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Organocatalysis

Total Synthesis of (−)-Platensimycin by Advancing Oxocarbenium- and Iminium-Mediated Catalytic Methods

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Dedicated to Professor Emeritus Masahiro Hirama for his mentorship and lasting contributions to complex and applied total synthesis

Abstract: (−)-Platensimycin is a potent inhibitor of fatty acid synthase that holds promise in the treatment of metabolic disorders (e.g., diabetes and "fatty liver") and pathogenic infections (e.g., those caused by drug-resistant bacteria). Herein, we describe its total synthesis through a four-step preparation of the aromatic amine fragment and an improved stereocontrolled assembly of the ketolide fragment, (−)-platensic acid. Key synthetic advances include 1) a modified Lieben haloform reaction to directly convert an aryl methyl ketone into its methyl ester within 30 seconds, 2) an experimentally improved dialkylation protocol to form platensic acid, 3) a sterically controlled chemo- and diastereoselective organocatalytic conjugate reduction of a spiro-cyclized cyclohexadienone by using the trifluoroacetic acid salt of α-amino di-*tert*-butyl malonate, 4) a tetrabutylammonium fluoride promoted spiro-alkylative *para* dearomatization of a free phenol to assemble the cagelike ketolide core with the moderate leaving-group ability of an early tosylate intermediate, and 5) a bismuth(III)-catalyzed Friedel–Crafts cyclization of a free lactol, with $LiClO_4$ as an additive to liberate a more active oxocarbenium perchlorate species and suppress the Lewis basicity of the sulfonyloxy group. The longest linear sequence is 21 steps with an overall yield of 3.8% from commercially available eugenol.

Introduction

As bacterial strains have evolved mechanisms according to Darwinian selection principles to foil drug treatments, the effectiveness of antibiotics has diminished steadily.[1] Hospitals worldwide have been plagued with the continual emergence of drug resistance, and multiple-drug-resistant strains of pathogenic Gram-positive bacteria are becoming more prevalent in the clinic. These include the potent strains of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE).[2] Most antibiotics used in clinics today generally work on limited biochemical processes, such as blocking the synthesis of the bacterial cell wall, deformation of the cell membrane, or inhibition of bacterial protein production. Henceforth, new classes of antibiotics will be continually needed in this enduring battle against the increasing drug resistance of microbes.

In 2006, Merck researchers reported the discovery of a new and potent antibiotic, (−)-platensimycin (**1**, Figure 1), isolated from *Streptomyces platensis* strain MA7327, which originated from South Africa.[3] A collection of 250000 natural product extracts was screened by using an antisense/RNA-based differential sensitivity assay in a search for new antibacterial agents targeting the fatty acid synthesis (FAS) pathway.[4] In vitro studies and in vivo assays with mice models showed that platensimycin possessed strong and broad-spectrum Gram-positive antibacterial activity.[3] Owing to its unique mode of action, platensimycin demonstrated no cross-resistance to an array of major antibiotic-resistant microbes. In view of its architectural complexity, platensimycin swiftly generated tremendous efforts in the chemical synthesis community; for example, the first total synthesis, in racemic form, was achieved by Nicolaou and co-workers just four months after the discovery of platensimycin was reported in 2006.[5–7] Despite unfavorable pharmacokinetics hindering the clinical progress of platensimycin in the

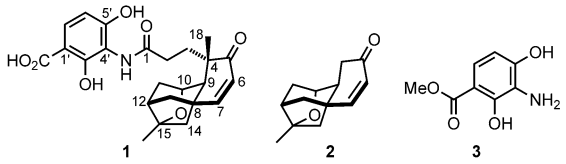

Figure 1. Structure of (−)-platensimycin (**1**) and common synthetic targets **2** and **3**.

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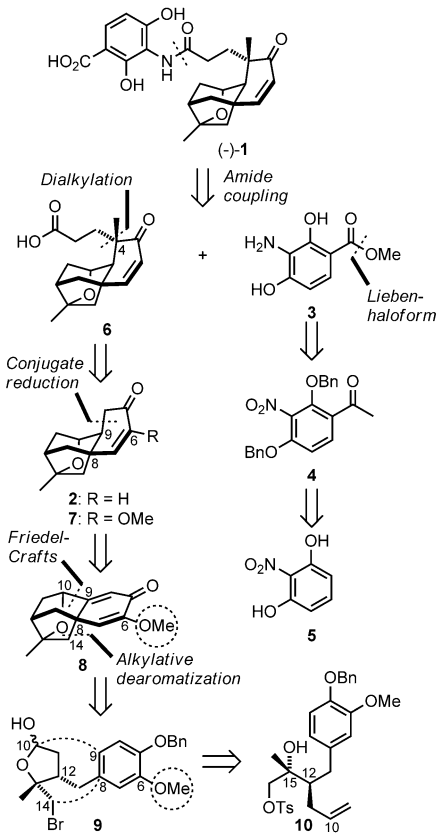
antibiotics pipeline hitherto, the highly selective mammalian FAS activity of this natural product continues to be of interest against metabolic disorders like diabetes and "fatty liver" steatosis,[8] and the structural complexity has resulted in numerous synthetic analogues of platensimycin.[9]

Synthetically, the development of a stereocontrolled route with convenient access to the *cis*-C8/C9 ring junction of the key tetracyclic ketolide, that is, the Nicolaou group's intermediate (−)-**2**, has been nontrivial.[7,9] The intermolecular Diels–Alder strategy has been successfully applied in the highly stereoselective assembly of the (±)-*cis*-decalin of the tetracyclic core,[6n,q,r] whereas high diastereoselectivity has been achieved under high-pressure asymmetric hydrogenation conditions.[6b,f] We have previously reported a high-yielding, enantioselective synthesis of **2** by developing a new Bi^{III}-catalyzed Friedel–Crafts cyclization to assemble the cagelike core, and we realized a stereocontrolled organocatalytic conjugate reduction to install the desired C8/C9 stereochemical configuration.[7h] Herein, we report a detailed account of our studies that led to the development of these key transformations to construct the intricate tetracyclic core **2**, as well as the development of a highly practical route to the tetrasubstituted aniline fragment **3** and completion of the total synthesis of (−)-**1** after further improvements in synthetic methods and practical matters.

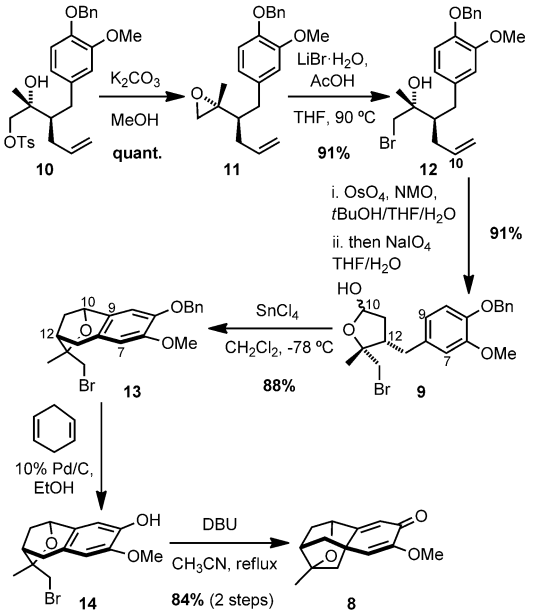
Results and Discussion

Our strategic disconnection (Scheme 1) of (−)-platensimycin (**1**) commenced at the amide bond to provide the aniline ester **3** and platensic acid (**6**). Ester **3** would be derived from the protected acetophenone **4** by a newly modified Lieben haloform reaction, which we developed during these synthetic studies and subsequently applied to the rapid oxidative esterification of aromatic methyl ketones.[10] Intermediate **4** would, in turn, be traced back through a double benzylation and a Friedel–Crafts acylation to commercially available 2-nitroresorcinol (**5**). A double disconnection of the propionate and methyl side arms of platensic acid (**6**) revealed the key tetracyclic enone **2** or the 6-methoxy version **7** as the primary synthetic subtarget. The inherent structural bias of the cagelike intermediate **2** (or **7**) would clearly provide the necessary α-facial stereocontrol in constructing the all-carbon, quaternary C4 stereocenter. The 6-methoxy group of the logical dienone precursor **8** was anticipated to provide a possible means to achieve the needed electronic and steric control in securing the desired *cis*-C8/C9-ring juncture in **7** reductively (see below). It should be noted, however, that the exact chemo- and diastereoselective conjugate conditions required for this reduction step were not obvious to us during our early retrosynthetic planning stages. Disconnection of the C9/C10 bond in **8** by way of a retro Friedel–Crafts cyclization[11] traced our synthesis back to lactol **9**. We were thus attracted to Marson type oxocarbenium chemistry as a straightforward approach to construct the oxabicyclo[3.2.1]octane motif and install the C10 stereocenter.[12] The *para*-directing 6-methoxy group in **9** was again expected to generate the desired C9/C10 regiocontrol. Additionally, a Masamune-inspired intramolecular spiro-alkylative dearomatization strategy[13] would complete the cagelike core of **8** from **9**. Lactol **9** could, in turn, be derived from the readily available monotosylated 1,2-diol **10** through a series of standard functional-group interconversions.



Scheme 1. Retrosynthetic analysis of (−)-platensimycin (**1**). Bn: benzyl; Ts: toluene-4-sulfonyl.

As reported previously in our initial communication, **10** was prepared from natural eugenol in a high overall yield of 75% over 7 steps and 91% *ee* through catalytic Sharpless epoxidation.[7h] Compound **10** was converted into bromohydrin **12** through epoxide-ring closure with K_2CO_3 in MeOH and subsequent regioselective reopening with LiBr (Scheme 2).[14] Two equivalents of AcOH were found to be necessary to realize the latter transformation in good, reliable yields. Oxidative double-bond cleavage with concomitant cyclization then furnished the *cis*-bromolactol **9** in 91% yield over 2 steps. Efforts to cyclize **9** into the benzotetrahydrofuran **13** were nontrivial. The initial conditions to drive the Marson cyclization with stoichiometric or excess amounts of Lewis acids, such as $BF_3{\cdot}Et_2O$[12b,c,15] and TMSOTf (TMS: trimethylsilyl; Tf: trifluoromethanesulfonyl), or a Brønsted acid, for example, TfOH, were either sluggish or resulted in complex mixtures. Significant decomposition of **13** into the original lactol **9** (major product) and the benzobromohydrin **16** (minor product) were always observed when the reaction was quenched with conventional aqueous protocols. The situation did not improve when the reaction mixture was treated with either an organic base or silica gel. After considerable experimentation, exposure to 5 equivalents of $SnCl_4$ at

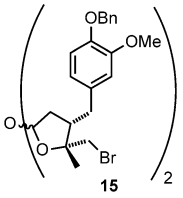


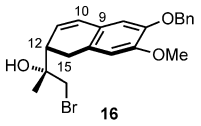
Scheme 2. Preparation of the tetracyclic dienone **8**. NMO: 4-methylmorpholine *N*-oxide; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene.

Table 1. Lewis acid promoted Friedel–Crafts arylation of bromolactol **9**.[a]

Entry	Lewis acid	mol%	*t* [h]	**13** [%]	**15**[b] [%]	**16** [%]	**9** [%]
1	$Al(OTf)_3$	50	12	–	67	–	–
2	$Sc(OTf)_3$	25	12	30	59	–	–
3	$La(OTf)_3$	25	12	54	33	–	–
4	$Bi(OTf)_3$	25	1.25	94	–	4	–
5	$FeCl_3$	50	1.5	78	–	trace	–
6	$InCl_3$	25	3	85	–	–	–
7	$AuCl_3$	50	2	82	–	–	–
8	$GaCl_3$	100	1	_[c]	_[c]	_[c]	_[c]
9	$Ph_3PAuCl/AgOTf$	50/50	12	–	62	–	22
10	$ZnCl_2$	100	12	–	72	–	10
11[d,e]	$HNTf_2$	40	2	59	–	–	–
12[d,e]	HOTf	25[f]	2	22	34	–	–
13	$Bi(OTf)_3$	10	1.5	88	–	trace	–
14	$Bi(OTf)_3$	2	4	62	31	–	–
15[g]	$Bi(OTf)_3$	5	1.5	92	–	2	–

[a] Conditions: **9** (20–30 mg), Lewis acid, 4 Å molecular sieves, CH_2Cl_2, room temperature; yields after isolation are shown. [b] Compound **15** could be converted into **13** with 10 mol% $Bi(OTf)_3$ in 80% yield. [c] A complex mixture was obtained. [d] Reaction was carried out at 0 °C. [e] TLC streaking and blotting of unidentified baseline material was observed. [f] One equivalent of HOTf liberated a complex mixture. [g] Reaction with compound **9** at the 540 mg scale.





−78 °C, coupled with quenching with a half-saturated Rochelle salt solution, provided **13** reliably in good yields at practical scales.[16] Excellent regio- and stereocontrol toward C9/C10 bond formation were achieved through the chiral center at the C12 atom by virtue of the *para*-directing 6-methoxy group. The alternative C7/C10 regioisomer and, notably, the C8/C10 *ipso* isomer were not detected.

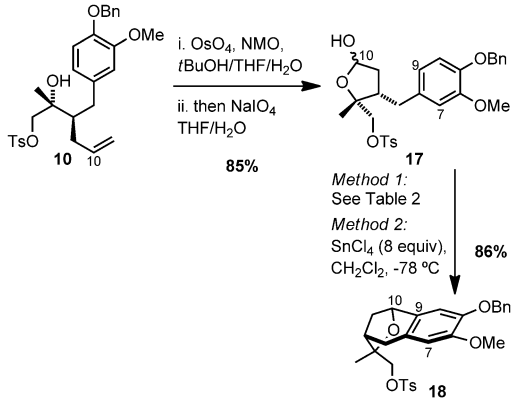
Debenzylation of **13** with ammonium formate in refluxing acetone[6e] resulted in an undesirable 1:1 mixture of the bromophenol **14** and its debromo derivative. A switch to 1,4-cyclohexadiene as the hydrogen source furnished **14** cleanly and quantitatively. This phenol was directly subjected to intramolecular alkylative dearomatization conditions without further purification. Treatment of **14** with strongly anionic bases, such as NaH and NaO*t*Bu, was unsuccessful in promoting the classical Winstein Ar-3′ spiro-cyclization,[17] and hydrolysis of the alkyl bromide was observed instead. Exposure of **14** to the conditions described by Boger et al. (DBU in refluxing CH_3CN)[13b,c] were also explored and successfully drove the alkylative dearomatization to afford the tetracyclic 6-methoxydienone **8** in 84% yield over 2 steps.

A practical limitation of this strategy was the excessive requirement for highly toxic and ecologically harmful $SnCl_4$ to drive the Friedel–Crafts arylation; thus, we were keen to develop a direct catalytic Friedel–Crafts method to form the tricyclic system **13**. Initially, **9** was treated with various oxophilic Lewis acids at 25–100 mol% loadings in the presence of 4 Å molecular sieves (Table 1, entries 1–10). The results collectively suggested that the Lewis acid activated transformation of the free lactol to its oxocarbenium species occurred readily, but the ensuing alkylative cyclization onto the aromatic ring appeared to be subtly encumbered. Competitive formation of the dimeric ether **15** was observed, with the Lewis acids showing little or none of the desired catalytic activity, including $Al(OTf)_3$, $Sc(OTf)_3$, Au^I/Ag^I, and $ZnCl_2$ (Table 1, entries 1, 2, 9, 10). Further experimentation revealed $Bi(OTf)_3$, $FeCl_3$, $InCl_3$, and $AuCl_3$ to be more effective than $SnCl_4$ in promoting the cyclization at substoichiometric amounts (Table 1, entries 4–7). Triflimide, a strong Brønsted acid, also furnished **13** in a modest yield of 59% (Table 1, entry 11). $Bi(OTf)_3$ was found to be the most superior in reactivity and afforded **13** in 94% yield within 1.25 h (Table 1, entry 4). The increasing use of bismuth(III) salts as oxophilic Lewis acids in organic reactions is attributed to their ecofriendliness, tolerance to air and moisture, and inexpensiveness.[18] The contrastingly poor results obtained with one equivalent or substoichiometric amounts of triflic acid (Table 1, entry 12) supported our hypothesis that the Bi^{III} Lewis acid was primarily responsible for catalyzing the Friedel–Crafts process. Furthermore, in the absence of 4 Å molecular sieves, cyclization with $Bi(OTf)_3$ generated several byproducts, which suggested that the presence of HOTf (likely generated in situ in the reaction mixture) was undesirable.

Next, the catalyst loading was reduced and the efficiency of the reaction was examined (Table 1, entries 13–15). This demonstrated that 5 mol% $Bi(OTf)_3$ was sufficient to drive the cyclization of **9** efficiently. Lower catalyst loadings (for example, 2 mol%; Table 1, entry 14) were not optimal and, in turn, led to the sluggish formation of **13** and undesired dimerization into **15**. Dimer **15** could, in turn, be conveniently transformed into

13 by simply adding more $Bi(OTf)_3$ (Table 1, footnote [b]). A secondary limitation with $Bi(OTf)_3$ as the catalyst was the undesired, ready formation of the relatively stable bromohydrin–olefin **16** upon quenching with saturated aqueous NH_4Cl. Alternative quenching with Rochelle salt solutions generated even more of the furan-opened olefin **16**. This unwanted benzylic ether cleavage of the tetrahydrofuran system in **13** could be minimized with reduced catalyst loadings.

In efforts to expand the substrate scope of our catalytic arylation protocol and to employ earlier intermediates of our synthesis, we investigated the Lewis acid mediated cyclization of the *cis*-tosyl lactol **17**, which could be accessed directly by oxidative cyclization of **10** (Scheme 3). Treatment of **17** under the



Scheme 3. Synthesis of the tosylbenzotetrahydrofuran **18**.

optimized conditions (Table 1, entry 13) gave the tosyl benzotetrahydrofuran **18** in 16% yield, even after 12 h (Table 2, entry 1). At stoichiometric quantities of $Bi(OTf)_3$, only a modest yield of 52% of **18** was observed after 12 h (Table 2, entry 2). In both situations, the initial lactol **17** was recovered and none of the dimeric ether was observed. This suggested that tosylate **17** was not as reactive as the bromo analogue **9** toward $Bi(OTf)_3$-catalyzed oxocarbenium formation. In additional stoichiometric studies, the treatment of **17** with $SnCl_4$ required an even greater excess (8–10 equiv) to achieve a high-yielding

Table 2. $Bi(OTf)_3$-promoted Friedel–Crafts arylation of tosyllactol **17**.[a]

Entry	Lewis acid	Amount	*t* [h]	**18** [%]	**17** [%]
1	$Bi(OTf)_3$	5 mol%	12	16	67
2	$Bi(OTf)_3$	1 equiv	12	52	38
3	$Bi(OTf)_3/LiClO_4$	25 mol%/1 equiv	16	83	–
4	$Bi(OTf)_3/LiClO_4$	25 mol%/3 equiv	3	96	–
5[b]	$Bi(OTf)_3/LiClO_4$	5 mol%/3 equiv	3.5	94	–
6	$Bi(OTf)_3/LiClO_4$	2.5 mol%/3 equiv	6	82	trace
7	$LiClO_4$	3 equiv	5	no reaction[c]	

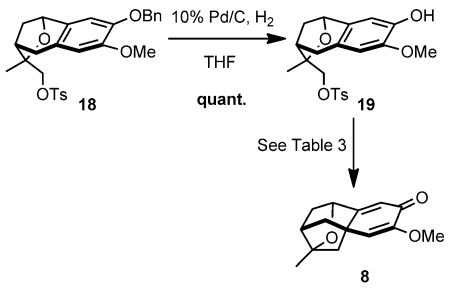
[a] Conditions: **17** (30–50 mg), Lewis acid, 4 Å molecular sieves, CH_2Cl_2, room temperature; yields after isolation are shown. [b] Reaction was performed at the 50 and 760 mg scales with comparable yields. [c] Without isolation of **17**, 10 mol% $Bi(OTf)_3$ was added into the same pot and **18** was afforded in 74% yield after 3 h.

Friedel–Crafts transformation. As such, we rationalized that the sulfonate group likely retarded the reactivity of the Lewis acid. Accordingly, a Lewis acid cocatalyst was sought to circumvent the poor catalytic activity experienced with tosylate **17**.

Inspired by Bartoli, Sambri, and co-workers,[19] we eventually turned to $LiClO_4$ as a cocatalyst to $Bi(OTf)_3$ to help drive the Friedel–Crafts cyclization of **17**. Although lower equivalencies were not productive, 1 equivalent of $LiClO_4$ and 25 mol% $Bi(OTf)_3$ gave a better conversion into **18** after stirring overnight (16 h) at room temperature (Table 2, entry 3). The best catalytic combination of 5 mol% $Bi(OTf)_3$ with 3 equivalents of $LiClO_4$ eventually furnished **18** in 94% yield within 3.5 h (Table 2, entries 4–6). In a control experiment, $LiClO_4$ alone was incapable of promoting the cyclization, but the subsequent addition of a catalytic amount of $Bi(OTf)_3$ provided **18** in 74% yield (Table 2, entry 7). We rationalized that the combination of $Bi(OTf)_3$ and $LiClO_4$ possibly resembled Mukaiyama's catalyst system, $SbCl_5/LiClO_4$, which is speculated to form a highly reactive oxocarbenium perchlorate species, reported to promote the Friedel–Crafts acylation of aromatic compounds with acid anhydrides.[20] Likewise, a more active cationic species "$Bi(OTf)_2(ClO_4)$"[21] could have been generated to strongly interact with **17** and favor the formation of more reactive oxocarbenium ions, which, in turn, can promote nucleophilic ring closure. Additionally, in comparison with the Friedel–Crafts conditions between **9** and **17**, we also reasoned that Li^+ ions could compete and coordinatively saturate the Lewis basic sulfonyloxyl group, which would release any trapped Bi^{III} catalyst and thereby allow a catalytic cycle to persist.

Although the $Bi(OTf)_3$-catalyzed Friedel–Crafts cyclization of electron-rich aromatics **9** and **17** could be reproduced on practical scales, the cyclization of their 6-demethoxy counterparts could not be achieved, either at high catalyst loadings or with excess catalyst, at various temperatures.[22] No other Lewis or Brønsted acid combinations, such as $SnCl_4$, TfOH, and $InCl_3$, were found to cyclize the free lactol in the absence of the *para*-methoxy group. Furthermore, the activation of the less reactive lactol in the form of an activated furanosyl donor (including the use of *O*-acetates, trichloroacetimidates, or halides) has provided little success in promoting the desired aryl C-glycosylation reaction with different Lewis acid treatments. The results from these feasibility studies on Friedel–Crafts ring closure onto the *meta* position of monoactivated aryl systems support our choice of employing a *para*-methoxy group to impart the needed electronic control for realizing the Marson type cyclization. Neither *ortho*-cyclized C10/C7 products nor *ipso*-cyclized C10/C8 products were observed from **9** or **17**, as expected because of the steric constraints enforced by the C12/C13 stereochemistry of the tetrahydrofuranyl moiety.

After reliable catalytic Friedel–Crafts cyclization conditions had been secured, the benzyl deprotection of **18** and alkylative dearomatization were investigated (Scheme 4). Although debenzylation proceeded quantitatively over catalytic Pd/C, the resulting tosylphenol **19** cyclized in only 21% yield when treated with excess DBU under CH_3CN reflux (Table 3, entry 1). This result was in contrast to the efficient cyclization observed for the bromophenol **13** under the same conditions (Scheme 2).



Scheme 4. Synthesis of the dienone **8**.

Table 3. Alkylative cyclodearomatization of tosylphenol **19**.[a]

Entry	Scale [mg]	Base[b] (equiv)	Solvent	*T* [°C]	*t* [h]	**8** [%]
1	30	DBU (15)	MeCN	85	20	21
2	19	DBU (15)	$EtNO_2$	120	12	–
3	28	DBU (15)	PrCN	130	12	47
4	20	DIPEA (20)	MeCN	100	36	10
5	23	TBAF (20)	PrCN	130	12	70
6	14	TBAF (20)	xylene	130	12	80
7	54	TBAF (5)	xylene	130	4	82
8[c]	790	TBAF (5)	xylene	130	4	86
9[d]	320	TBAF (5)	xylene	130	4	90

[a] Mixture of isomers. [b] DIPEA: *N*,*N*-diisopropylethylamine; TBAF:tetrabutylammonium fluoride. [c] **19**, crude, obtained from quantitative debenzylation of **18**. [d] Cyclodearomatization of the bromophenol **14**.

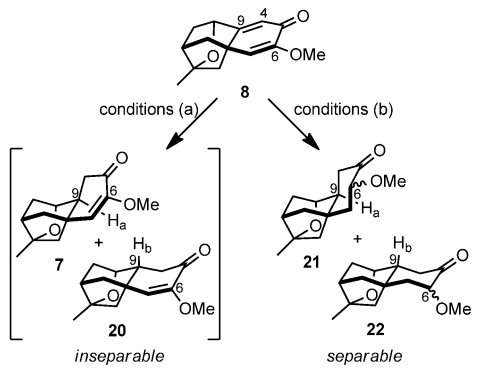
At the higher refluxing temperature of nitroethane, a complex mixture resulted, presumably due to solvent participation (Table 3, entry 2). A switch to butyronitrile and heating to reflux at above 130 °C gave a significant improvement in yield, but byproduct formation remained significant (Table 3, entry 3). Next, the strongly basic DBU was replaced with the less basic Hünig's base, DIPEA (Table 3, entry 4), in an attempt to reduce the competing side reactions, but the conversion only furnished **8** in 10% yield at best. Further screening led to heating of phenol **19** with excess TBAF as a relatively mild base[23] in butyronitrile. This gave the desired **8** in a 70% yield after isolation (Table 3, entry 5). Xylene was explored as a more practical solvent to sequester the residual water in TBAF and increase the basicity of the fluoride anion (Table 3, entry 6). Eventually, the dienone cagelike core was achieved reliably in 82–86% yield (Table 3, entries 7 and 8) with the use of 5 equivalents of TBAF. This protocol importantly circumvented the need to resort to stronger leaving groups (than OTs) or phenol silyl ether activation methods.[6b,e,13b,d] The same conditions could be successfully applied to the alkylative dearomatization of bromophenol **14** in excellent yield (Table 3, entry 9). We rationalized that the success in employing TBAF at 130 °C to effect the cyclodearomatization may be due to the mild basicity of both the fluoride anion and the possible in situ generatation of tributylamine, which can occur through Hofmann elimination of TBAF.

With dienone **8** in hand, the stage was set for installing the *cis*-C8/C9 ring junction. With neither specialized apparatus nor reagents, a chemo- and stereocontrolled conjugate reduction of the electron-deficient C4–C9 olefin in **8** was anticipated to be challenging to achieve in a practically convenient manner under pure substrate control (Table 4). In our initial investigations, for example, atmospheric hydrogenation of **8** over catalytic Pd/C afforded a 1:3 d.r. at the C9 atom in favor of the undesired *trans*-C8/C9 decalin, **22**, over the desired *cis*-C8/C9 decalin, **21** (Table 4, entry 1). Double hydrogenation with Crabtree's Ir catalyst[7c] only led to recovery of the initial dienone (Table 4, entry 2). The substrate also proved to be resilient towards various nonchiral hydride 1,4-reduction methods, because efforts to selectively furnish 6-methoxyenone **7** were futile (Table 4, entries 3–6). 1,4-Hydrosilylation with Wilkinson's catalyst, likewise, only afforded an inseparable 1:1 diastereomeric mixture of **7** and the C9 epimer **20** in 9% yield (Table 4, entry 7).[7e] A practical point to note here is that, although the stereocenter at the C6 position is inconsequential to the final synthesis, it nevertheless complicated these optimization studies.

1,4-Reduction of **8** with a bisphosphine copper hydride species was investigated under the conditions of Buchwald and co-workers,[24] and *rac*-BINAP was used as the ligand to initially examine the substrate reactivity. Although smooth 1,4-reduction of the C4–C9 olefin occurred, over-reduction of the carbonyl group also occurred in the same pot. Reoxidation of the resulting 6-methoxycyclohexenol with Dess–Martin periodinane provided undesired **20** in preference over the desired diastereomer **7** in a 1:7.6 d.r., although a better yield of 59% over 2 steps was achieved (Table 4, entry 8). The procedure was repeated with an in situ prepared (*R*)-*p*-tol-BINAP-stabilized CuH complex, which also afforded a 1:4 d.r. mixture in favor of **20** over **7** (Table 4, entry 9). Alternative CuH conditions that utilized copper(II)acetate as the air-stable copper source over the air-sensitive copper(I)chloride[25] were, however, found to be less powerful in the conjugate reduction of **8**. In the presence of either (*R*)-BINAP (Table 4, entry 10) or (*R*)-*p*-tol-BINAP (Table 4, entry 11), the initial dienone was mainly recovered, whereas with (*S*)-BINAP the formation of undesired **20** was favored exclusively (Table 4, entry 12).

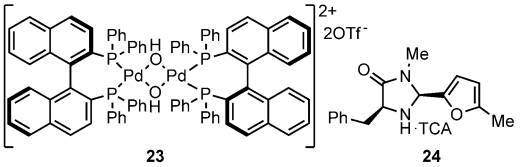
Collectively, these results suggested a subtle but over-riding substrate-controlled steric effect that enforces β-facial attack onto dienone **8** and leads to preferential formation of **20** and the doubly reduced ketone **22**. These results are also consistent with Tiefenbacher and Mulzer's first investigation into nonchiral catalytic hydrogenation methods, which only furnished a 1.3:1 *cis*/*trans*-C8/C9 decalin mixture, at best, from a 6-demethoxy analogue of **8** under atmospheric Crabtree's conditions.[7c] To circumvent substrate bias, only high pressures of hydrogen with highly optimized chiral reagents, including Corey's 600 psi Rh^{I}/2,3-alkylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane-catalyzed hydrogenation[6b] and the Ir^{I}/*P*,*N*-ligand-catalyzed hydrogenation procedure at 50 bar of pressure used by Mulzer, Pfaltz, and co-workers,[6f] have delivered the desired stereocontrolled reduction. Nevertheless, we conceived that high diastereoselectivity of the C8/C9 ring junction could still be achieved by applying amine-based organocatalytic mechanistic rationales to relay steric information under substrate control. By blocking the more accessible

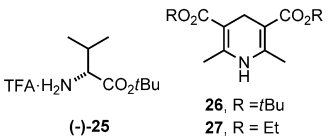
Table 4. Conjugate reduction study of tetracyclic dienone (−)-**8**.[a]



Entry	Conditions (a) or (b)[b]	Yield [%]	d.r.[c]
1	(b) cat. Pd/C, H_2, EtOAc/ethanolic KOH, 2 h	70	1:3
2	(b) cat. [Ir(cod)Py(PCy_3)]PF_6, H_2, CH_2Cl_2, 12 h	NR[d]	–
3	(a) $Na_2S_2O_4$, $NaHCO_3$, 1,4-dioxane/H_2O, 50 °C, 6 h[26]	UCM[e]	–
4	(a) Me_2PhSiH, *t*BuOO*t*Bu, nBu_3SnH, toluene, 120 °C, 24 h[27]	trace	ND[f]
5	(a) **27**,[28] silica gel, benzene, reflux, 24 h[29]	NR[d]	–
6	(a) cat. Cp_2TiCl_2, Zn dust, collidine·HCl, THF, 10 h[30]	NR[d]	–
7	(a) cat. $RhCl(PPh_3)_3$, Me_2PhSiH, toluene, 60 °C, 24 h	9	1:1
8	(a) 1. cat. CuCl/NaO*t*Bu/*rac*-BINAP, PMHS, toluene, 48 h; 2. DMP, CH_2Cl_2, 7 h	59	1:7.6
9	(a) 1. cat. CuCl/NaO*t*Bu/ (*R*)-tol-BINAP, PMHS, toluene, 5 d; 2. DMP, CH_2Cl_2, 7 h	56	1:4
10	(a) cat. (*R*)-BINAP/$Cu(OAc)_2·H_2O$, PMHS, *t*BuOH/THF, 36 h	trace	ND[f]
11	(a) cat. (*R*)-tol-BINAP/$Cu(OAc)_2·H_2O$, PMHS, *t*BuOH/THF, 36 h	8	2:3
12	(a) cat. (*S*)-BINAP/$Cu(OAc)_2·H_2O$, PMHS, *t*BuOH/THF, 36 h	17	**20** only
13	(a) cat. **23**, EtOH, 48 h[31]	NR[d]	–
14	(a) cat. **24**, **26**; 1. THF, 0 °C, 24 h; 2. 1,4-dioxane, 85 °C, 48 h	NR[d]	–
15	(a) (−)-**25**, **27**, 1,4-dioxane, 60 °C, 48 h	30[g]	3.5:1

[a] Reactions were performed on 10–20 mg scales. TCA: trichloroacetic acid; TFA: trifluoroacetic acid. [b] cod:cycloocta-1,5-diene; Py: pyridine; Cy: cyclohexyl; tol: tolyl; Cp: cyclopentyl; BINAP: 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; PHMS: polymethylhydrosiloxane; DMP: Dess–Martin Periodinane. [c] The d.r. at the C9 position was calculated based on a ^1H NMR comparison of yields after isolation for **7**/**20** (inseparable mixture) or for **21**/**22** (separable mixture). [d] NR: no reaction. [e] UCM: Unresolved complex mixture. [f] ND: not determined. [g] 95% based on recovered **8**.





β face selectively through bulky groups on the organocatalyst, the facial preference of **8** towards 1,4-hydride delivery could be conceivably reversed via a 6-methoxy group directed, putative *trans*-iminium species **30** (Figure 2).

Although treatment with imidazolidinone catalyst **24** and *tert*-butyl Hantzsch hydride donor **26**, in accordance with the work of MacMillan and co-workers,[32] gave no reaction (Table 4, entry 14), *tert*-butyl D-valinate TFA salt (−)-**25**[7h] with Hantzsch ethyl ester **27**, as described by Martin and List,[33] afforded a promising 3.5:1 d.r. in favor of desired **7** over **20**, albeit in only 30% yield (Table 4, entry 15). Gratifyingly, when more equivalents of **27** were used with substoichiometric amounts of (−)-**25**, the reduction yield was improved to 62% over 2 steps (Table 5, entries 1–3). Although elevated temperatures helped to promote the reaction, the drawback was an accompanying drop in diastereoselectivity. More hours of heating also led to over-reduction of the C6–C7 olefin of the resulting enones **7**/**20** to further afford minor amounts of the tetrahydrogenated ketones **21**/**22** (Table 5, entry 3). It is otherwise noteworthy that this organocatalytic 1,4-specific reductive procedure displayed high chemoselectivity for the more electron-deficient C4–C9 olefin, as expected by electronic moderation through the 6-methoxy group.

The application of Martin and List's optimal antipodal catalyst combination, the (*S*)-3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl-hydrogenphosphate ((*S*)-TRIP) salt of D-valine tert-butyl ester, **28**, however, gave only poor conversion and a diastereoselectivity of 1.2:1 d.r. (**7**/**20**), which suggested the likely presence of competing, although still unclear, steric effects (Table 5, entry 4). Higher catalytic activity and selectivity were eventually achieved with the unreported TFA salt of the *tert*-butyl ester of D-phenylalanine, (−)-**29**;[7h] however, further reduction of **7**/**20** into **21**/**22** could not be avoided (Table 5, entries 5–7). The use of fewer equivalents of **27** (with ≥98% purity) was possible with little adverse affect on the reactivity and further aided the purification. Other etheral solvents were also examined and proved unfavorable for the conjugate reduction of **8** (Table 5, entries 8 and 9). The best selectivity was, thus, furnished with 20 mol% (−)-**29** in 1,4-dioxane at 60 °C under Ar. This afforded an inseparable mixture of **7** and **20** in 61% yield and 8:1 d.r. (Table 5, entry 7). A marginally separable mixture of **21** and **22** (4:1 d.r. at the C9 position) could be isolated in 73% yield over 2 steps by further subjecting the **7**/**20** mixture to Pd/C-mediated hydrogenation.

We rationalized that the observed π-facial selectivity in the Hantzsch ester hydride delivery to **8** could have occurred via the D-phenylalanine-derived *trans*-iminium intermediate **31** (Figure 2). Conceivably, the sterically more congested α-face would preferentially relay the benzyl group (compared with the smaller isopropyl group in (−)-**25**) and the *tert*-butyl ester group to the opposite (β) face and thereby make the bottom (α) face comparatively more accessible to incoming Hantzsch hydride donors. Such iminium intermediates are also suggested to be stabilized by an additional trifluoroacetate counteranion hydrogen-bonding network.[33] Although we were unable to provide experimental evidence for intermediate **31** or such mecha-

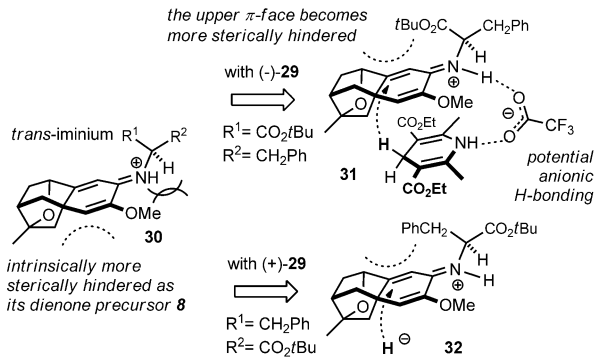
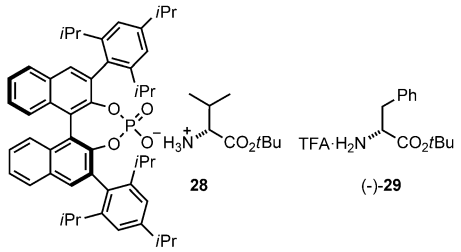


Figure 2. Putative *trans*-iminium **30** species derived from **8** and the amine catalyst **29**.[33]

Table 5. Organocatalytic conjugate reduction of **8** based on amino acids.[a]

Entry	Cat. (mol%)	**27**[b] [equiv]	*T* [°C]	*t* [h]	Yield [%]	d.r.[c]
1	(−)-**25** (100)	2.4	60	48	30[d]	3.5:1
2	(−)-**25** (25)	5	60	80	46[d]	3.5:1
3	(−)-**25** (25)	5	80	130	62[e]	3.1:1
4[f]	**28** (25)	5	85	120	10	1.2:1
5	(−)-**29** (20)	1.8	60	80	53[d]	5:1[g]
6	(−)-**29** (20)	5	60	130	70[e]	3.9:1
7	(−)-**29** (20)	3.2	60	130	61	8:1[h]
					73[e]	4:1
8[f]	(−)-**29** (20)	3.2	60	130	26	2.8:1
9[i]	(−)-**29** (20)	3.2	60	80	20	2.5:1

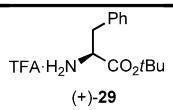
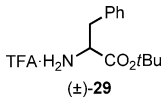
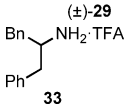
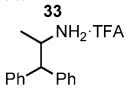
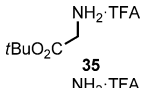
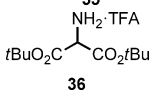
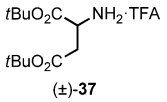
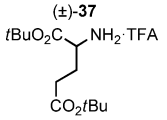
[a] Reactions were performed on 30–40 mg scales in 0.05–0.1 M 1,4-dioxane and sealed under Ar. [b] **27** with ≥98% purity gave better yields. [c] The d.r. at the C9 position was calculated based on a ^{1}H NMR comparison for **7**/**20** (inseparable mixture) or yields after isolation for **21**/**22** (separable mixture) in entries 3, 6, and 7(ii). [d] 90% (entry 1), 91% (entry 2), and 88% (entry 5) yields based on recovered **8**. [e] Yield after isolation of a separable mixture of **21**/**22** after hydrogenation of an inseparable mixture of **7**/**20** over cat. Pd/C in EtOAc/ethanolic KOH for 1 h (yield after two steps). [f] The reaction was carried out in 0.05 M nBu_2O. [g] Compounds **21**/**22** were also isolated in <5% yield (≈2:1). [h] Compounds **21**/**22** were also isolated in 17% yield (≈1:1). [i] The reaction was carried out in 0.05 M THF.



nisms, this steric-reversal reasoning could account for the low reactivity and diastereoselectivity observed with Martin and List's TRIP catalyst;[33a] thus, the large TRIP counteranion probably engenders severe steric clashes with both faces of **31** through the putative hydrogen-bonding network (Figure 2). In addition, we reason that (−)-**29** is more acidic than (−)-**25** (the pK_a value of Phe is lower than that of Val), which favors *trans*-iminium formation and thus further activates Hantzsch hydride reduction.[33b]

The speculated mechanistic model (Figure 2) also formulates an equally feasible 6-methoxy-directed *trans*-iminium intermediate **32** with the other enantiomer (+)-**29** to provide the desired stereocontrol necessary for the conjugate reduction of the C4–C9 olefin. Gratifyingly, the Martin and List inspired organocatalytic reduction[33a] of **8** occurred under similar chemo- and diastereoselectivity to afford comparable yields, irrespective of the use of the (−), (+), or even (±) forms of the phenylalanine *tert*-butyl ester **29** (Table 6, entries 1 and 2). Some TFA salts of achiral and racemic primary amines were also explored as possible catalysts, through the speculated intermediate **30**, for the modified conjugate reduction process. Treatment with 1,3-diphenylacetone-derived amine catalyst **33**, through reductive amination, and its structural isomer (±)-**34** (Table 6, entries 3 and 4) showed that the *tert*-butyl ester group was critical for both suitable activity and selectivity. The TFA salt of *tert*-butyl glycinate, **35**, however, exhibited poor reactivity with

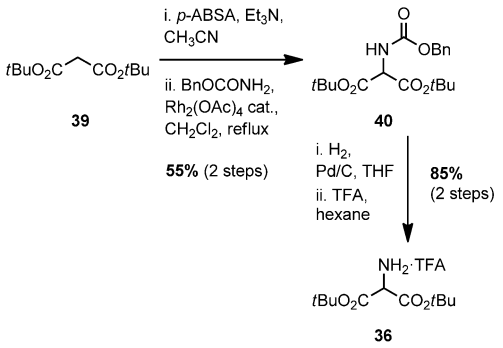
Table 6. Organocatalytic conjugate reduction of **8** with nonchiral primary amine catalysts.[a]

Entry	Catalyst	Yield [%]		d.r.[b]	
		7/**20**	**21**/**22**	**7**:**20**	**21**:**22**
1	 (+)-**29**	–	68[c]	–	4.2:1
2	 (±)-**29**	–	70[c]	–	4:1
3	 **33**	8	trace	2.9:1	ND[d]
4	 (±)-**34**	5	–	2.2:1	–
5	 **35**	18	8	1.3:1	1:1
6	 **36**	74	6	5:1	5:1
7	 (±)-**37**	–	70[c]	–	5:1
		39	10	3.2:1	2.5:1
8	 (±)-**38**	22	trace	2.5:1	ND[d]

[a] Reactions were performed on 30–40 mg scales with the TFA salt of the amine catalyst (20 mol%) and **27** (3.2 equiv) in 0.08 M 1,4-dioxane, sealed under Ar at 60 °C for 120–130 h. [b] The d.r. at the C9 position was calculated based on a ^{1}H NMR comparison for **7**/**20** (inseparable mixture) or yields after isolation for **21**/**22** (separable mixture). [c] Yield after isolation of a separable mixture of **21**/**22** after hydrogenation of an inseparable mixture of **7**/**20** over cat. Pd/C in EtOAc/ethanolic KOH for 1 h (yield after two steps). [d] ND: not determined.

almost no selectivity (Table 6, entry 5). This suggested the importance of a *sec*-alkyl amine for good stereocontrol.

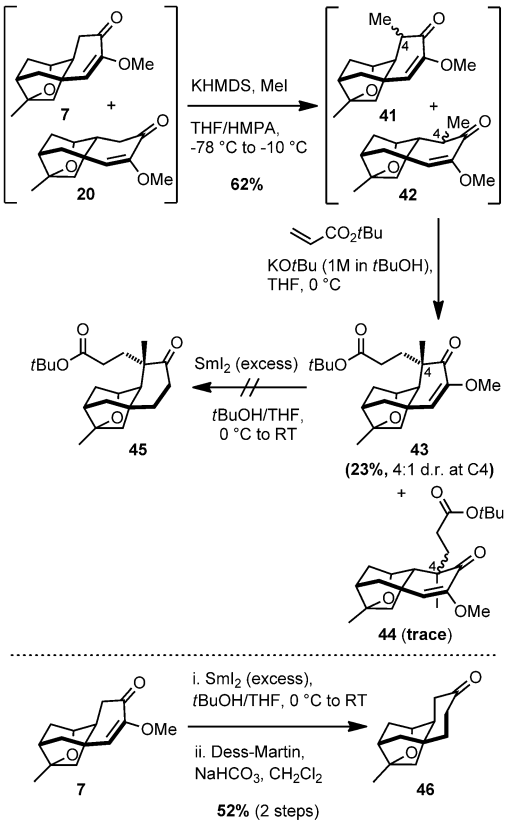
On the basis of these results, the TFA salt of α-amino di-*tert*-butyl malonate, **36**, was investigated, which was prepared from the malonate ester **39** in 47% yield over 4 steps (Scheme 5). Regitz diazo transfer with *p*-ABSA installed the requisite diazo group on **39**, and subsequent Rh(II)-catalyzed



Scheme 5. Preparation of the TFA salt of α-amino di-*tert*-butyl malonate **36**. *p*-ABSA: *para*-acetamidobenzenesulfonyl amide.

NH insertion[34] with benzyl carbamide furnished the benzyloxycarbonyl-protected amino malonate **40**. Deprotection of the benzyloxy carbamate revealed the free amine, and TFA treatment furnished the amine salt **36**. Amine **36** was found to possess catalytic activity noticeably superior to that of **29** at 20 mol% (Table 6, entry 6). Greater chemoselectivity for the C4–C9 olefin was also exhibited, because over-reduction to the 6-methoxyketones **21**/**22** was lower. A higher diastereoselectivity in preference of the desired **21** over **22** with 5:1 d.r. at the C9 position was achievable via the sequential Hantzsch-based and Pd/C-mediated reduction of **8** in a good, reliable yield of 70% over 2 steps. Subsequent examination of the catalytic activities of homologated analogues of **36**, including DL-aspartate-derived (±)-**37** (Table 6, entry 7) and DL-glutamate-derived (±)-**38** (Table 6, entry 8) were found to catalyze the conjugate reduction with inferior resultant yields and stereoselectivities.

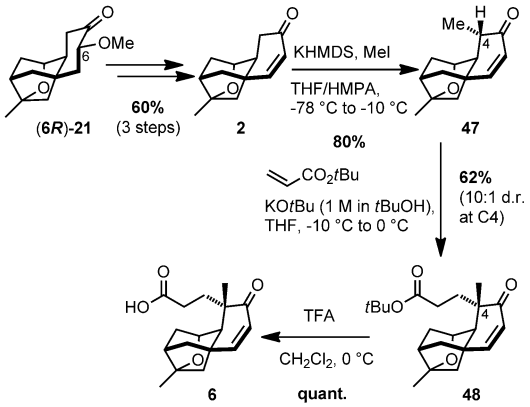
With the *cis*-C8/C9 ring junction secured, we went on to explore different approaches to furnish the doubly alkylated tetracyclic enone core. The first strategy was to methylate the inseparable mixture **7**/**20** (8:1) under the conditions reported by Nicolaou et al.,[6d] which afforded an inseparable C9-epimeric mixture of the methylated caged intermediates **41**/**42**, along with their inconsequential 4-methyl epimers, in 62% yield (Scheme 6). The second alkylation through 1,4-addition to *tert*-butyl acrylate provided a separable C9-epimeric mixture of the *tert*-butyl 6-methoxyplatensinoates **43**/**44**. In this case, the reaction favored the formation of **43** and its inseparable C4 epimer in only 23% yield and 4:1 d.r. Unlike the 6-demethoxy analogue, compound **7** demonstrated reduced reactivity and poor substrate control toward the Michael addition reaction. Additionally, the reductive cleavage of the methyl enol ether and installation of the conjugated C6–C7 double bond proceeded with limited success.



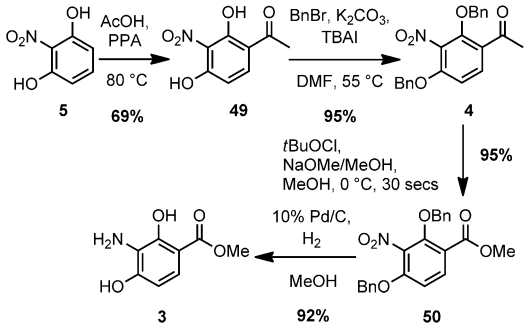
Scheme 6. Attempted synthesis of the *tert*-butyl-6,7-dihydroplatensinoate **45**. KHMDS: potassium hexamethyldisilazanide; HMPA: hexamethylphosphoramide.

A model study with enantiomerically pure **7** showed that radical reduction of the conjugated olefin, followed by a second electron-transfer α-demethoxylation, was achievable with SmI_2 and *t*BuOH as the proton source. However, nonselective 1,2-reduction occurred, and reoxidation with Dess–Martin periodinane was necessary to furnish the late-stage intermediate, the tetrahydroketone **46**, as reported by Lalic and Corey[6b] and by Tiefenbacher and Mulzer.[7c] The anticipated reduction of **43** into the desired tetracyclic ketone **45** under these Sm^{II} conditions was, nevertheless, unsuccessful, and the starting material was recovered quantitatively. The search for alternative methods to selectively generate the unprotected enol in **43** for a palladium-catalyzed reductive detriflation sequence to platensinoate **45** turned out to be unsuccessful. The electronically stable methyl enol ether proved to be highly robust towards a large variety of conditions, including transition-metal-catalyzed hydrolysis[35] and oxidation with ceric ammonium nitrate,[36] $Hg(OAc)_2$,[37] *meta*-chloroperoxybenzoic acid, or the conditions of Inoue and co-workers,[38] as well as Brønsted and Lewis acidic treatments. With little success in this initial approach, we next decided to target the known tetracyclic enone **2** from (6*R*)-**21** and then follow the dialkylation sequence of Nicolaou et al.[6d] to synthesize platensinoate **45** (Scheme 7).

In our earlier communication, we demonstrated that the tetracyclic enone **2** could be obtained from the 6-methoxyketone (6*R*)-**21** through a three-step sequence: 1) Lewis acid promoted



Scheme 7. Synthesis of platensic acid (**6**) via tetracyclic enone **2**.

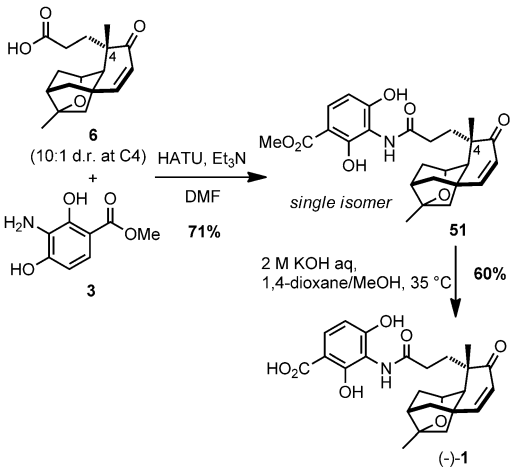


Scheme 8. High-yielding synthesis of the aniline ester **3**. PPA: polyphosphoric acid; TBAI: tetrabutylammonium iodide.

demethylation, 2) mesylation of the resulting acyloin, and 3) α-dehydrohalogenation of the mesylate to generate the conjugated double bond.[7h] The ^{1}H and ^{13}C NMR spectra of **2** were found to be identical to those reported by Nicolaou et al.[6d] and others. Methylation of **2** with KHMDS in THF/HMPA (5:1) then afforded the methylated caged intermediate **47** in 80% yield with almost complete stereoselectivity. Relative to the reaction with the 6-methoxy analogue **7**, it is noteworthy that the alkylation of **2** improved in reactivity and diastereoselectivity in the absence of the methoxy functionality. The subsequent 1,4-addition with alkyl acrylates to install the propionate side chain under the reported conditions from Yeung and Corey,[9g] Nicolaou et al.,[6d] and Tiefenbacher and Mulzer[39] was nontrivial. In our hands, the reaction was consistently plagued by inefficient conversion due to significant byproduct formation, even though **47** was completely consumed. After considerable experimentation, the alkylation with *tert*-butyl acrylate was found to proceed optimally with 1 M KO*t*Bu (0.8 equiv) in *t*BuOH to furnish the *tert*-butyl platensinoate **48** in 62% yield and a 10:1 d.r. at the C4 position. Fewer byproducts were observed under these improved conditions. The *tert*-butyl ester cleavage under TFA treatment proceeded uneventfully and furnished platensic acid (**6**) in quantitative yield.

During our total synthesis efforts, two unique syntheses of the aromatic fragment of platensimycin **1** were reported. The aniline precursor **3** has been prepared by Heretsch and Giannis in two steps from methyl 2,4-dihydoxybenzoate in 28% yield.[40] Our synthesis of **3** proceeded in 4 practical steps from 2-nitroresorcinol (**5**) with an overall yield of 57% (Scheme 8). In contrast to the other synthesis by Nicolaou et al.,[5] we achieved the carboxylation of **5** without the need for an additional aniline protection–deprotection sequence. Thus, our synthesis commenced with an early Friedel–Crafts acylation of **5** with AcOH in hot PPA to afford the acetophenone **49** in 69% yield.[41] Bisbenzylation of both phenolic groups then occurred uneventfully under classical conditions with BnBr, K_2CO_3, and a catalytic amount of TBAI. With the resulting bis-Bn acetophenone **4** in hand, our new direct oxidative esterification to the methyl benzoate **50** could be realized in excellent yield upon treatment of **4** with *tert*-butyl hypochlorite in methanolic sodium methoxide solution.[10] The high-yielding reaction was complete in less than a minute. This is in contrast to the conventional and less efficient two-step synthesis via an acid intermediate. Catalytic hydrogenation of **50** subsequently led to a global reduction of the nitro group and hydrogenolysis of the bis-Bn ethers to give the aniline unit **3** in 92% yield. No further purification was required, and **3** was immediately carried forward to the next step because it was found to be unstable.

The end-game amide coupling between platensic acid (**6**) and the aniline unit **3** was carried out by treatment with *N*-[(dimethylamino)-1*H*-1,2,3-triazole[4,5-*b*]-pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate (HATU) and Et_3N to provide the desired amide **51**, gratifyingly, as a single diastereomer in 71% yield after preparative TLC (Scheme 9). The C4 epimer of **51** was not detected by any means. Unexpectedly, the final deprotection step, hydrolysis of the methyl benzoate ester, was found to be problematic. Basic hydrolysis with aqueous LiOH/THF and aqueous NaOH/MeOH only afforded 30–40% yields (at best) of platensimycin, due to poor conversions. In this case, we suspected the methyl ester was deactivated by the strongly electron-donating *ortho*- and *para*-phenolic groups, which may account for its poorer reactivity, relative to



Scheme 9. Completion of the synthesis of (−)-platensimycin (**1**).

the hydrolysis of the known methoxymethyl-protected analogue.[5] Eventually, ester hydrolysis of **51** was significantly improved by treatment with 2 M aqueous KOH in a 1,4-dioxane/MeOH mixture at 35 °C to furnish (−)-platensimycin (**1**) in 60% yield. The ^{1}H and ^{13}C NMR spectra of (−)-**1** were found to be identical to those reported by Nicolaou et al.[6d]

Conclusion

In summary, we have achieved a unique and stereoselective route to (−)-platensimycin (**1**) from commercially available eugenol that is competitive in practice with the diverse synthetic approaches continually appearing in the literature for this highly intriguing ketolide natural product. The synthesis features the tactical employment of a 6-methoxy group to impart needed electronic and steric controls to help advance three key transformations toward platensic acid (**6**). These key steps are 1) a direct and efficient *para*-arylation of an oxocarbenium species in a novel Bi(OTf)$_3$-catalyzed Marson type Friedel–Crafts cyclization of the free lactols **9** and **17**, 2) a superior TBAF-mediated alkylative cyclodearomatization of the free phenol **19** without undue silyl preactivation or use of more powerful leaving groups than OTs, and 3) a chemo- and diastereoselective conjugate reduction of the 6-methoxydienone **8** mediated by the TFA salt of di-*tert*-butyl α-amino malonate, **36**, to reverse the strongly intrinsic, unfavorable π-facial selectivity of the substrate with readily available laboratory resources and techniques.

Demethoxylation of the 6-methoxyenone **7** was necessary before final elaboration to (−)-**1**. This was achieved either through radical reduction with SmI$_2$ and *t*BuOH or through the utilization of our previously established demethylation–dehydrohalogenation sequence.[7h] The total synthesis of (−)-**1** was further progressed to completion by virtue of practical efforts in optimizing a substrate-controlled double alkylation sequence from the enone **6** and the development of an efficient four-step synthesis of the aromatic domain, which showcases a key oxidative esterification methodology under study in our laboratory.[10] Application of this total synthesis and the methods developed en route for fatty acid synthase probe studies will be the subject of future bioorganic investigations.[43]

Experimental Section

General information

All moisture-sensitive reactions were performed in flame-dried round-bottom flasks under an inert Ar atmosphere with freshly distilled dry solvents: THF from Na/benzophenone; Et$_2$O from Na wire; CH$_2$Cl$_2$ and 1,4-dioxane from CaH$_2$; MeOH from Mg. Dry CH$_3$CN and toluene were directly obtained from Glass Contour's solvent dispensing system. Commercial reagents were used as received without further purification. (*S*)-TRIP was kindly donated by Professor Benjamin List from the Max-Planck-Institut für Kohlenforschung. Molecular sieves (4 Å) were activated by heating in a furnace at 300 °C for 20 h before storing in a dry dessicator. Yields refer to chromatographically and spectroscopically homogeneous materials. Reaction progress was monitored by TLC with 0.25 mm Merck precoated silica gel plates (60F-254) by using UV light at 254 nm as the visualizing agent, with ceric ammonium molybdate, KMnO$_4$, or ninhydrin as developing stains. Flash column chromatography was performed on silica gel 60 (0.040–0.063 mm), and preparative TLC was performed on 1 mm thickness Merck precoated silica gel plates (60F-254). ^{1}H NMR and ^{13}C NMR spectra were recorded on either Bruker AMX500 or Bruker ACF300 NMR spectrometers in deuterated solvents as indicated. Chemical shifts (δ) are reported in ppm, and the residual solvent peak was used as an internal reference (CDCl$_3$: δH = 7.26 ppm, δC = 77.0 ppm; CD$_3$OD: δH = 3.33 ppm, δC = 49.05 ppm). ^{1}H NMR coupling constants (*J*) are reported in Hertz (Hz), and multiplicities are represented as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dt (doublet of triplet), td (triplet of doublet), and br (broad). Low-resolution mass spectra were obtained on a Finnigan/MAT LCQ spectrometer in ESI mode. High-resolution ESI mass spectra were obtained on a Shimadzu LCMS-IT-TOF spectrometer, and high-resolution EI mass spectra were obtained on a Micromass VG7035 double-focusing mass spectrometer. Samples for infrared measurements were prepared as thin films, either neat or in CH$_2$Cl$_2$ solution, spread on NaCl cells, and the spectra were recorded on a BIO-RAD FTS 165 FTIR spectrometer. Optical rotations were recorded on a Jasco DIP-1000 polarimeter with an Na lamp of 589 nm wavelength.

Compound syntheses

Synthesis of bromohydrin 12: K$_2$CO$_3$ (0.415 g, 3.00 mmol) was added to a solution of monotosylated diol **10** (0.766 g, 1.50 mmol) in MeOH (AR grade, 20 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h before it was concentrated in vacuo. The resulting white precipitate was redissolved in sat. aq. NH$_4$Cl and extracted with Et$_2$O (3×). The combined organic extracts were washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. Dried LiBr·H$_2$O (0.95 g, 9.06 mmol) and glacial AcOH (0.17 mL, 3.00 mmol) were added to the crude epoxide **11** in THF (23 mL) at room temperature. The LiBr·H$_2$O was predried in vacuo for 3 h at 125 °C. The resulting mixture was heated to reflux at 90 °C for 5 h, before it was cooled to room temperature and brine was added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3×). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. Flash column chromatography of the crude product over silica gel (5% EtOAc/hexane → 20% EtOAc/hexane) afforded bromohydrin **12** (0.573 g, 91% over two steps) as a colorless oil. R_f = 0.29 (silica, 20% EtOAc in hexanes); $[\alpha]_D^{25} = +25.2$ (c = 0.57, CHCl$_3$); IR (thin film): ν_{max} = 3512, 2938, 1594, 1512, 1453, 1385, 1263, 1229, 1138, 1144, 1028, 816, 737 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.44 (d, J = 7.6 Hz, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 7.3 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 6.77 (d, J = 1.3 Hz, 1H), 6.69 (dd, J = 1.9, 8.2 Hz, 1H), 5.79–5.70 (m, 1H), 5.12 (s, 2H), 5.01–4.96 (m, 2H), 3.88 (s, 3H), 3.62 (d, J = 10.7 Hz, 1H), 3.56 (d, J = 10.1 Hz, 1H), 3.02 (dd, J = 3.8, 14.5 Hz, 1H), 2.44–2.39 (m, 1H), 2.17–2.05 (m, 3H), 1.32 ppm (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 149.7, 146.6, 137.4, 137.4, 134.6, 128.4, 127.7, 127.3, 121.2, 116.1, 114.5, 113.2, 73.9, 71.3, 56.1, 47.6, 45.6, 34.9, 34.4, 22.4 ppm; HRMS (EI): *m/z* calcd for $C_{22}H_{27}O_3{}^{79}Br^+$ $[M]^+$: 418.1144; found: 418.1139; *m/z* calcd for $C_{22}H_{27}O_3{}^{81}Br^+$ $[M]^+$: 420.1123; found: 420.1119 (intensity ratio 1:1).

Synthesis of *cis*-bromolactol 9: A solution of NMO (50% w/w in H$_2$O, 0.524 g, 2.24 mmol) in H$_2$O (6 mL) and OsO$_4$ (2 mol%) were added to a solution of **12** (0.782 g, 1.87 mmol) in *t*BuOH (30 mL) and THF (12 mL) at room temperature. The resulting mixture was stirred at room temperature for 12 h, before it was cooled to 0 °C

and quenched with $NaHSO_3$ (1.4 g, 3 M in H_2O). The mixture was warmed to room temperature and stirred for 45 min. The organic layer was separated and concentrated in vacuo, and EtOAc was added to redissolve the residue that formed. The aqueous layer was extracted with EtOAc (3×), and the combined organic layers were washed with H_2O (1×) followed by brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. $NaIO_4$ (1.0 g, 4.68 mmol) was added to this crude diol in THF (30 mL) and H_2O (15 mL) at room temperature, and the mixture was stirred for 2 h. The resulting mixture was carefully concentrated to less than half its volume by removing THF under vacuum. The mixture was diluted with water and extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography of the crude product over silica gel (10% EtOAc/hexane → 45% EtOAc/hexane) afforded *cis*-bromolactol **9** (0.713 g, 91% over 2 steps) as a white solid. $R_f = 0.39$ (silica, 50% EtOAc/hexane); m.p. 52.8–56.1 °C; $[\alpha]_D^{25} = +15.7$ ($c = 0.71$, $CHCl_3$); IR (thin film): $\nu_{max} = 3421$, 2936, 1591, 1512, 1456, 1419, 1379, 1263, 1229, 1140, 1020, 737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.43$ (d, $J = 7.6$ Hz, 2H), 7.36 (t, $J = 7.6$ Hz, 2H), 7.30 (t, $J = 7.3$ Hz, 1H), 6.81 + 6.80 (d each, $J = 8.2$ Hz, 1H), 6.71 + 6.69 (d each, $J = 1.9$ Hz, 1H), 6.66–6.63 (m, 1H), 5.52–5.50 (m, 1H), 5.13 (s, 2H), 3.89 + 3.88 (s each, 3H), 3.81 + 3.44 (d_1, $J_1 = 10.1$ Hz + d_2, $J_2 = 10.7$ Hz, 1H), 3.49 + 3.37 (d_1, $J_1 = 10.1$ Hz + d_2, $J_2 = 10.7$ Hz, 1H), 3.09 + 2.81–2.71 (m each, 2H), 2.56 (dd, $J = 10.8$, 13.3 Hz, 1H), 2.41–2.27 (m, 1H), 2.00–1.92 + 1.81–1.76 (m each, 1H), 1.46 + 1.36 ppm (s each, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 149.8$, 149.7, 146.80, 146.8, 137.2, 133.1, 133.0, 128.5, 127.8, 127.3, 127.3, 120.6, 120.5, 114.4, 112.4, 97.8, 97.2, 83.6, 83.1, 71.2, 56.1, 56.0, 50.8, 47.9, 39.8, 39.5, 39.4, 39.3, 35.4, 34.8, 27.4, 25.0 ppm; HRMS (EI): *m/z* calcd for $C_{21}H_{25}O_4{}^{79}Br^+$ $[M]^+$: 420.0936; found: 420.0929; *m/z* calcd for $C_{21}H_{25}O_4{}^{81}Br^+$ $[M]^+$: 422.0916; found: 422.0922 (intensity ratio 25:22).

Synthesis of bromobenzotetrahydrofuran 13 (through $SnCl_4$-mediated Friedel–Crafts cyclization): $SnCl_4$ (0.96 mL, 8.20 mmol) was quickly added to a solution of **9** (0.685 g, 1.63 mmol) in CH_2Cl_2 (20 mL) at −78 °C. The solution gave a strong orange color after 10–15 min of stirring at −78 °C. The solution was stirred at −78 °C for 75 min, before it was quenched with half-saturated Rochelle salt aq. solution. The half-saturated Rochelle salt (90 g in 200 mL H_2O) was cooled to 0 °C with vigorous stirring. The reaction mixture was lifted above the −78 °C dry ice/acetone bath, and its contents were immediately poured into the half-saturated Rochelle salt upon removing the rubber septum. After the transfer was complete and the resulting organic layer became colorless in less than 1 min, the mixture was diluted with some H_2O, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography of the crude product over silica gel (5% EtOAc/hexane → 18% EtOAc/hexane) afforded bromobenzotetrahydrofuran **13** (0.578 g, 88%) as a colorless oil. $R_f = 0.63$ (silica, 30% EtOAc/hexanes); $[\alpha]_D^{25} = +106.7$ ($c = 0.67$, $CHCl_3$); IR (thin film): $\nu_{max} = 2943$, 1607, 1510, 1452, 1325, 1267, 1223, 1119, 1049, 972, 866, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.43$ (d, $J = 7.0$ Hz, 2H), 7.36 (t, $J = 7.6$ Hz, 2H), 7.30 (t, $J = 7.3$ Hz, 1H), 6.67 (s, 1H), 6.64 (s, 1H), 5.12 (d, $J = 12.0$ Hz, 1H), 5.07 (d, $J = 12.0$ Hz, 1H), 4.72 (d, $J = 5.1$ Hz, 1H), 3.86 (s, 3H), 3.30 (d, $J = 10.1$ Hz, 1H), 3.21 (d, $J = 10.1$ Hz, 1H), 3.19 (d, $J = 5.0$ Hz, 1H), 3.01 (dd, $J = 4.4$, 17.7 Hz, 1H), 2.56 (br s, 1H), 2.52–2.48 (d, $J = 5.4$ Hz, 1H), 2.00 (d, $J = 11.4$ Hz, 1H), 1.45 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 149.7$, 146.2, 137.2, 132.8, 128.5, 127.8, 127.3, 126.8, 113.1, 112.2, 84.1, 78.1, 71.3, 56.1, 41.4, 38.5, 35.3, 31.8, 26.2 ppm; HRMS (EI): *m/z* calcd for $C_{21}H_{23}O_3{}^{79}Br^+$ $[M]^+$: 402.0831; found: 402.0827; *m/z* calcd for $C_{21}H_{23}O_3{}^{81}Br^+$ $[M]^+$: 404.0810; found: 404.0813 (intensity ratio 1:1).

Synthesis of bromophenol 14: 10% Pd on carbon (20% wt/wt, 55.2 mg), followed by 1,4-cyclohexadiene (1.6 mL, 17.1 mmol) was added to a solution of **13** (0.276 g, 0.684 mmol) in absolute EtOH (6 mL) at room temperature under an atmosphere of N_2. The resulting mixture was stirred at room temperature for 3 h, before it was filtered through a pad of Celite, eluted with EtOAc, and concentrated in vacuo. Flash column chromatography of the crude product over silica gel (10% EtOAc/hexane → 40% EtOAc/hexane) afforded bromophenol **14** (0.213 g, 99%) as a colorless viscous oil. $R_f = 0.29$ (silica, 30% EtOAc/hexane); $[\alpha]_D^{26} = +26.2$ ($c = 0.27$, $CHCl_3$); IR (thin film): $\nu_{max} = 2924$, 2853, 1652, 1510, 1452, 1348, 1275, 1218, 1170, 1107, 968, 814 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.65$ (s, 1H), 6.62 (s, 1H), 5.45 (s, 1H), 4.76 (d, $J = 5.5$ Hz, 1H), 3.87 (s, 3H), 3.30 (d, $J = 10.0$ Hz, 1H), 3.22–3.18 (m, 2H), 3.00 (dd, $J = 4.4$, 17.6 Hz, 1H), 2.56–2.49 (m, 2H), 2.00 (d, $J = 10.7$ Hz, 1H), 1.45 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 146.6$, 143.4, 133.4, 125.4, 113.3, 111.0, 84.1, 78.0, 56.0, 41.4, 38.5, 35.3, 31.8, 26.2 ppm; ESI-MS: *m/z* calcd for $C_{14}H_{16}{}^{79}BrO_3^-$ $[M-H]^-$: 311.0; found: 311.3.

General procedure for the Lewis acid catalyzed Marson type Friedel–Crafts cyclization of 9: Activated 4 Å molecular sieves (1.0 g $mmol^{-1}$) were added to **9** (20–30 mg) under an atmosphere of Ar, followed by CH_2Cl_2 (0.01–0.02 M) to make a suspension. The Lewis acid was weighed, either in the open or in an N_2-filled Aldrich AtmosBag glove bag, and transferred to the solution of **9** at room temperature under Ar. The resulting mixture was stirred at room temperature until TLC indicated the complete consumption of **9**. At higher catalyst loadings of $Bi(OTf)_3$, the colorless solution turns a persistent pink color, which indicates completion of the reaction. The reaction mixture was poured into ice-cooled sat. aq. NH_4Cl with vigorous stirring, before the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography of the crude product over silica gel (5% EtOAc/hexane → 18% EtOAc/hexane) afforded bromobenzotetrahydrofuran **13** as a colorless oil. Further elution at 22% EtOAc/hexane gave the bromolactol dimeric ether **15** as a colorless viscous oil and benzobromohydrin **16** was obtained as a yellow oil with 30% EtOAc/hexane.

Compound **15**: $R_f = 0.47$ (silica, 30% EtOAc/hexane); $[\alpha]_D^{26} = -61.4$ ($c = 0.48$, $CHCl_3$); IR (thin film): $\nu_{max} = 3059$, 2924, 2853, 1589, 1512, 1452, 1377, 1263, 1231, 1140, 1011, 961, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.44$ (d, $J = 7.6$ Hz, 2H), 7.36 (t, $J = 7.6$ Hz, 2H), 7.30 (t, $J = 8.2$ Hz, 1H), 6.82–6.80 (m, 1H), 6.69 (d, $J = 1.9$ Hz, 1H), 6.67–6.63 (m, 1H), 5.56–5.54 + 5.45–5.44 (m each, 1H), 5.13 + 5.12 (s each, 2H), 3.89 + 3.88 (s each, 3H), 3.73 + 3.41–3.35 (d_1, $J_1 = 10.1$ Hz + m_2, 2H), 2.81–2.73 (m, 1H), 2.58–2.32 + 2.02–1.96 (m each, 3H), 1.86–1.82 + 1.77–1.72 (m each, 1H), 1.33 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 149.8$, 149.7, 146.8, 146.8, 137.3, 133.4, 133.1, 128.5, 127.8, 127.3, 120.7, 120.5, 114.4, 114.3, 112.7, 112.4, 99.8, 98.7, 83.3, 82.9, 71.2, 56.1, 56.1, 50.4, 48.2, 39.7, 39.0, 38.8, 35.6, 34.9, 29.7, 27.4, 24.5 ppm; HRMS (EI): *m/z* calcd for $C_{42}H_{48}O_7{}^{79}Br_2^+$ $[M]^+$: 822.1767; found: 822.1796; *m/z* calcd for $C_{21}H_{25}O_4{}^{79}Br^{81}Br^+$ $[M]^+$: 824.1746; found: 824.1783; *m/z* calcd for $C_{21}H_{25}O_4{}^{81}Br^{81}Br^+$ $[M]^+$: 826.1726; found: 826.1788 (intensity ratio 1:2:1).

Compound **16**: $R_f = 0.35$ (silica, 30% EtOAc/hexane); $[\alpha]_D^{26} = -157.3$ ($c = 0.15$, $CHCl_3$); IR (thin film): $\nu_{max} = 2955$, 2922, 2853, 1510, 1454, 1379, 1260, 1227, 1119, 1022, 854, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.43$ (d, $J = 6.9$ Hz, 2H), 7.36 (t, $J = 7.6$ Hz, 2H), 7.30 (t, $J = 7.6$ Hz, 1H), 6.70 (s, 1H), 6.62 (s, 1H), 6.42 (dd, $J = 1.9$, 10.1 Hz, 1H), 5.74 (dd, $J = 4.4$, 10.1 Hz, 1H), 5.11 (s, 2H), 3.88 (s, 3H), 3.61 (d,

J=10.7 Hz, 1H), 3.47 (d, J=10.1 Hz, 1H), 2.94 (d, J=2.5 Hz, 2H), 2.78–2.77 (m, 1H), 2.02 (s, 1H), 1.20 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=149.2, 146.6, 137.3, 129.3, 128.5, 128.0, 127.8, 127.3, 125.9, 124.7, 113.1, 112.0, 73.7, 71.5, 56.1, 44.6, 41.6, 28.0, 22.3 ppm; HRMS (EI): m/z calcd for $C_{21}H_{23}O_3{}^{79}Br^+$ $[M]^+$: 402.0831; found: 402.0815; m/z calcd for $C_{21}H_{23}O_3{}^{81}Br^+$ $[M]^+$: 404.0810; found: 404.0816 (intensity ratio 1:1).

Synthesis of 6-methoxydienone 8 from 14: DBU (1.5 mL, 10.2 mmol) was added to a stirred solution of **14** (0.213 g, 0.68 mmol) in CH_3CN (35 mL) at room temperature, and the mixture was heated at 70–75 °C for 10 h. The resulting mixture was concentrated in vacuo to half its volume and added 10% aq. citric acid to adjust the pH value of the solution to approximately pH 3. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with water (2×), followed by brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography of the crude product over silica gel (20% EtOAc/hexane → 65% EtOAc/hexane) afforded 6-methoxydienone **8** (0.134 g, 85%) as a pale yellowish-white solid. R_f=0.25 (silica, 60% EtOAc/hexane); m.p. 76.1–78.4 °C; $[\alpha]_D^{26}$=+44.7 (c=0.68, $CHCl_3$); IR (thin film): ν_{max}=2957, 2916, 1668, 1659, 1616, 1475, 1213, 1171, 1140, 1113, 1084, 1016 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.16 (s, 1H), 5.55 (s, 1H), 4.72 (d, J=4.5 Hz, 1H), 3.67 (s, 3H), 2.56 (t, J=6.3 Hz, 1H), 2.24–2.16 (m, 2H), 1.99 (d, J=11.4 Hz, 1H), 1.93 (dd, J=3.2, 11.3 Hz, 1H), 1.75 (d, J=11.4 Hz, 1H), 1.52 (d, J=3.2 Hz, 1H), 1.50 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=182.0, 160.6, 152.2, 121.4, 117.9, 86.7, 79.6, 55.9, 54.9, 49.7, 44.1, 42.5, 22.2 ppm; HRMS (IT-TOF): m/z calcd for $C_{14}H_{16}O_3Na^+$ $[M+Na]^+$: 255.0997; found: 255.0999.

Synthesis of *cis*-tosyllactol 17: A solution of NMO (50% w/w in H_2O, 2.10 g, 8.96 mmol) in H_2O (10 mL) and OsO_4 (2 mol%) were added to a solution of monotosylated diol **10** (3.80 g, 7.44 mmol) in *t*BuOH (50 mL) and THF (20 mL) at room temperature. The resulting mixture was stirred at room temperature for 12 h before it was cooled to 0 °C and quenched with $NaHSO_3$ (5.6 g, 3 M in H_2O). The mixture was warmed to room temperature and stirred for 45 min. The organic layer was separated and concentrated in vacuo, and EtOAc was added to redissolve the residue that formed. The aqueous layer was extracted with EtOAc (3×), and the combined organic layers were washed with H_2O (1×), followed by brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. $NaIO_4$ (4.10 g, 19.2 mmol) was added to this crude diol in THF (100 mL) and H_2O (50 mL) at room temperature, and the mixture was stirred for 2 h. The resulting mixture was carefully concentrated to less than half its volume by removing THF in vacuo. The mixture was diluted with water and extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography of the crude product over silica gel (10% EtOAc/hexane → 60% EtOAc/hexane) afforded *cis*-tosyllactol **17** (3.24 g, 85% over two steps) as a white solid foam. R_f=0.29 (silica, 50% EtOAc/hexane); m.p. 64.4–65.9 °C; $[\alpha]_D^{25}$=+21.1 (c=0.51, $CHCl_3$); IR (thin film): ν_{max}=3524, 3061, 2938, 1595, 1512, 1456, 1360, 1265, 1229, 1177, 1096, 1022, 972, 839, 814, 737 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 7.83 + 7.80 (d each, J=8.2 Hz, 2H), 7.43 (d, J=7.0 Hz, 2H), 7.36 (t, J=6.9 Hz, 4H), 7.29 (t, J=7.3 Hz, 1H), 6.80–6.77 (m, 1H), 6.70 + 6.66 (d each, J=1.9 Hz, 1H), 6.60–6.57 (m, 1H), 5.39 + 5.34 (m each, 1H), 5.11 (s, 2H), 4.13–4.10 + 3.94 (m_1 + d_2, J_2=10.1 Hz, 1H), 4.05 + 3.86–3.85 (d_1, J_1=10.1 Hz + m_2, 1H), 3.87 (s, 3H), 2.73–2.70 + 2.62–2.48 (m each, 3H), 2.45 (s, 3H), 2.26–2.24 + 1.93–1.84 (m each, 2H), 1.70–1.67 (m, 1H), 1.20 + 1.17 ppm (s each, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=149.7, 146.7, 144.9, 137.3, 137.2, 133.1, 133.1, 132.8, 132.7, 129.9, 129.9, 128.5, 128.0, 127.9, 127.8, 127.8, 127.3, 120.5, 120.5, 114.4, 112.5, 112.5, 98.1, 97.4, 83.5, 82.4, 72.8, 72.5, 71.2, 60.4, 56.1, 50.1, 47.2, 40.4, 40.2, 34.8, 34.4, 25.2, 23.5, 21.6 ppm; HRMS (IT-TOF): m/z calcd for $C_{28}H_{32}O_7SNa^+$ $[M+Na]^+$: 535.1766; found: 535.1772.

Synthesis of tosylbenzotetrahydrofuran 18 (through $SnCl_4$-mediated Friedel–Crafts cyclization): $SnCl_4$ (0.68 mL, 5.81 mmol) was quickly added to a solution of *cis*-tosyllactol **17** (0.392 g, 0.765 mmol) in CH_2Cl_2 (38 mL) at −78 °C. The solution gave a bright yellow color after 65 min of stirring at −78 °C. After stirring at −78 °C for 75 min, the reaction vessel was lifted above the dry ice/acetone bath and, upon removal of the rubber septum, its contents were immediately poured into precooled (0 °C) half-saturated Rochelle salt solution (80 g in 150 mL H_2O) with vigorous stirring. After the transfer was complete and the resulting organic layer became colorless, typically within 1 min, the mixture was diluted with some H_2O, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography of the crude product over silica gel (5% EtOAc/hexane → 22% EtOAc/hexane) afforded tosylbenzotetrahydrofuran **18** (0.325 g, 86%) as a colorless oil.

Synthesis of tosylbenzotetrahydrofuran 18 (through $Bi(OTf)_3$/$LiClO_4$-catalyzed Friedel–Crafts cyclization): Activated 4 Å molecular sieves (1.0 g mmol^{-1}) were added to *cis*-tosyllactol **17** (0.518 g, 1.01 mmol) under an atmosphere of Ar, followed by CH_2Cl_2 (50 mL). $LiClO_4$ (0.326 g, 3.06 mmol) was added to **17** at room temperature under Ar, and the mixture was stirred for 45 min before $Bi(OTf)_3$ (5 mol%, 35 mg) was added to the reaction at the same temperature under Ar. The resulting mixture was stirred at room temperature for 3.5 h, before it was poured into an ice-cooled sat. aq. NH_4Cl with vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography of the crude product over silica gel (5% EtOAc/hexane → 22% EtOAc/hexane) afforded tosylbenzotetrahydrofuran **18** (0.469 g, 94%) as a colorless oil. R_f=0.46 (silica, 30% EtOAc/hexane); $[\alpha]_D^{25}$= +45.5 (c=0.47, $CHCl_3$); IR (thin film): ν_{max}=3034, 2951, 1607, 1510, 1452, 1358, 1329, 1269, 1177, 1130, 1111, 1045, 970, 862, 829, 735 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.72 (d, J=8.2 Hz, 2H), 7.42 (d, J=7.6 Hz, 2H), 7.36 (t, J=7.3 Hz, 2H), 7.31–7.28 (m, 3H), 6.56 (s, 1H), 6.46 (s, 1H), 5.09 (d, J=12.0 Hz, 1H), 5.04 (d, J= 12.6 Hz, 1H), 4.63 (d, J=5.1 Hz, 1H), 3.83 (s, 3H), 3.77 (d, J=8.9 Hz, 1H), 3.70 (d, J=8.9 Hz, 1H), 2.93 (dd, J=4.4, 17.7 Hz, 1H), 2.83 (d, J=17.7 Hz, 1H), 2.47 (br s, 1H), 2.45 (s, 3H), 2.40–2.36 (m, 1H), 1.92 (d, J=11.4 Hz, 1H), 1.21 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=149.7, 146.3, 144.8, 137.2, 132.5, 132.4, 129.8, 128.5, 128.1, 127.8, 127.3, 126.3, 113.0, 112.3, 81.9, 77.9, 73.3, 71.2, 56.1, 41.2, 34.8, 31.6, 25.4, 21.6 ppm; HRMS (IT-TOF): m/z calcd for $C_{28}H_{30}O_6SNa^+$ $[M+Na]^+$: 517.1661; found: 517.1661.

Synthesis of tosylphenol 19: 10% Pd on carbon (10% wt/wt, 0.11 g) was added to a solution of **18** (1.06 g, 2.14 mmol) in THF (45 mL) at room temperature. The resulting mixture was stirred under a hydrogen atmosphere (balloon) for 2.5 h, before it was filtered through a pad of Celite, eluted with EtOAc, and concentrated in vacuo. Flash column chromatography of the crude product over silica gel (50% EtOAc/hexane) afforded tosylphenol **19** (0.867 g, 100%), which was recrystallized from CH_2Cl_2/EtOAc as white crystals.[7h] R_f=0.19 (silica, 30% EtOAc/hexane); $[\alpha]_D^{25}$=+20.3 (c=0.27, $CHCl_3$); IR (thin film): ν_{max}=3462, 2924, 2853, 1653, 1510, 1458, 1368, 1348, 1275, 1175, 1108, 968, 833, 812 cm^{-1}; ^{1}H NMR

(500 MHz, $CDCl_3$): $\delta = 7.71$ (d, $J = 8.2$ Hz, 2H), 7.29 (d, $J = 8.2$ Hz, 2H), 6.55 (s, 1H), 6.46 (s, 1H), 5.46 (s, 1H), 4.65 (d, $J = 5.1$ Hz, 1H), 3.84 (s, 3H), 3.83 (d, $J = 8.9$ Hz, 1H), 3.68 (d, $J = 9.5$ Hz, 1H), 2.93 (dd, $J = 3.8$, 17.7 Hz, 1H), 2.85 (d, $J = 17.7$ Hz, 1H), 2.47 (br s, 1H), 2.43 (s, 3H), 2.41–2.37 (m, 1H), 1.93 (d, $J = 11.4$ Hz, 1H), 1.20 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 146.5$, 144.7, 143.4, 133.2, 132.4, 129.7, 128.1, 124.9, 113.1, 110.9, 81.8, 77.7, 73.4, 56.0, 41.3, 34.8, 31.6, 25.3, 21.6 ppm; HRMS (IT-TOF): *m/z* calcd for $C_{21}H_{24}O_6SNa^+$ $[M+Na]^+$: 427.1191; found: 427.1196.

Synthesis of 6-methoxydienone 8 from 19: TBAF (1 M in THF, 10.8 mL, 10.8 mmol) was added to a solution of **19** in xylene (98 mL) at room temperature, and the mixture was heated at 130 °C for 4 h in a sealed tube. The resulting mixture was concentrated in vacuo to half its volume, and 10% aq. citric acid was added to adjust the pH value of the solution to approximately pH 3. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with water (1×), followed by brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography of the crude product over silica gel (20% EtOAc/hexane → 65% EtOAc/hexane) afforded 6-methoxydienone **8** (0.428 g, 86% over two steps) as a pale yellowish-white solid.

Preparation of the TFA salt of 1,3-diphenylisopropylamine 33: NH_4OAc (0.147 g, 1.91 mmol) and $NaBH_3CN$ (0.179 g, 2.85 mmol) were added to a solution of 1,3-diphenylacetone (100 mg, 0.476 mmol) in MeOH (5 mL) at room temperature. The resulting mixture was stirred at room temperature for 40 h, before it was concentrated in vacuo, and the residue was partitioned between 1 M HCl and Et_2O. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2×). The aqueous layer was basified with 2 M NaOH to pH 10–11, before it was extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. TFA (36 μL, 0.485 mmol) was added to this crude amine in a mixture of hexane (AR, 2 mL) and CH_2Cl_2 (AR, 2 mL) at 0 °C. The resulting mixture was stirred at room temperature for 3 h before it was concentrated in vacuo. The crude product was repeatedly washed with hexane, filtered, and dried in vacuo to obtain the TFA salt of 1,3-diphenylisopropylamine **33** (43.3 mg, 28% over two steps) as a white solid. M.p.: decomposed at 132.3–134.4 °C; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.79$ (br, 2H), 7.33–7.19 (m, 10H), 3.62–3.56 (m, 1H), 3.02–2.92 ppm (m, 4H); ESI-MS: *m/z* calcd for $C_{15}H_{18}N^+$ $[M]^+$: 212.1; found: 212.3; *m/z* calcd for $C_2F_3O_2^-$ $[M]^-$ 113.0; found: 113.0.

Preparation of the TFA salt of 1,1-diphenylisopropylamine (±)-34: The same procedure as that used for the preparation of **33** was repeated with 1,1-diphenylacetone (50 mg, 0.238 mmol) to afford the TFA salt of 1,1-diphenylisopropylamine (±)-**34** (14.7 mg, 19% over two steps) as a white solid. M.p. 148.1–148.9 °C; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.78$ (br, 2H), 7.38–7.20 (m, 10H), 4.08–3.99 (m, 1H), 1.28 ppm (d, $J = 5.7$ Hz, 3H); ESI-MS: *m/z* calcd for $C_{15}H_{18}N^+$ $[M]^+$: 212.1; found: 212.3; *m/z* calcd for $C_2F_3O_2^-$ $[M]^-$: 113.0; found: 113.0.

Synthesis of the TFA salt of glycine *tert*-butyl ester 35: 10% Pd on carbon (10% wt/wt, 10 mg) was added to a solution of Cbz-protected glycine *tert*-butyl ester (87.2 mg, 0.329 mmol) in THF (freshly distilled over Na/benzophenone, 3.5 mL) at room temperature. The resulting mixture was stirred under a hydrogen atmosphere (balloon) for 3 h, before it was filtered through a pad of Celite, eluted with CH_2Cl_2, and concentrated in vacuo at 28 °C. TFA (25 μL, 0.335 mmol) was added to this crude amine in hexane (AR, 5 mL) at 0 °C. A white precipitate was immediately observed upon addition of the TFA. The resulting mixture was stirred at room temperature for 3 h, before it was filtered, repeatedly washed with hexane, and dried in vacuo to afford the TFA salt of glycine *tert*-butyl ester **35** (62.9 mg, 78% over two steps) as a white solid. M.p. 120.8–122.6 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.79$ (s, 2H), 1.38 ppm (s, 9H); ESI-MS: *m/z* calcd for $C_6H_{14}O_2N^+$ $[M]^+$: 132.1; found: 132.3; *m/z* calcd for $C_2F_3O_2^-$ $[M]^-$: 113.0; found: 113.0.

Preparation of the TFA salt of DL-aspartate di-*tert*-butyl ester (±)-37: 1) Synthesis of Cbz-protected di-*tert*-butyl DL-aspartate: 1,4-Dioxane (12 mL) and H_2O (12 mL) were added to a mixture of DL-aspartic acid (500 mg, 3.76 mmol) and Na_2CO_3 (1.59 g, 15.0 mmol) at room temperature. The resulting mixture was cooled to 0 °C, before CbzCl (1.15 mL, 7.52 mmol) was added, and the reaction was stirred at room temperature for 16 h. Water was added, and the aqueous mixture was extracted with Et_2O (2×). The aqueous layer was acidified with 1 N HCl to pH 1–2, before it was extracted with EtOAc (3×). The combined EtOAc extracts were washed with water (1×), followed by brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give crude Cbz-protected DL-aspartic acid (1.121 g) as a colorless oil. Concentrated H_2SO_4 (0.54 mL, 9.72 mmol) was added to a suspension of anhydrous $MgSO_4$ (2.65 g, 22.0 mmol) in CH_2Cl_2 (6 mL) at room temperature and stirred under Ar for 15 min. A solution of crude Cbz-protected DL-aspartate (0.587 g, 2.20 mmol) in CH_2Cl_2 (6 mL) was added to this mixture, before anhydrous *t*BuOH (2.5 mL, 26.1 mmol) was added at the same temperature. The resulting mixture was tightly stoppered and stirred at room temperature for 40 h, before it was carefully quenched with sat. aq. $NaHCO_3$ to dissolve the $MgSO_4$, and the solution was basified. After dilution with water, the organic layer was separated, and the aqueous layer was extracted with Et_2O (3×). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography of the crude product over silica gel (10% EtOAc/hexane) afforded the Cbz-protected di-*tert*-butyl DL-aspartate (76.2 mg, 11% over two steps) as a colorless oil. IR (thin film): $\nu_{max} = 3317$, 2976, 2938, 1726, 1708, 1552, 1464, 1334, 1228, 1155, 1055, 828, 743 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.35$–7.29 (m, 5H), 5.75 (d, $J = 8.2$ Hz, 1H), 5.11 (s, 2H), 4.47–4.44 (m, 1H), 2.86 (dd, $J = 4.4$, 16.4 Hz, 1H), 2.71 (dd, $J = 4.4$, 17.0 Hz, 1H), 1.44 + 1.42 ppm (s each, 18H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.0$, 169.7, 156.0, 136.4, 128.4, 128.0, 127.9, 82.1, 81.4, 66.8, 51.0, 37.8, 28.0, 27.8 ppm; ESI-MS: *m/z* calcd for $C_{20}H_{30}O_6N^+$ $[M+H]^+$: 380.2; found: 380.2.

2) Synthesis of (±)-**37**: 10% Pd on carbon (10 mg) was added to a solution of the Cbz-protected di-*tert*-butyl DL-aspartate (76.2 mg, 0.236 mmol) in THF (freshly distilled over Na/benzophenone, 10 mL) at room temperature. The resulting mixture was stirred under a hydrogen atmosphere (balloon) for 4 h, before it was filtered through a pad of Celite, eluted with CH_2Cl_2, and concentrated in vacuo at 28 °C. TFA (18 μL, 0.242 mmol) was added to this crude amine in hexane (AR, 10 mL) at 0 °C. A white precipitate was immediately observed upon addition of the TFA. The resulting mixture was stirred at room temperature for 3 h before it was filtered, repeatedly washed with hexane, and dried in vacuo to afford the TFA salt of DL-aspartate di-*tert*-butyl ester (±)-**37** (60.7 mg, 85% over two steps) as a white solid. M.p. 157.0–158.4 °C; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.14$–4.12 (m, 1H), 3.06–2.96 (m, 2H), 1.48 + 1.46 ppm (s each, 18H); ESI-MS: *m/z* calcd for $C_{12}H_{24}O_4N^+$ $[M]^+$: 246.2; found: 246.3; *m/z* calcd for $C_2F_3O_2^-$ $[M]^-$: 113.0; found: 113.0.

Preparation of the TFA salt of DL-glutamate di-*tert*-butyl ester (±)-38: 1) Synthesis of Cbz-protected di-*tert*-butyl DL-glutamate: The same procedures as those used for the preparation of Cbz-protected di-*tert*-butyl DL-aspartate were repeated with DL-glutamic

acid (500 mg, 3.40 mmol). The crude Cbz-protected DL-glutamic acid (0.635 g, 2.26 mmol) was used to furnish the Cbz-protected di-*tert*-butyl DL-glutamate (67.2 mg, 9% over two steps) as a colorless oil under the previously used conditions. IR (thin film): ν_{max} = 3337, 2978, 2936, 1730, 1710, 1563, 1456, 1368, 1274, 1231, 1155, 1055, 845, 743 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.27 (m, 5H), 5.40 (d, J = 6.9 Hz, 1H), 5.09 (s, 2H), 4.26–4.25 (m, 1H), 2.36–2.22 (m, 2H), 2.15–2.11 (m, 1H), 1.93–1.85 (m, 1H), 1.45 + 1.43 ppm (s each, 18H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0, 171.0, 155.9, 136.3, 128.4, 128.0, 128.0, 82.2, 80.6, 66.8, 53.9, 31.4, 28.0, 27.9 ppm; ESI-MS: *m/z* calcd for $C_{21}H_{32}O_6N^+$ $[M+H]^+$: 394.2; found: 394.2.

2) Synthesis of (±)-**38**: The same procedure as that used for the synthesis of (±)-**37** was repeated with the Cbz-protected di-*tert*-butyl DL-glutamate (67.2 mg, 0.199 mmol) to afford the TFA salt of DL-aspartate di-*tert*-butyl ester (±)-**38** (49.9 mg, 79% over two steps) as a white solid. M.p. 136.8–138.1 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 4.04–4.02 (m, 1H), 2.52–2.49 (m, 2H), 2.23–2.16 (m, 2H), 1.49 + 1.44 ppm (s each, 18H); ESI-MS: *m/z* calcd for $C_{13}H_{26}O_4N^+$ $[M]^+$: 260.2; found: 260.3; *m/z* calcd for $C_2F_3O_2^-$ $[M]^-$: 113.0; found: 113.0.

Synthesis of Cbz-protected amino malonate 40: *p*-ABSA (0.566 g, 2.36 mmol) and Et_3N (0.37 mL, 2.65 mmol) were added to a solution of di-*tert*-butyl malonate **39** (0.35 mL, 1.56 mmol) in CH_3CN (10 mL) at room temperature, and the mixture was stirred for 72 h. Flash column chromatography of the crude product over silica gel (10% EtOAc/hexane) afforded the di-*tert*-butyl diazomalonate (0.302 g, 80%) as a pale yellow oil. R_f = 0.29 (silica, 10% EtOAc/hexane); IR (thin film): ν_{max} = 2093, 1688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.50 (major) + 1.47 ppm (minor) (s each, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.3, 82.7, 28.3 (major) + 27.9 ppm (minor); ESI-MS: *m/z* calcd for $C_{11}H_{18}O_4N_2Na^+$ $[M+Na]^+$: 265.1; found: 266.0.

A solution of the di-*tert*-butyl diazomalonate (40 mg, 0.165 mmol) in CH_2Cl_2 (3 mL) was slowly added to a stirred solution of benzyl carbamide (30 mg, 0.198 mmol) and $Rh_2(OAc)_4$ (3 mg, 6.79 μmol) in CH_2Cl_2 (5 mL) with heating at gentle reflux over a period of 5–10 min. The resulting mixture was heated at a gentle reflux at 50 °C for 16 h, before it was concentrated in vacuo. Flash column chromatography of the crude product over silica gel (hexane → 8% EtOAc/hexane) afforded Cbz-protected aminomalonate **40** (41.5 mg, 69%) as a colorless oil. R_f = 0.24 (silica, 10% EtOAc/hexane); IR (thin film): ν_{max} = 3375, 2982, 2936, 1760, 1742, 1721, 1503, 1366, 1325, 1175, 1065, 1022, 868 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.29 (m, 5H), 5.73 (d, J = 7.0 Hz, 1H), 5.12 (s, 2H), 4.79 (d, J = 7.5 Hz, 1H), 1.51 + 1.49 ppm (s each, 18H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.8, 165.5, 155.4, 136.1, 128.6, 128.1, 128.1, 83.2, 83.2, 67.1, 59.1, 27.8, 27.3 ppm; ESI-MS: *m/z* calcd for $C_{19}H_{28}O_6N^+$ $[M+H]^+$: 366.1917; found: 366.1923.

Synthesis of TFA salt of amino di-*tert*-butyl malonate 36: 10% Pd on carbon (10 mg) was added to a solution of **40** (41.5 mg, 0.114 mmol) in THF (freshly distilled over Na/benzophenone, 10 mL) at room temperature. The resulting mixture was stirred under a hydrogen atmosphere (balloon) for 4 h, before it was filtered through a pad of Celite, eluted with CH_2Cl_2, and concentrated in vacuo at 28 °C. TFA (8.8 μL, 0.118 mmol) was added to this crude amine in hexane (AR, 10 mL) at 0 °C. A white precipitate was immediately observed upon addition of the TFA. The resulting mixture was stirred at room temperature for 3 h, before it was filtered, repeatedly washed with hexane, and dried in vacuo to obtain the TFA salt of amino di-*tert*-butyl malonate **36** (33.3 mg, 85% over two steps) as a white fluffy solid. M.p. 141.0–143.2 °C; ^1H NMR (500 MHz, CD_3OD): δ = 4.68 (s, 1H), 1.55 ppm (s, 18H); HRMS (IT-TOF): *m/z* calcd for $C_{11}H_{22}O_4N^+$ $[M]^+$: 232.1543; found: 232.1548; *m/z* calcd for $C_2F_3O_2^-$ $[M]^-$: 112.9856; found: 112.9852.

General procedure for the preparation of 6-methoxyketone 21: 1) Amine-based organocatalytic reduction of 6-methoxydienone **8**: The TFA salt of the amine catalyst (0.0268 mmol, 20 mol%) and Hantzsch ethyl ester **27** (105 mg, 0.414 mmol) were added to a solution of **8** (30 mg, 0.129 mmol) in 1,4-dioxane (1.6 mL) at room temperature. The resulting mixture was tightly sealed under an argon atmosphere and stirred at 60 °C for 130 h, before it was diluted with EtOAc and treated with 2 N aq.NaOH solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc (1×). The combined organic layers were washed with water (1×), followed by brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography of the crude product over Et_3N-deactivated silica gel [0.05% Et_3N v/v (30% EtOAc/hexane → 45% EtOAc/hexane)] under N_2 afforded an inseparable mixture of 6-methoxyenones **7**/**20** and the separable mixture of 6-methoxyketones **21**/**22**, separated, as yellow-white solids. Mixture of **7** (major) + **20*** (minor): R_f = 0.34 (silica, 60% EtOAc/hexane); m.p. 76.1–78.4 °C; $[\alpha]_D^{25}$ = −68.1 (c = 0.16, $CHCl_3$); IR (thin film): ν_{max} = 2955, 2872, 1690, 1620, 1454, 1371, 1277, 1202, 1161, 1080, 1042, 949, 864, 824 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.46* (s), 5.45 (s, 1H), 4.12 (br s, 1H), 4.06* (d, J = 4.4 Hz), 3.56 (s, 3H), 2.81* (dd, J = 15.2, 17.7 Hz), 2.44–2.37 (m, 3H), 2.36–2.34* (m), 2.26 (t, J = 6.3 Hz, 1H), 2.03–1.95* (m), 1.92–1.89 (m, 2H), 1.82 (d, J = 11.4 Hz, 1H), 1.76–1.70 (m, 2H), 1.61 (d, J = 11.4 Hz, 1H), 1.53–1.47* (m), 1.40 (s, 3H), 1.38* ppm (s); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.3, 150.9, 121.4, 120.7*, 86.5, 86.0*, 78.9*, 78.6, 54.8, 52.4, 48.2*, 47.6*, 45.4, 45.2*, 44.6*, 44.1, 43.0, 42.6, 41.9*, 41.6*, 39.4*, 38.0, 37.2, 37.1*, 27.8*, 23.1, 22.8* ppm; HRMS (EI): *m/z* calcd for $C_{14}H_{18}O_3^+$ $[M]^+$: 234.1256; found: 234.1254.

2) Hydrogenation over Pd/C to form **21**: 10% Pd on carbon (20% wt/wt, 5 mg) was added to a mixture of **7**/**20** and, optionally separated, 6-methoxyketones **21**/**22** in EtOAc (6 mL) and 0.3 N KOH in EtOH (3 mL) at room temperature. The resulting mixture was stirred under a hydrogen atmosphere (balloon) for 1.5 h, before it was quickly filtered through a pad of Celite, eluted with EtOAc, and concentrated in vacuo. Flash column chromatography of the crude product over Et_3N-deactivated silica gel [0.05% Et_3N v/v (10% EtOAc/hexane → 32% EtOAc/hexane)] under N_2 afforded 6-methoxyketones **21** and **22**, separated, as white solids.

(6*R*)-21: R_f = 0.37 (silica, 60% EtOAc/hexane); m.p. 50.2–51.8 °C; $[\alpha]_D^{25}$ = −35.1 (c = 0.31, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 4.11 (t, J = 3.5 Hz, 1H), 3.82 (dd, J = 6.3, 12.6 Hz, 1H), 3.44 (s, 3H), 2.32–2.30 (m, 3H), 2.07 (t, J = 9.5 Hz, 1H), 2.02 (dd, J = 3.5, 12.0 Hz, 1H), 1.93 (dd, J = 6.3, 12.6 Hz, 1H), 1.86 (m, 2H), 1.78–1.71 (m, 2H), 1.55 (d, J = 11.4 Hz, 2H), 1.41 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.9, 85.6, 82.0, 78.9, 58.1, 52.7, 45.9, 45.3, 44.9, 42.5, 41.1, 40.9, 37.2, 23.0 ppm; HRMS (EI): *m/z* calcd for $C_{14}H_{20}O_3^+$ $[M]^+$: 236.1412; found: 236.1409.

(6*S*)-21: R_f = 0.67 (silica, 30% EtOAc/hexane); m.p. 49.8–51.6 °C; $[\alpha]_D^{25}$ = +42.6 (c = 0.23, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 4.09 (br s, 1H), 3.48 (br s, 1H), 3.27 (s, 3H), 2.75 (dd, J = 12.6, 13.9 Hz, 1H), 2.30 (dd, J = 3.8, 12.6 Hz, 1H), 2.25 (t, J = 6.3 Hz, 1H), 2.10–2.03 (m, 2H), 1.88–1.83 (m, 4H), 1.63 (dd, J = 3.2, 11.4 Hz, 1H), 1.52 (d, J = 11.4 Hz, 2H), 1.39 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.7, 85.3, 83.6, 79.4, 57.3, 53.4, 46.3, 45.6, 43.3, 42.9, 40.9, 38.1, 37.4, 23.0 ppm.

(6*R*)-22: R_f = 0.38 (silica, 60% EtOAc/hexane); $[\alpha]_D^{25}$ = +38.7 (c = 0.32, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 4.01 (d, J = 4.5 Hz, 1H), 3.78 (dd, J = 6.3, 12.6 Hz, 1H), 3.45 (s, 3H), 2.79 (t, J = 13.9 Hz, 1H), 2.31–2.27 (m, 3H), 2.01–1.99 (m, 1H), 1.93 (dd, J = 6.3, 12.6 Hz, 1H), 1.77–1.70 (m, 4H), 1.48–1.43 (m, 1H), 1.42 (s, 3H), 1.34 ppm (d, J =

11.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.8, 85.5, 82.0, 78.9, 58.1, 52.6, 45.8, 44.8, 42.5, 41.1, 40.8, 37.2, 23.0 ppm.

Synthesis of methylated 6-methoxyenones 41/42: 0.5 M KHMDS in toluene (0.4 mL, 0.200 mmol) was added to a solution of the inseparable mixture of 6-methoxyenones **7/20** (31 mg, 0.132 mmol) in THF (2 mL) at −78 °C. The bright yellow solution was stirred at the same temperature for 30 min before the addition of HMPA (0.4 mL) and MeI (70 μL, 1.12 mmol). The resulting mixture was stirred at −78 °C and gradually warmed to −10 °C over 4 h, before it was quenched with saturated aq. $NaHCO_3$ and briefly stirred at room temperature. The mixture was diluted with water and extracted with EtOAc (3×). The combined organic extracts were washed with water (1×), followed by brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography of the crude product over silica gel (5% EtOAc/hexane → 20% EtOAc/hexane → 40% EtOAc/hexane) afforded an inseparable C4-diastereomeric mixture of methylated 6-methoxyenones **41/42** (20.3 mg, 62%) as a white solid. R_f = 0.30 (silica, 30% EtOAc/hexane); m.p. 76.2–80.4 °C; IR (thin film): ν_{max} = 2956, 2875, 1694, 1608, 1554, 1474, 1327, 1250, 1181, 1080, 1022, 949, 864, 821 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.38 + 5.41 (s each, 1H), 4.33 + 4.41 (br s each, 1H), 3.58 + 3.56 (s each, 3H), 2.45–2.41 (m, 1H), 2.34–2.28 (m, 1H), 2.06–2.04 (m, 1H), 1.96–1.67 (m, 4H), 1.63–1.58 (m, 1H), 1.42–1.40 (m, 3H), 1.22–1.21 + 1.15–1.13 ppm (m each, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.8, 150.4, 120.5, 86.6, 77.6, 54.9, 52.7, 48.4, 45.1, 44.3, 43.4, 41.4, 37.0, 23.2, 11.7 ppm; EI-MS: *m/z* calcd for $C_{15}H_{21}O_3^+$ $[M+H]^+$: 249.1; found: 249.3.

Synthesis of *tert*-butyl 6-methoxyplatensinoates 43: 1 M KO*t*Bu in *t*BuOH (0.17 mL) was added to a solution of **41/42** (21 mg, 0.0846 mmol) in THF (1.2 mL) at 0 °C. The resulting bright yellow solution was stirred at 0 °C for 20 min before the addition of *tert*-butyl acrylate (50 μL, 0.341 mmol). The resulting mixture was stirred at 0 °C for a further 3 h, before it was quenched with saturated aq. NH_4Cl and briefly stirred at room temperature. The mixture was diluted with water and extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography of the crude product over silica gel (10% EtOAc/hexane → 36% EtOAc/hexane) afforded an inseparable C4-diastereomeric mixture of *tert*-butyl 6-methoxyplatensinoate **43** (7.4 mg, 23%), with a 4:1 d.r. at the C4 position, as a pale yellow oil. R_f = 0.26 (silica, 30% EtOAc/hexane); IR (thin film): ν_{max} = 2975, 2880, 1686, 1441, 1378, 1276, 1218, 1153, 1104, 1042, 989, 864, 832 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.34 (s, 1H), 4.37 (br s, 1H), 3.58 (s, 3H), 2.39–2.36 (m, 1H), 2.33 (s, 1H), 2.26–2.22 (m, 2H), 2.17–2.10 (m, 1H), 2.05–1.97 (m, 3H), 1.84 (dd, *J* = 3.8, 10.7 Hz, 1H), 1.75–1.67 (m, 2H), 1.58 (d, *J* = 11.3 Hz, 1H), 1.43 (s, 3H), 1.41 (s, 9H), 1.25 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.9, 172.5, 149.1, 120.2, 86.8, 80.2, 76.5, 56.1, 55.0, 46.9, 45.7, 44.6, 44.4, 44.2, 40.4, 31.1, 30.3, 28.1, 24.9, 23.1 ppm; EI-MS: *m/z* calcd for $C_{22}H_{32}O_5^+$ $[M]^+$: 376.2; found: 376.5. *tert*-Butyl 6-methoxyplatensinoate **44** was observed in trace amounts contaminated with unknown by-products.

Synthesis of tetrahydroketone 46: 1) Preparation of 0.1 M solution of SmI_2 in THF: Sm powder (≈40 mesh, 50 mg, 0.33 mmol) was added to a flame-dried round-bottom flask, followed by addition of diiodoethane (85 mg, 0.3 mmol). The round-bottom flask was placed on the vacuum line to evacuate the air and was refilled with Ar. This procedure was repeated twice before the flask was immediately sealed and an Ar balloon was attached. THF (3 mL) was added to the stirring mixture at room temperature, the Ar balloon was removed, and the reaction flask was tightly sealed. The resulting mixture in the flask was partially submerged to the solvent level in the sonicator and sonicated for 5 min to trigger the reaction.[42] The resulting deep blue solution of SmI_2 was stirred at room temperature for 12 h before it was directly used in the subsequent step.

2) Preparation of **46**: Anhydrous *t*BuOH (15 μL, 0.157 mmol) was added to a solution of 6-methoxyenone **7** (major isomer; 3.6 mg, 0.0154 mmol) in THF (1 mL) at room temperature. The solution was cooled to 0 °C, before 0.1 M SmI_2 in THF (2 mL) was added through a gas-tight syringe. The resulting mixture was stirred at 0 °C → room temperature over 5 h, before the reaction was quenched with water. The mixture was extracted with EtOAc (3×), and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was briefly purified through flash column chromatography over silica gel, eluted with EtOAc, before it was used in the subsequent step. $NaHCO_3$ (10.4 mg, 0.124 mmol) and Dess–Martin periodinane (21.5 mg, 0.0507 mmol) were added to a solution of this tetrahydroalcohol (2.8 mg) in CH_2Cl_2 (1 mL) at room temperature. The resulting mixture was stirred at room temperature for 7 h, before it was quenched with saturated aq. $NaHCO_3$ and saturated aq. $Na_2S_2O_3$ solutions (1:1) and stirred at room temperature to obtain a clear solution. The mixture was diluted with water and extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Preparative TLC of the crude product (35% EtOAc/hexane × 03 elution) spread over a 16×10 cm glass plate afforded tetrahydroketone **46** (1.7 mg, 52% over two steps) as a white solid. R_f = 0.26 (silica, 30% EtOAc/hexane); $[\alpha]_D^{27}$ = −58.9 (*c* = 0.05, $CHCl_3$); IR (thin film): ν_{max} = 2972, 2854, 1710, 1538, 1424, 1326, 1277, 1211, 1150, 1072, 956, 831 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.08 (s, 1H), 2.39–2.21 (m, 5H), 2.09–2.02 (m, 2H), 1.91–1.77 (m, 3H), 1.70 (dd, *J* = 3.1, 11.3 Hz, 1H), 1.65–1.60 (m, 1H), 1.52 (overlapped by impurity, 1H), 1.42–1.39 ppm (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.6, 86.1, 79.3, 52.8, 45.2, 45.0, 44.4, 41.6, 40.0, 39.2, 37.1, 35.1, 23.1 ppm; HRMS (EI): *m/z* calcd for $C_{13}H_{18}O_2^+$ $[M]^+$: 206.1307; found: 206.1302.

Synthesis of methylated tetracyclic enone 47: 0.5 M KHMDS in toluene (0.22 mL, 0.110 mmol) was added to a solution of tetracyclic enone (−)-**2** (14 mg, 0.0685 mmol) in THF (1.2 mL) and HMPA (0.24 mL) at −78 °C. The bright yellow solution was stirred at the same temperature for 20 min before the addition of MeI (35 μL, 0.562 mmol). The resulting mixture was stirred at −78 °C and gradually warmed to −10 °C over 3 h, before it was quenched with saturated aq. $NaHCO_3$ and briefly stirred at room temperature. The mixture was diluted with water and extracted with EtOAc (3×). The combined organic extracts were washed with water (1×), followed by brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography of the crude product over silica gel (5% EtOAc/hexane → 20% EtOAc/hexane) afforded methylated tetracyclic enone **47** (11.9 mg, 80%), with almost complete C4 diastereoselectivity, as a white solid. R_f = 0.30 (silica, 20% EtOAc/hexane); m.p. 79.1–81.0 °C; $[\alpha]_D^{25}$ = −42.2 (*c* = 0.26, $CHCl_3$); IR (thin film): ν_{max} = 2966, 2855, 1734, 1674, 1602, 1568, 1454, 1379, 1282, 1181, 1080, 1040, 946, 854, 813 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.53 (d, *J* = 10.0 Hz, 1H), 5.92 (d, *J* = 9.9 Hz, 1H), 4.35 (br s, 1H), 2.40–2.31 (m, 2H), 2.09–2.05 (m, 1H), 1.97–1.73 (m, 5H), 1.61 (d, *J* = 11.1 Hz, 1H), 1.43 (s, 3H), 1.13 ppm (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.2, 154.1, 128.1, 77.6, 51.8, 48.5, 46.7, 44.4, 42.5, 41.2, 37.1, 23.0, 10.9 ppm; HRMS (IT-TOF): *m/z* calcd for $C_{14}H_{18}O_2Na^+$ $[M+Na]^+$: 241.1204; found: 241.1210.

Synthesis of *tert*-butyl platensinoate 48: 1 M KO*t*Bu in *t*BuOH (48 μL) was added to a solution of **47** (12 mg, 0.0550 mmol) in THF (1 mL) at −10 °C. The resulting bright yellow solution was stirred at −10 °C for 10 min, before the addition of *tert*-butyl acrylate (23 μL,

0.154 mmol). The resulting mixture was stirred at −10 °C → 0 °C for a further 2 h, before it was quenched with saturated aq. $NaHCO_3$ and briefly stirred at room temperature. The mixture was diluted with water and extracted with EtOAc (4×). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography of the crude product over silica gel (10% EtOAc/hexane → 25% EtOAc/hexane) afforded an inseparable C4-diastereomeric mixture of *tert*-butyl platensinoate **48** (11.9 mg, 62%), with a 10:1 d.r. at the C4 position, as a colorless oil. $R_f = 0.21$ (silica, 20% EtOAc/hexane); $[\alpha]_D^{25} = -31.6$ ($c = 0.18$, $CHCl_3$); IR (thin film): $\nu_{max} = 2967$, 2870, 1690, 1623, 1456, 1395, 1378, 1266, 1208, 1161, 1101, 1080, 1024, 948, 844, 832 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.45$ (d, $J = 10.1$ Hz, 1H), 5.87 (d, $J = 10.1$ Hz, 1H), 4.39 (br s, 1H), 2.41–2.38 (m, 1H), 2.34 (s, 1H), 2.24–2.21 (m, 2H), 2.14–2.06 (m, 2H), 2.03–1.99 (m, 2H), 1.84 (dd, $J = 3.1$, 10.7 Hz, 1H), 1.77–1.73 (m, 1H), 1.69–1.64 (m, 1H), 1.61–1.59 (m, 3H), 1.44 (s, 3H), 1.42 (s, 9H), 1.22 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 203.3$, 172.6, 153.4, 127.3, 87.0, 80.2, 76.5, 55.0, 46.2, 46.0, 46.0, 44.7, 43.2, 40.6, 30.8, 30.3, 28.1, 24.6, 23.0 ppm; HRMS (IT-TOF): *m/z* calcd for $C_{21}H_{31}O_4^+$ $[M+H]^+$: 347.2222; found: 347.2226.

Synthesis of platensic acid 6: TFA (0.6 mL) was added to a solution of **48** (6 mg, 0.0173 mmol) in CH_2Cl_2 (0.6 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 12 h before it was concentrated in vacuo. The crude platensic acid **6** was placed under high vacuum pull for 12 h to afford a white solid (5 mg, 100%), which was used in the subsequent step without further purification. $R_f = 0.14$ (silica, 60% EtOAc/hexane); $[\alpha]_D^{26} = -35.1$ ($c = 0.16$, MeOH); IR (thin film): $\nu_{max} = 2972$, 2932, 1712, 1646, 1471, 1444, 1390, 1248, 1202, 1121, 1090, 1048, 968, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.47$ (d, $J = 10.1$ Hz, 1H), 5.89 (d, $J = 10.1$ Hz, 1H), 4.41 (br s, 1H), 2.42–2.40 (t, 1H), 2.36–2.24 (m, 4H), 2.13–1.99 (m, 3H), 1.87 (dd, $J = 3.1$, 11.3 Hz, 1H), 1.79–1.75 (m, 2H), 1.61 (d, $J = 10.7$ Hz, 1H), 1.44 (s, 3H), 1.24 ppm (s, 3H); HRMS (IT-TOF): *m/z* calcd for $C_{17}H_{23}O_4^+$ $[M+H]^+$: 291.1596; found: 291.1591.

Synthesis of acetophenone 49: PPA (11 g per 100 mg of **5**) was heated at 50 °C until it became less viscous, and then glacial AcOH (0.51 mL, 8.86 mmol) and 2-nitroresorcinol (**5**; 0.55 g, 3.58 mmol) were added at the same temperature. The temperature was raised to 75–80 °C, and the resulting mixture was stirred for 2 h, before it was cooled to room temperature and quenched with cold water (180 mL). The resulting mixture was extracted with EtOAc (4×), and the combined organic layers were washed with H_2O (1×), followed by brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography of the crude product over silica gel (CH_2Cl_2, then 5% MeOH/CH_2Cl_2 to eventually flush out the tailing) afforded acetophenone **49** (0.482 g, 69%) as a yellow crystalline solid. $R_f = 0.23$ (silica, 2% MeOH/CH_2Cl_2); m.p. 123.4–125.8 °C; IR (thin film): $\nu_{max} = 1629$, 1535, 1370, 1286, 1163, 1061, 981, 887, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 14.84$ (s, 1H), 11.34 (s, 1H), 7.90 (d, $J = 9.0$ Hz, 1H), 6.64 (d, $J = 9.0$ Hz, 1H), 2.62 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 202.9$, 161.9, 161.4, 137.6, 125.1, 113.5, 108.9, 26.6 ppm; HRMS (IT-TOF): *m/z* calcd for $C_8H_5O_5N^{2-}$ $[M-2H]^{2-}$: 195.0179; found: 195.0168.

Synthesis of bisbenzylacetophenone 4: Anhydrous K_2CO_3 (1.50 g, 10.8 mmol), TBAI (0.133 g, 0.361 mmol), and BnBr (644 μL, 5.42 mmol) were added to a solution of **49** (0.356 g, 1.81 mmol) in anhydrous DMF (12 mL) at room temperature. The resulting mixture was warmed to 55 °C and stirred for 12 h, before it was cooled to room temperature and quenched with cold water. Vigorous stirring was maintained for 5–10 min until a homogenous layer was obtained, and the reaction mixture was extracted with Et_2O (3×). The combined organic extracts were washed with water (1×), followed by brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography of the crude product over silica gel (5% EtOAc/hexane → 25% EtOAc/hexane) afforded bisbenzylacetophenone **4** (0.647 g, 95%) as a pale yellow oil. $R_f = 0.34$ (silica, 30% EtOAc/hexane); IR (thin film): $\nu_{max} = 2987$, 2949, 1685, 1601, 1536, 1461, 1376, 1266, 1094, 1001, 924, 814 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.76$ (d, $J = 9.4$ Hz, 1H), 7.39–7.35 (m, 10H), 6.89 (d, $J = 9.5$ Hz, 1H), 5.25 (s, 2H), 5.03 (s, 2H), 2.54 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 196.8$, 153.6, 151.0, 135.0, 134.7, 132.5, 128.9, 128.9, 128.7, 128.6, 128.6, 127.1, 126.9, 109.3, 79.5, 71.4, 30.1 ppm; HRMS (IT-TOF): *m/z* calcd for $C_{22}H_{19}O_5NNa^+$ $[M+Na]^+$: 400.1161; found: 400.1168.

Synthesis of methyl benzoate 50: 1) Preparation of *tert*-butylhypochlorite: The reaction was carried out with minimal exposure to light. A solution of *t*BuOH (5 mL) and glacial AcOH (3 mL) was added in a single portion to a vigorously stirring 14% NaOCl solution placed in a conical flask wrapped in aluminum foil and immersed in an ice bath at 0 °C. The resulting mixture was stirred for 3–4 min, before it was transferred to a separatory funnel, and the aqueous layer was separated. The yellow organic layer was washed with saturated aq. $NaHCO_3$ (1×), followed by water, dried over Na_2SO_4, filtered, and used in the following reaction immediately.

2) Preparation of **50**: 25% NaOMe in MeOH (0.6 mL) was added to a stirred solution of **4** (0.166 g, 0.440 mmol) in MeOH (HPLC grade, 14 mL), followed by dropwise addition of *t*BuOCl (0.6 mL), at 5 °C with minimal exposure to light. The resulting mixture was stirred at room temperature for 1 h, before acetone was added to decompose the excess *t*BuOCl. The resulting mixture was concentrated in vacuo, and the residue was partitioned between 1 M HCl and EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2×). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography of the crude product over silica gel (5% EtOAc/hexane → 25% EtOAc/hexane) afforded methyl benzoate **50** (0.164 g, 95%) as a white crystalline solid. $R_f = 0.29$ (silica, 30% EtOAc/hexane); m.p. 101.2–102.6 °C; IR (thin film): $\nu_{max} = 3099$, 2960, 2844, 1720, 1609, 1536, 1436, 1381, 1268, 1189, 1102, 992, 818 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.00$ (d, $J = 9.0$ Hz, 1H), 7.48–7.33 (m, 10H), 6.87 (d, $J = 8.9$ Hz, 1H), 5.21 (s, 2H), 5.15 (s, 2H), 3.88 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 164.2$, 153.7, 151.9, 138.2, 135.8, 134.7, 134.2, 128.7, 128.4, 128.4, 127.0, 117.8, 108.9, 78.7, 71.2, 52.2 ppm; HRMS (IT-TOF): *m/z* calcd for $C_{22}H_{19}O_6NNa^+$ $[M+Na]^+$: 416.1110; found: 416.1114.

Synthesis of aniline presursor 3: 10% Pd on carbon (10 mg) was added to a solution of **50** (22.4 mg, 56.8 μmol) in MeOH (5 mL) at room temperature. The resulting mixture was stirred under a hydrogen atmosphere (balloon) for 16 h, before it was filtered through a pad of Celite, eluted with 5% MeOH/EtOAc, and concentrated in vacuo to afford the aniline precursor **3** (9.5 mg, 92%) as a white crystalline solid. No further purification was required, and the crude aniline **3** was carried forward to the next step. ^1H NMR (500 MHz, CD_3OD): $\delta = 7.19$ (d, $J = 8.8$ Hz, 1H), 6.35 (d, $J = 8.8$ Hz, 1H), 3.87 ppm (s, 3H); ESI-MS: *m/z* calcd for $C_8H_8O_4N^-$ $[M-H]^-$: 182.0; found: 182.1; *m/z* calcd for $C_8H_{10}O_4N^-$ $[M+H]^+$: 184.1; found: 184.0.

Synthesis of amide 51: Et_3N (14.5 μL, 0.104 mmol) and HATU (26.3 mg, 69.2 μmol) were added to a solution of platensic acid (**6**; 5 mg, 17.3 μmol) in anhydrous DMF (1 mL) at room temperature. The resulting mixture was stirred at room temperature for 10–15 min before the addition of a solution of **3** (9.5 mg, 51.9 μmol) in anhydrous DMF (1 mL). The resulting mixture was stirred at room temperature for 25 h, before it was poured into brine and extracted with EtOAc (4×). The combined organic extracts were back-

washed with brine (1×), dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography of the crude product over silica gel (5% acetone/hexane → 24% acetone/hexane → 100% acetone), followed by preparative TLC (25% acetone/hexane × 02 elution) spread over a 20×10 cm glass plate afforded amide **51** (6.1 mg, 71%, single epimer at the C4 position by HPLC analysis) as a pale yellow viscous oil. R_f=0.21 (silica, 40% acetone/hexane); $[\alpha]_D^{24}=-39.3$ (c=0.21, $CHCl_3$); IR (thin film): ν_{max}=3225, 2965, 2872, 1668, 1654, 1610, 1530, 1424, 1381, 1270, 1206, 1181, 1086, 1025, 950, 884, 814 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=11.64 (s, 1H), 11.07 (br s, 1H), 8.10 (s, 1H), 7.56 (d, J=8.8 Hz, 1H), 6.52–6.50 (m, 2H), 5.93 (d, J=10.0 Hz, 1H), 4.44 (br s, 1H), 3.92 (s, 3H), 2.56–2.49 (m, 1H), 2.44–2.36 (m, 4H), 2.12–2.00 (m, 3H), 1.93–1.86 (m, 2H), 1.81–1.77 (m, 1H), 1.63 (d, J=11.3 Hz, 1H), 1.45 (s, 3H), 1.27 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=203.6, 173.6, 170.7, 154.9, 153.9, 153.8, 127.4, 127.2, 114.4, 111.3, 104.1, 87.0, 76.4, 54.9, 52.2, 46.7, 46.2, 46.1, 44.7, 43.1, 40.6, 32.1, 31.6, 29.7, 24.2, 23.0 ppm; HRMS (EI): m/z calcd for $C_{25}H_{29}O_7N^+$ $[M]^+$: 455.1944; found: 455.1946.

Synthesis of (−)-platensimycin (1): 2 M aq. KOH (0.2 mL) was added to a solution of **51** (3.7 mg, 8.12 μmol) in 1,4-dioxane (0.2 mL) and MeOH (0.1 mL) at room temperature. The resulting mixture was tightly sealed and stirred at 35 °C for 16 h, before the solvents were concentrated in vacuo. The residue was then partitioned between water and CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×). The aqueous layer was acidified with 1 M HCl to pH 1–2 and extracted with EtOAc (5×). The combined EtOAc extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Preparative TLC of the crude product (60% EtOAc/hexane + 1% AcOH × 02 elution) spread over a 16×10 cm glass plate, followed by flash column chromatography over silica gel (10% acetone/hexane → 40% acetone/hexane → 70% acetone/hexane + 0.5% AcOH) afforded (−)-platensimycin (**1**; 2.5 mg, 60%) as a white solid. R_f= 0.12 (silica, 60% acetone/hexane); $[\alpha]_D^{23}=-48.2$ (c=0.11, MeOH); IR (thin film): ν_{max}=3321, 2962, 2928, 2879, 1665, 1652, 1605, 1542, 1438, 1392, 1278, 1212, 1150, 1090, 1001, 912, 820 cm^{-1}; ^1H NMR (500 MHz, C_5D_5N): δ=10.5 (s, 1H), 8.11 (d, J=8.8 Hz, 1H), 6.87 (d, J=8.8 Hz, 1H), 6.36 (d, J=10.0 Hz, 1H), 5.93 (d, J=9.4 Hz, 1H), 4.48 (br s, 1H), 2.86–2.65 (m, 3H), 2.44 (s, 1H), 2.20–2.18 (m, 1H), 2.07–2.00 (m, 1H), 1.91–1.89 (m, 1H), 1.80 (d, J=11.9 Hz, 1H), 1.72 (d, J=10.0 Hz, 1H), 1.58–1.54 (m, 1H), 1.47 (d, J=10.7 Hz, 1H), 1.39 (s, 3H), 1.14 ppm (s, 3H); ^{13}C NMR (125 MHz, C_5D_5N): δ=203.2, 174.7, 158.2, 153.9, 129.4, 127.2, 115.3, 110.0, 107.1, 86.8, 76.4, 54.9, 46.7, 46.6, 46.1, 45.0, 43.0, 40.8, 32.1, 31.8, 30.5, 24.4, 23.2 ppm; HRMS (EI): m/z calcd for $C_{24}H_{27}O_7N^+$ $[M]^+$: 441.1788; found: 441.1784.

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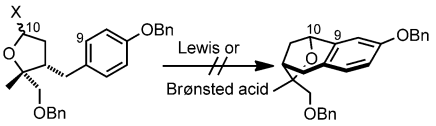

X = OH, OMe, OAc, $OC(NH)CCl_3$, Cl, Br

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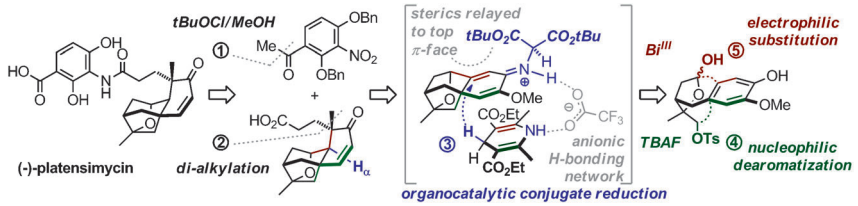

Relay tactics: The stereocontrolled assembly of the potent antibiotic (−)-platensimycin in 21 steps and 3.8% yield from eugenol is described (see scheme; TBAF: tetrabutylammonium fluoride; Ts: toluene-4-sulfonyl). Highlights are 1) a rapid oxidative esterification of an acyl aromatic, 2) a reliable dialkylation protocol to form platensic acid, 3) a π-facial conjugate reduction of a dienone, 4) a TBAF-promoted alkylative dearomatization of a free phenol, and 5) a Friedel–Crafts closure of a free lactol.

Organocatalysis

*S. T.-C. Eey, M. J. Lear**

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Total Synthesis of (−)-Platensimycin by Advancing Oxocarbenium- and Iminium-Mediated Catalytic Methods