions: a) (−)-**2** (1.0 equiv), **89** (4.0 equiv), HATU (2.0 equiv), Et_3N (5.0 equiv), DMF, 22 °C, 12 h, 81%; b) (−)-**2** (1.0 equiv), **86** (3.0 equiv), HATU (2.0 equiv), Et_3N (5.0 equiv), DMF, 22 °C, 12 h; c) 1 N aq. HCl/THF (1:1), 40 °C, 4 h, 85% (2 steps).



Scheme 19. Asymmetric Total Synthesis of Platensimide A [(−)-4][a]

[a] Reagents and conditions: a) $PhI(O_2CCF_3)_2$ (1.5 equiv), CH_3CN, water, 22 °C, 2 h; then Et_3N (10.0 equiv), Ac_2O (8.0 equiv), 30 min, 70%; b) H_2 (balloon), 10% Pd/C (0.1 equiv), EtOAc, 22 °C, 1 h, 92%; c) (−)-**2** (1.0 equiv), HOBt (3.0 equiv), EDC•HCl (3.0 equiv), CH_2Cl_2, 22 °C, 30 min; then (+)-**91** (3.0 equiv), 22 °C, 12 h, 94%; e) TFA/CH_2Cl_2 (1:1), 0 °C, 12 h, 99%.

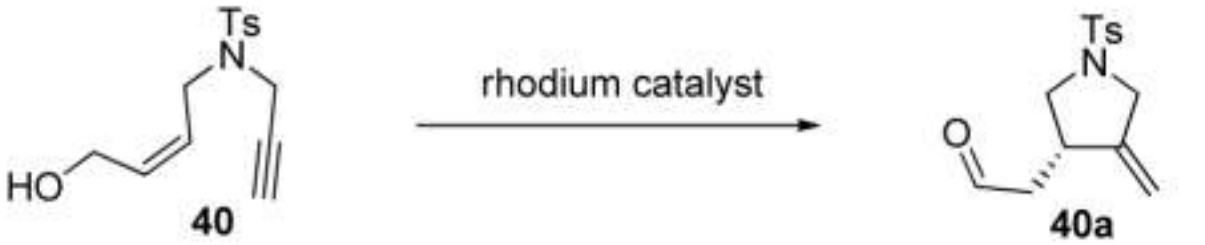


Scheme 20. Asymmetric Total Synthesis of Homoplatensimide A [(−)-5] and Homoplatensimide A Methyl Ester [(−)-6][a]

[a] Reagents and conditions: a) **95** (2.0 equiv), CH_2Cl_2, 22 °C, 3 h; b) 2 N aq. LiOH/THF (1:1) 50 °C, 12 h, 94%; c) H_2 (balloon), 10% Pd/C (0.1 equiv), EtOAc, 22 °C, 1 h, 90%; d) **97** (1.0 equiv), HOBt (3.0 equiv), EDC•HCl (3.0 equiv), CH_2Cl_2, 22 °C, 30 min; then (+)-**98** (3.0 equiv), 22 °C, 12 h, 82%; e) TFA/CH_2Cl_2 (1:1), 0 °C, 12 h, 98%; f) $TMSCHN_2$ (2.0 M in hexanes, 5.0 equiv), MeOH, 0 °C, 30 min, 98%.

Table 1

Catalyst Screening for the Asymmetric Cycloisomerization of Terminal Enyne **40**[a]



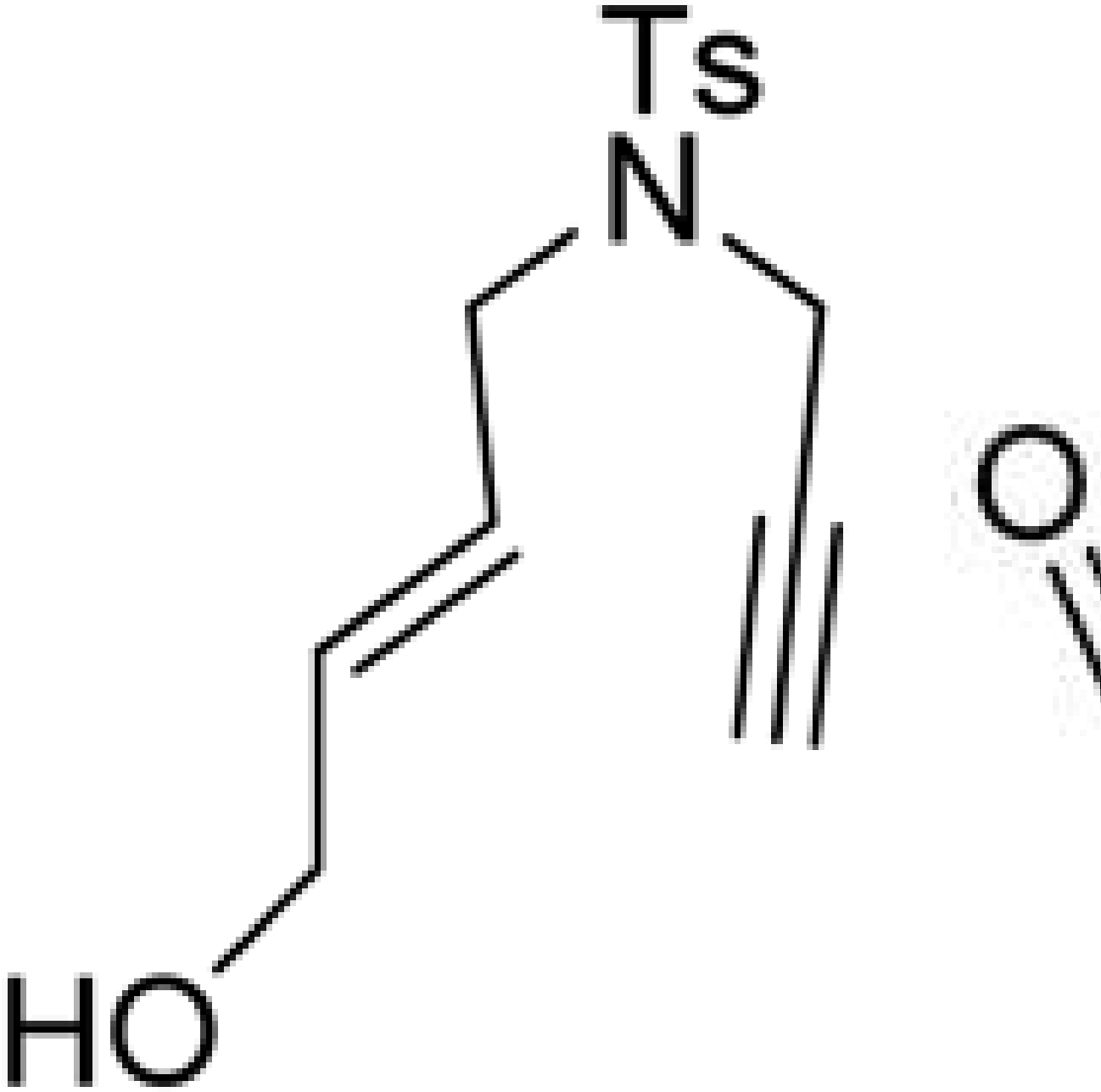
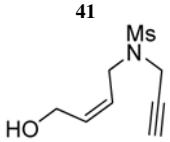
Entry	Catalyst	Yield of 40a (%)	ee (%)[b]
1	$[Rh(cod)(MeCN)_2]BF_4$, (*S*)-BINAP	36	90
2	$[Rh(cod)Cl]_2$, (*S*)-BINAP, AgOTf	60	91
3	$[Rh(cod)Cl]_2$, (*S*)-BINAP, $AgSbF_6$	65	95
4	*[Rh((S)-BINAP)]SbF_6*	*86*	*> 99*

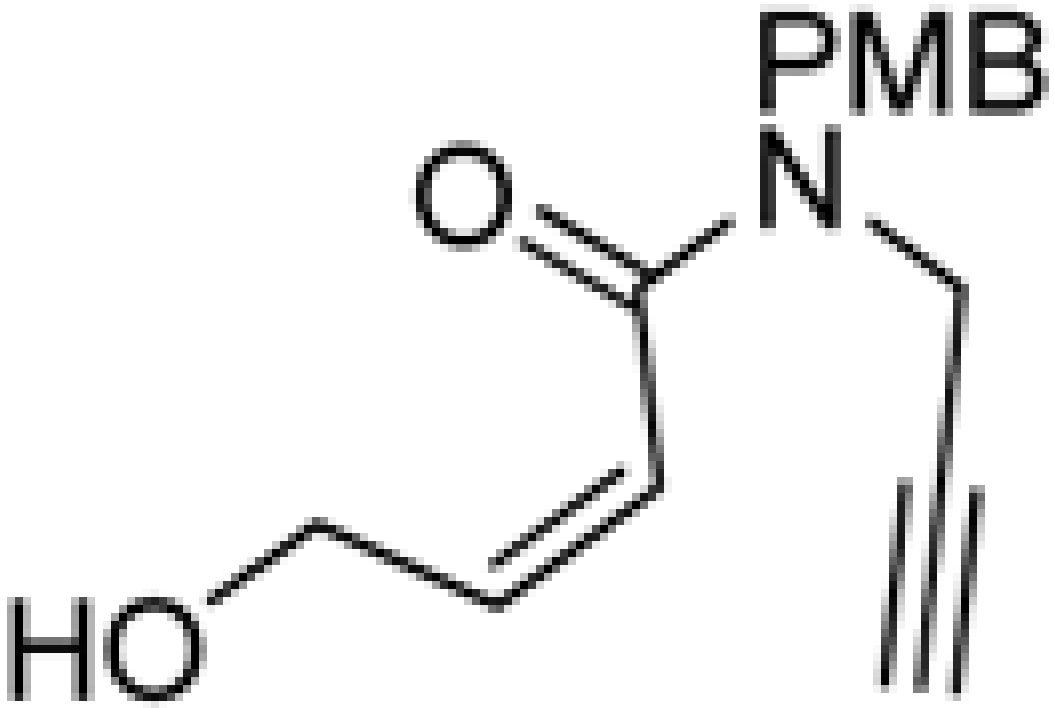
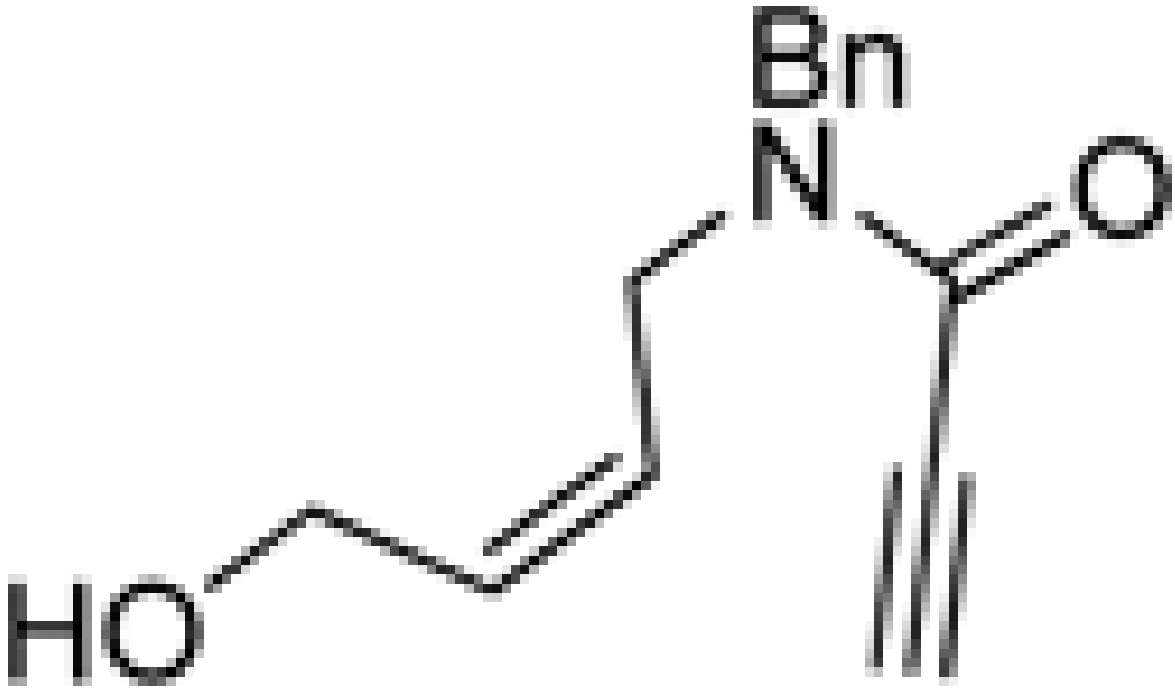
[a] Reactions were run in DCE (0.4 M) in the presence of 5–10 mol % catalyst at 23 °C for 12–16 h.

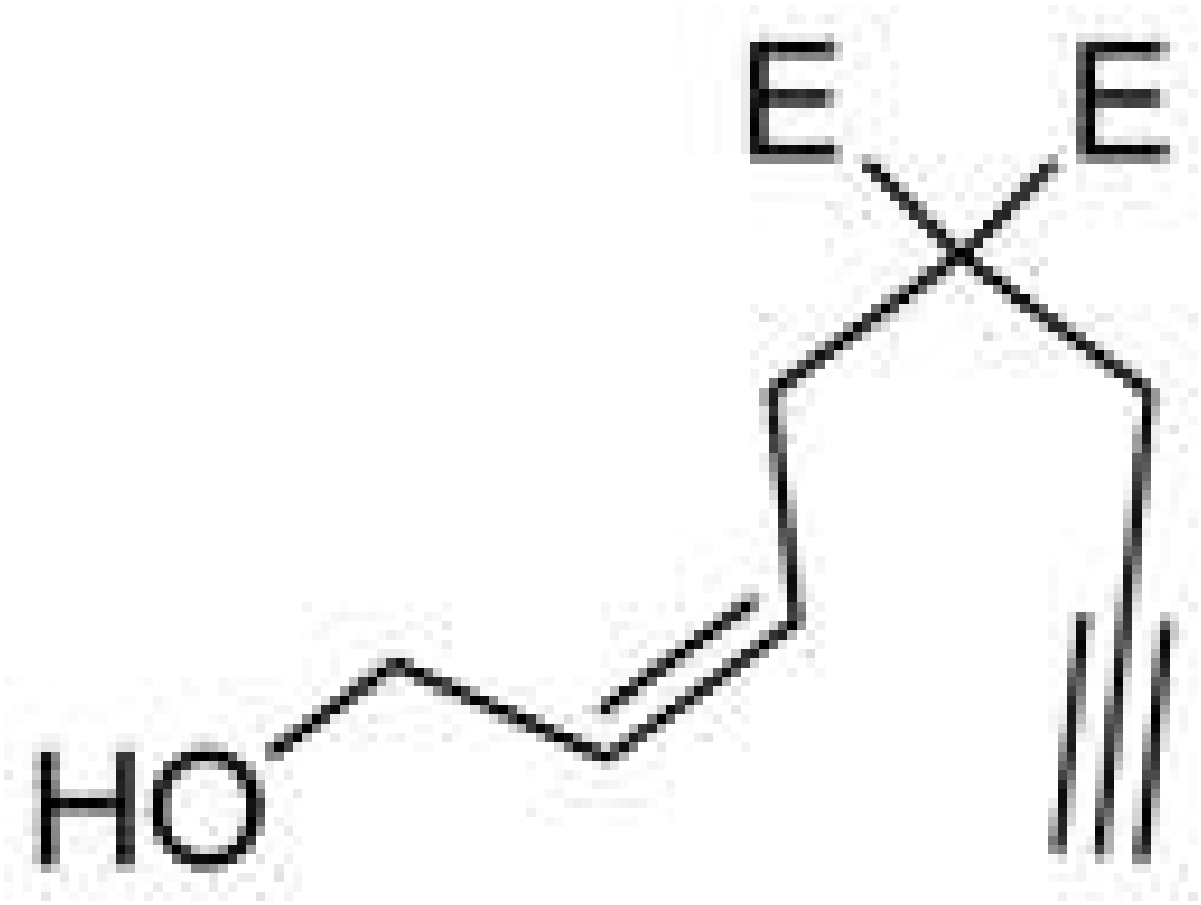
[b] Measured by chiral HPLC (OD-H column) after derivatization to the corresponding *p*-bromobenzoate ester.

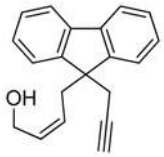
Table 2

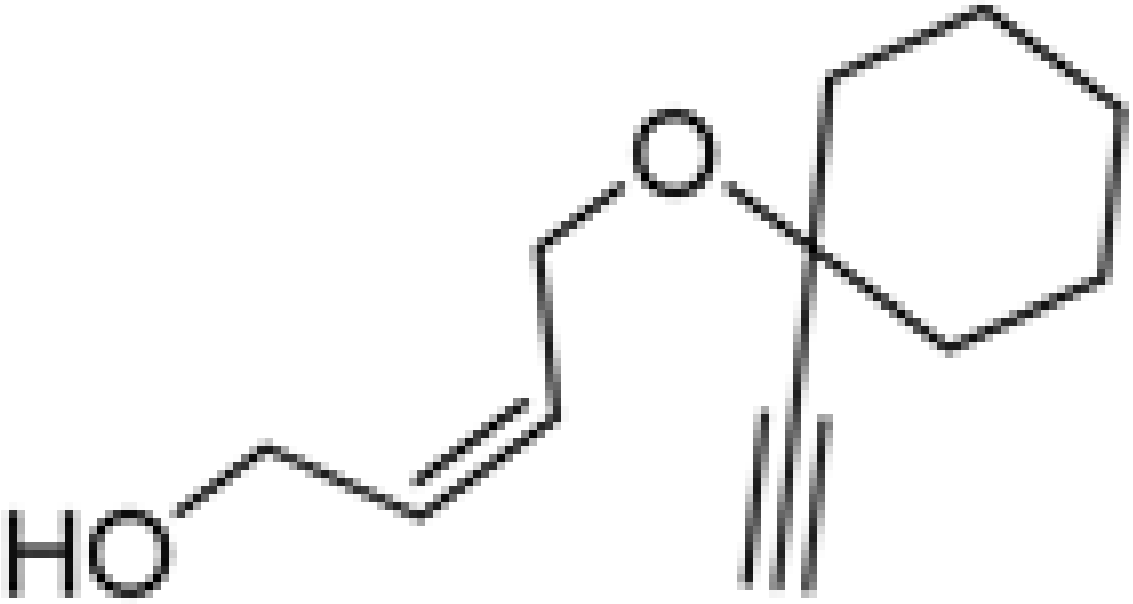
Asymmetric Cycloisomerization Reactions of Terminal Enynes[a]

Entry	Substrate
1	
2	**41**  **42**

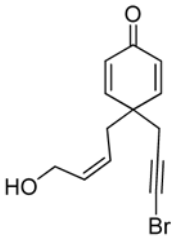
Entry	Substrate
3	 **43**
4[c]	 **44**

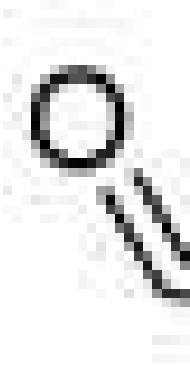
Entry	Substrate
5	 **45**: E = COOMe
6[c]	**46**: E = COO*i*-Pr
7[c]	**47**: E = SO_2Ph

Entry	Substrate
8	 **48**

Entry	Substrate
9	

49

Entry	Substrate
10	 **50**



[a] Reactions were run in DCE (0.4 M) in the presence of 10 mol % [Rh((*S*)-BINAP)]SbF_6 at 23 °C for 12–16 h.

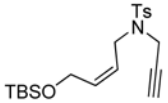
[b] Measured by ^1H and ^{19}F NMR spectroscopic analysis of the corresponding Mosher ester.

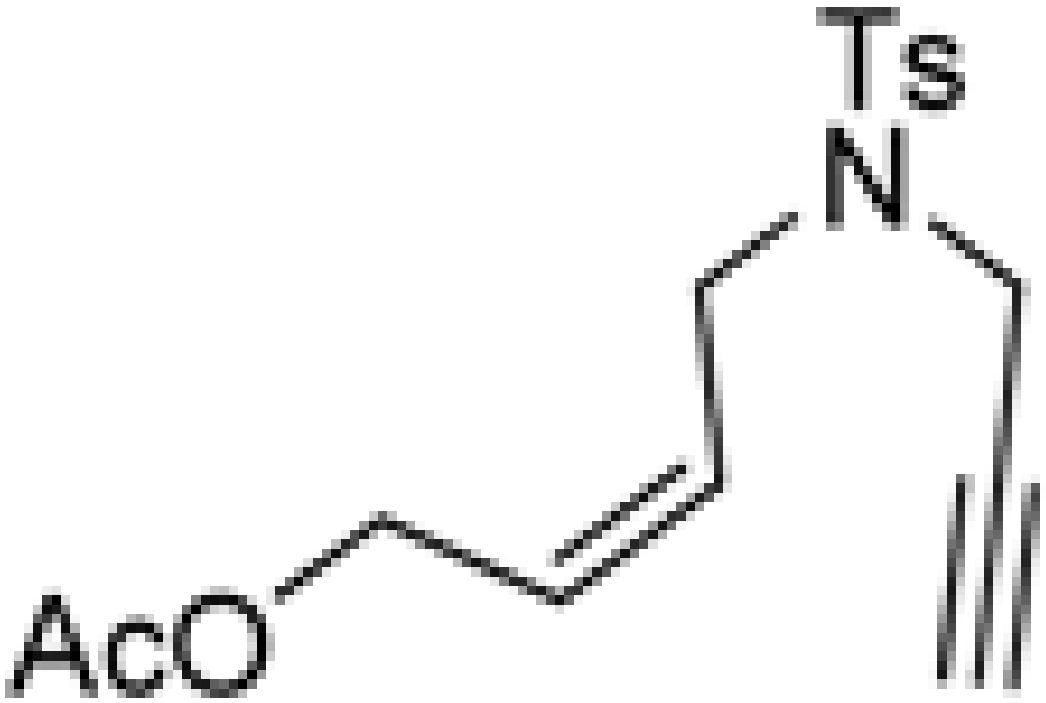
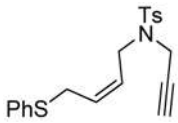
[c] Reaction was run in acetone as solvent.

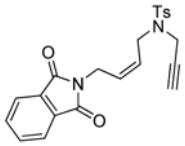
[d] Measured by chiral HPLC (OD-H column) after derivatization to the corresponding *p*-bromobenzoate ester or ethylene glycol acetal.

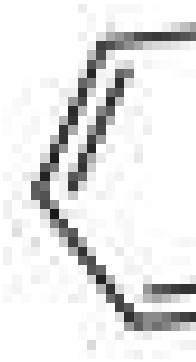
Table 3

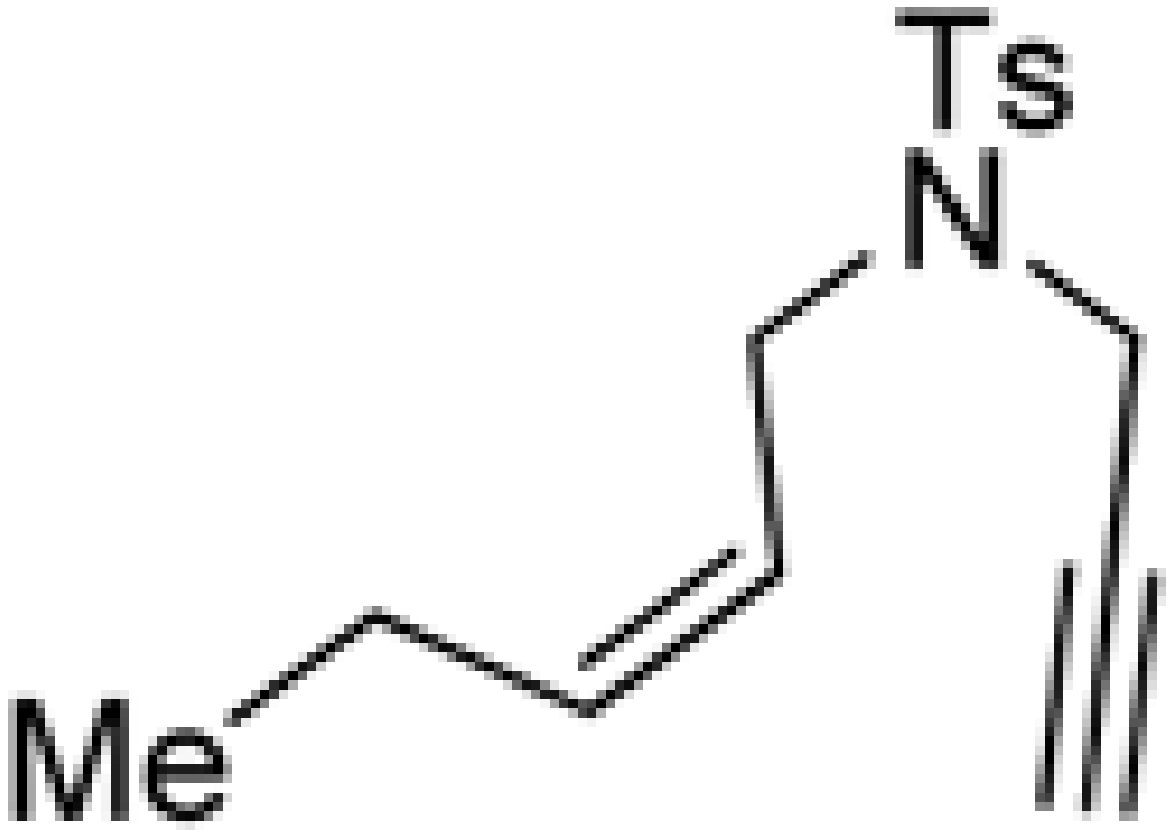
Further Examples of Asymmetric Cycloisomerization of Varying Enyne Substrates[a]

Entry	Substrate
1	 **51**

Entry	Substrate
2	 **52**
3	 **53**

Entry	Substrate
4	 **54**



Entry	Substrate	
5		**55**

[a] Reactions were run in acetone (0.4 M) in the presence of 10 mol % [Rh((*S*)-BINAP)]SbF_6 at 23 °C for 12–16 h.

[b] Measured by chiral HPLC (OD-H column) after derivatization to the corresponding *p*-bromobenzoate ester.

[c] $[\alpha]^{20}$ D = −64.3 (*c* = 0.79 in $CHCl_3$), suitable chiral HPLC conditions could not be found.

[d] Measured by ^{1}H NMR spectroscopic analysis of the corresponding Mosher ester prepared through sequential dihydroxylation-cleavage, reduction, and esterification.

[e] Measured by chiral HPLC (OD-H column) after sequential acid hydrolysis, reduction, and derivatization to the corresponding *p*-bromobenzoate ester.

Table 4

Optimization of the Dearomatization Reaction of Phenol (−)-**18** To Afford Spiro Hemiquinone (−)-**62** (Scheme 7)[a]

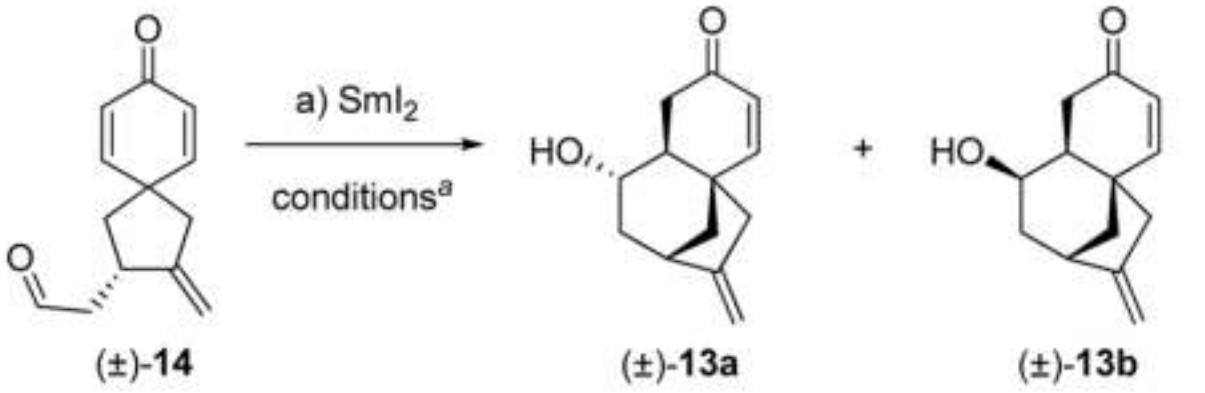
Entry	Oxidant	Solvent	Temperature (°C)	Yield of (−)-62 (%)[b]
1	$PhI(OAc)_2$	MeCN	0	10
2	$PhI(O_2CCF_3)_2$	TFE	0	49
3	PhIO	TFE	–10	26
4	*$PhI(OAc)_2$*	*TFE*	*–10*	*68*
5	$PhI(OAc)_2$	HFIP	–10	65

[a] Reactions were carried out at 0.030 M at the indicated temperature under an argon atmosphere.

[b] Yield of (−)-**62** isolated by aqueous work-up, followed by flash column chromatography.

Table 5

Samarium Diiodide-Mediated Cyclization of Aldehyde (±)-**14**[a]



Entry	Conditions	(±)-13a/13b yield (%)[b]	(±)-13a:13b ratio[c]
1	SmI_2 (2.2 eq.), 0 °C, 15 min	0d	–
2	SmI_2 (2.2 eq.), HMPA (10 eq.), 0 °C, 15 min	0d	–
3	SmI_2 (2.2 eq.), MeOH (1.5 eq.), 0 °C, 15 min	0d	–
4	SmI_2 (2.2 eq.), HMPA (10 eq.), MeOH (1.5 eq.), −78°C, 15 min	30	2:1
5	*SmI_2 (2.2 eq.), HMPA (10 eq.), HFIP (1.5 eq.), −78°C, 15 min*	*51*	*2.2:1*

[a]Reactions were carried out at 0.025 M in THF at the indicated temperatures under an argon atmosphere, using thoroughly degassed solvents and additives.

[b]Yield of a pure mixture of (±)-**13a/13b** isolated by aqueous work-up followed by flash silica column chromatography.

[c]Determined by ^{1}H NMR spectroscopic analysis of the inseparable mixture of (±)-**13a/13b** after purification.

[d]Complete consumption of (±)-**14** with no identifiable products.