DOI: 10.1002/ejoc.200801229

Stereocontrolled Preparation of Fully Substituted Cyclopentanes: Relevance to Total Synthesis

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Keywords: Natural products / Carbocycles / Cyclopentane / Total synthesis / Asymmetric synthesis / Diels–Alder reaction / Palau'amine

This Microreview aims to identify important advances in the asymmetric synthesis of fully substituted five-membered carbocyclic ring systems. Recent efforts directed towards the intricate and densely functionalized core substructures of three distinct classes of cyclopentane-based natural products will be examined. Strategies featuring high levels of stereocontrol and/or conciseness in the total number of synthetic steps required to access complex natural product ring fragments are highlighted. Stereoselective Diels–Alder cycloaddition approaches to access functionalized norbornene intermediates as latent chiral cyclopentanes in the tradition of Corey's elegant prostaglandin studies are a recurring theme.

1. Introduction

Dating back to the late 1960's, Corey's work on the prostaglandins is often regarded as a milestone in the field of synthetic chemistry.[1] Utilizing a bicyclo[2.2.1]heptane approach (Figure 1, B) to forge the oxygenated five-membered carbocyclic framework, stereocontrolled total syntheses of prostoglandins E_2 and $F_{2\alpha}$ (**1**) were accomplished[2] and subsequently rendered catalytic and enantioselective.[3] The Corey route intersects with a relatively uncommon chiral synthon: a fully substituted cyclopentane **8** bearing all of the requisite functionality for elaboration to **1**. This work remains particularly relevant as five-membered carbocyclic cores bearing stereopentads of comparable molecular complexity are found in a subset of the highly sought after pyrrole-imidazole family of marine alkaloids (e.g. **4** and **5**, Figure 1, A) as well as biologically relevant terpenoids (**2** and **3**) and aminocyclopentitol-based glycosidase inhibitors (**6** and **7**).

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To highlight important advances in the stereocontrolled synthesis of penta-substituted cyclopentanes, analyses of recent efforts directed towards the common E and D ring systems of oroidin dimers **4** and **5**, respectively, will be provided. Strategies and tactics regarded as being well-suited for application to new total syntheses will be emphasized. We will focus here only on the stereochemical challenges posed by the intricate and densely functionalized core cyclopentanes. Indeed, the eventual introduction and manipulation of the heterocycles at the periphery of the carbocycle is a daunting task of its own and has been discussed elsewhere.[4]

In addition, selected asymmetric approaches to the aminocyclopentitol core of trehazolin (**6**) will be discussed followed by an examination of Nicolaou's expedient entry into the polycyclic carbon backbone of vannusal B (**2**), which includes a fully substituted cyclopentane in the form of a bicyclo[2.2.1]heptane. Many of the approaches outlined below involve selective manipulation of a norbornene-type intermediate generated by a cleverly crafted Diels–Alder cycloaddition reaction and all are notable for either exquisite stereocontrol or conciseness in the total number of synthetic operations required to access highly complex cyclopentane-based molecular scaffolds.

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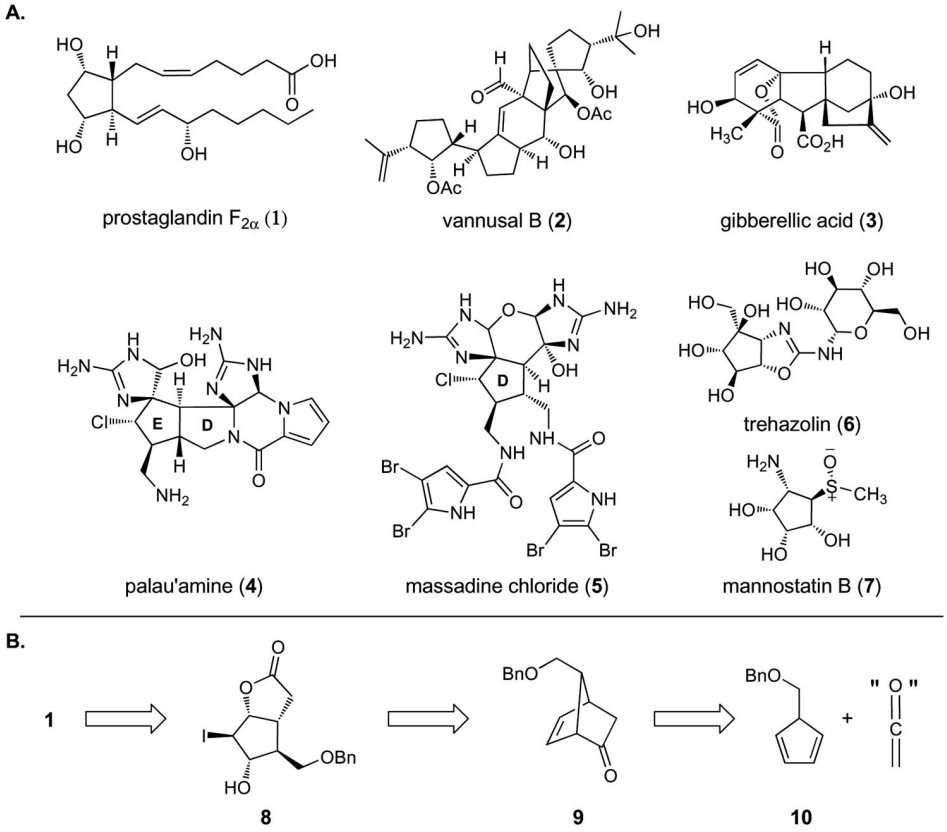


Figure 1. A: Biologically relevant natural products bearing a densely functionalized and stereochemically intricate cyclopentane core structure. B: Corey's bicyclo[2.2.1]heptane retrosynthetic dissection of prostaglandin $F_{2\alpha}$.

1.1. Corey's Prostaglandin Studies

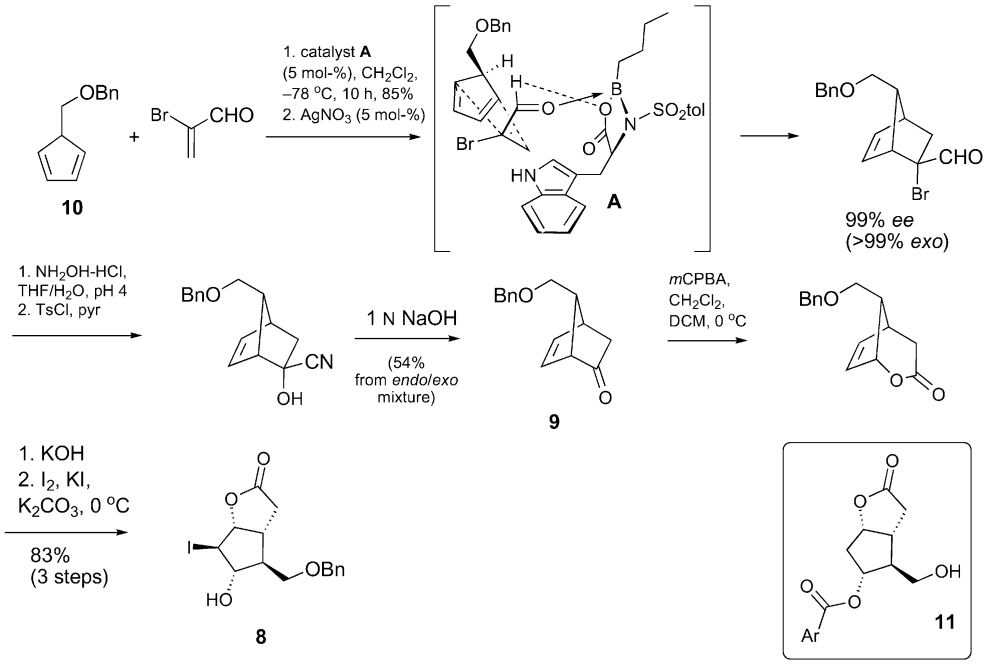
As an introduction to cyclic stereocontrol as it applies to the synthesis of complex cyclopentanes, a selection of Corey's groundbreaking prostaglandin studies will be briefly revisited for contextual purposes. A recent refinement of Corey's prostanoid-related methodologies (Scheme 1)[3] features a catalytic enantioselective Diels–Alder reaction between 5-alkyl cyclopentadiene **10** and 2-bromoacrolein. The bracketed transition-state pathway[3c,3d] relies on the ability of π-electron-rich indole to stabilize the *O*-coordinated dienophile in an *s*-cis conformation to bias the enantiofacial selectivity of the cycloaddition. The approach of the dienophile is from the face opposite to the 5-benzyloxymethyl group and the *exo* formyl adduct is obtained with high selectivity for steric reasons. The reaction is run at low temperature in part to suppress isomerization of the 5-substituted cyclopentadiene by a [1,5]-sigmatropic shift[2a,5a] that occurs readily at room temperature (vida infra).

The 5% diastereomeric *endo* contaminant reacts relatively quickly with silver nitrate due to its *exo*-oriented halogen and is thereby easily removed from the mixture by decomposition to water-soluble by-products. The cyanohydrin is then obtained by dehydration of the intermediate α-hydroxy oxime and the latent ketone functionality is revealed by hydrolysis to provide norbornene **9**. A regio- and chemoselective Baeyer–Villiger ring expansion occurs with migration of the more substituted alkyl group and subsequent hydrolysis provides a carboxylate substrate poised for iodo-lactonization. In the event, treatment with iodine under basic conditions provides the bicyclic iodo-lactone **8** as a single isomer with excellent efficiency. This fully substituted cyclopentane **8** can be easily elaborated to the "Corey lactone" **11**, a chiral synthon famous for its utility as an intermediate for the total synthesis of various prostanoids.

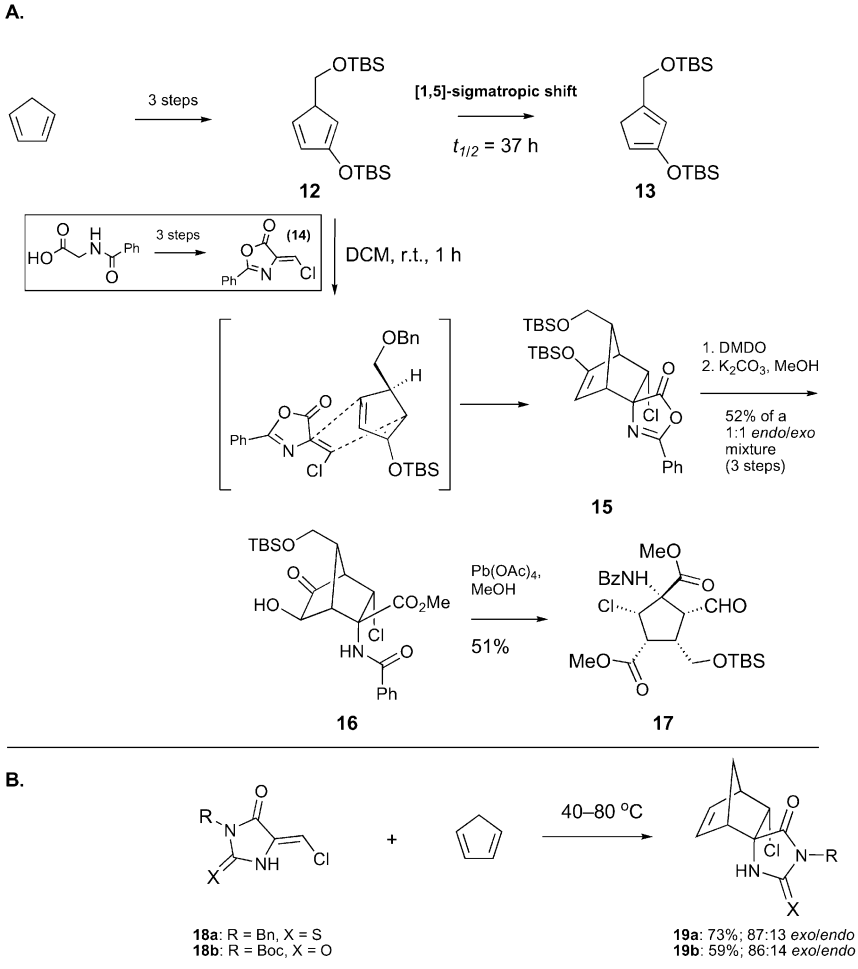
2. Oroidin Marine Alkaloids

2.1. Gleason's Diels–Alder Approach

Gleason and co-workers were inspired by Corey's prostanoid-directed studies to apply a related Diels–Alder strategy to the synthetic problem posed by the highly sterically congested cyclopentane E-ring of palau'amine (**4**). The authors were struck by the rare use of 5-alkyl cyclopentadienes in total synthesis and attributed this phenomenon to a facile [1,5]-sigmatropic rearrangement (e.g. **12**→**13**, Scheme 2, A)[2a,5a] that precludes preparation and use of the diene at ambient temperatures. It was shown that incorporation of a 2-silyloxy group into the diene system results in a 30-fold increase in the stability of **12** at 23 °C relative to 5-methylcyclopentadiene.[5a] This allows for the productive use of similar dienes in Diels–Alder cycloaddition reactions conducted at room temperature.



Scheme 1. Corey's catalytic enantioselective synthesis of a key prostaglandin intermediate.[3c]



Scheme 2. A: Gleason's concise route to the functionalized chlorocyclopentane core of palau'amine (original structure assignment).[5a] B: Diastereoselectivity results.[5b] For cycloadditions **12**→**15** and **18**→**19** the *endo* co-product has been omitted for clarity.

Diene **12** is competent in a variety of [4+2] reactions exhibiting varying levels of *endo*/*exo* selectivity.[5a] In one example, **12** underwent cycloaddition with β-chlorodehydroalanine oxazolone **14** at room temperature to deliver a 1:1 mixture of cycloadducts that were directly subjected to DMDO oxidation followed by methanolysis to provide separable hydroxy ketones **16** (*exo* adduct shown in Scheme 2A). Purified **16** was then oxidatively ring-opened in good yield to deliver the fully substituted cyclopentane **17**.

The complete lack of the desired *exo* diastereoselectivity in reactions of oxazolone **14** with cyclopentadienes is troubling. Fortunately, Gleason has shown (Scheme 2, B) that *exo*-selectivity can be realized with exomethylene thiohydantoins and hydantoins (e.g. **18a** and **b**, respectively) to produce spirocyclic norbornenes such as **19a** and **b**.[5b]

The authors provide an elegant solution to the problem of stereoselective introduction of the chlorine substituent into the palau'amine E-ring and the route is notable for its conciseness and creativity. Unfortunately, **17** bears a stereopentad with an *all-cis* configuration while a recently proposed structural revision[6,7] of palau'amine suggests that the chloride is disposed on the β-face of the molecule and that the D-E fusion is *trans* (cf. **4**, as depicted in Figure 1, A). This notion has not been confirmed by crystallographic data and awaits verification from total synthesis campaigns. For clarity, the stereochemical orientations of the original and revised core stereopentads are shown in Figure 2. It is noteworthy that the revised configuration is conserved amongst other oroidin alkaloids (e.g. **5**).

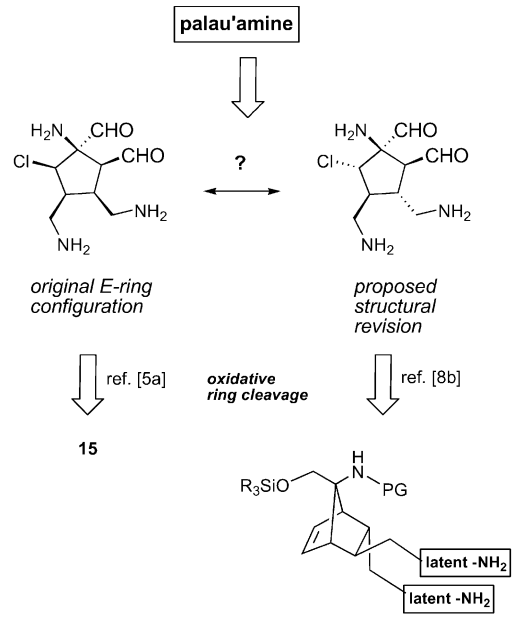
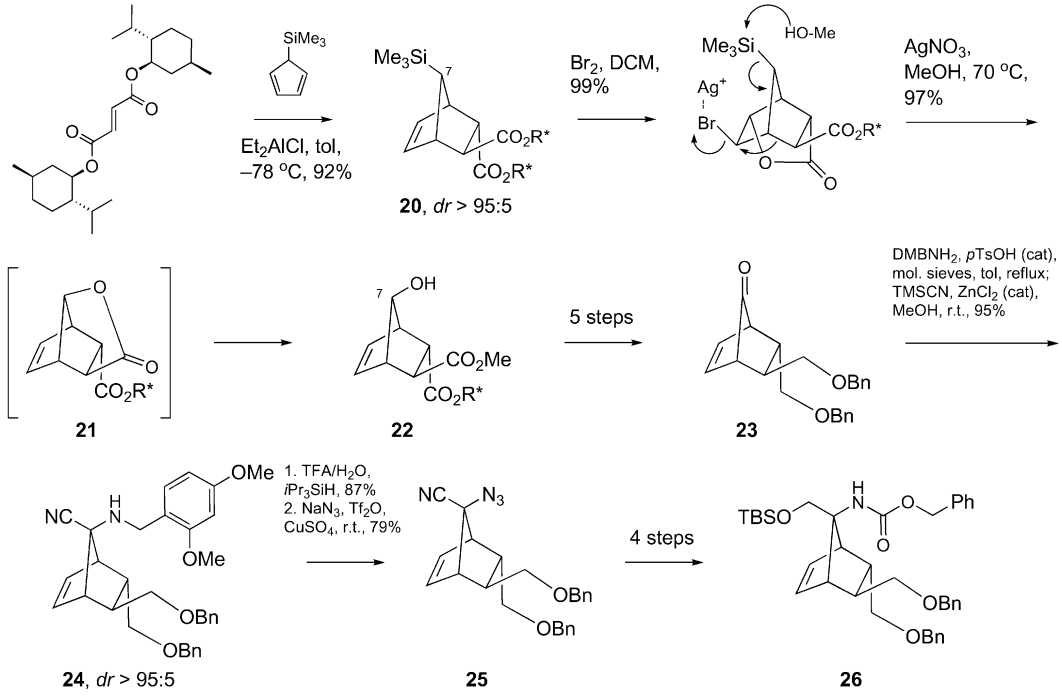


Figure 2. Insightful bicyclo[2.2.1]heptane (norbornene) approaches to the E-ring of palau'amine.[5a,8b]

2.2. Carreira's Synthesis of a Massadine Precursor

Carreira has exemplified a synthetic route[8] to access the fully substituted D-ring of massadine-type alkaloids.[9] The overall strategy (Figure 2) is to produce an enantiopure norbornene intermediate as the conformationally rigid cy-

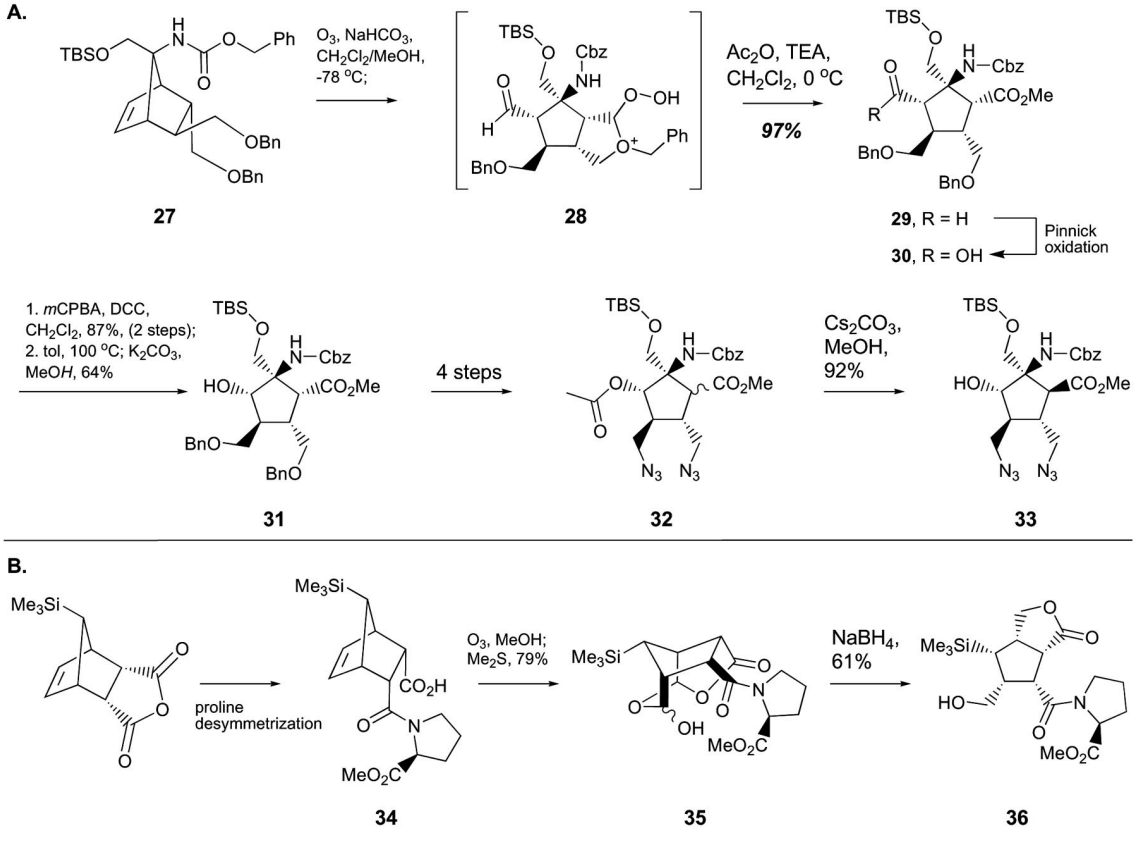


Scheme 3. Carreira's enantioselective synthesis of a massadine D ring precursor featuring a creative and efficient functionalization of the C7 position of norbornene and a highly diastereoselective Strecker reaction;[8b] R* = (–)-menthyl.

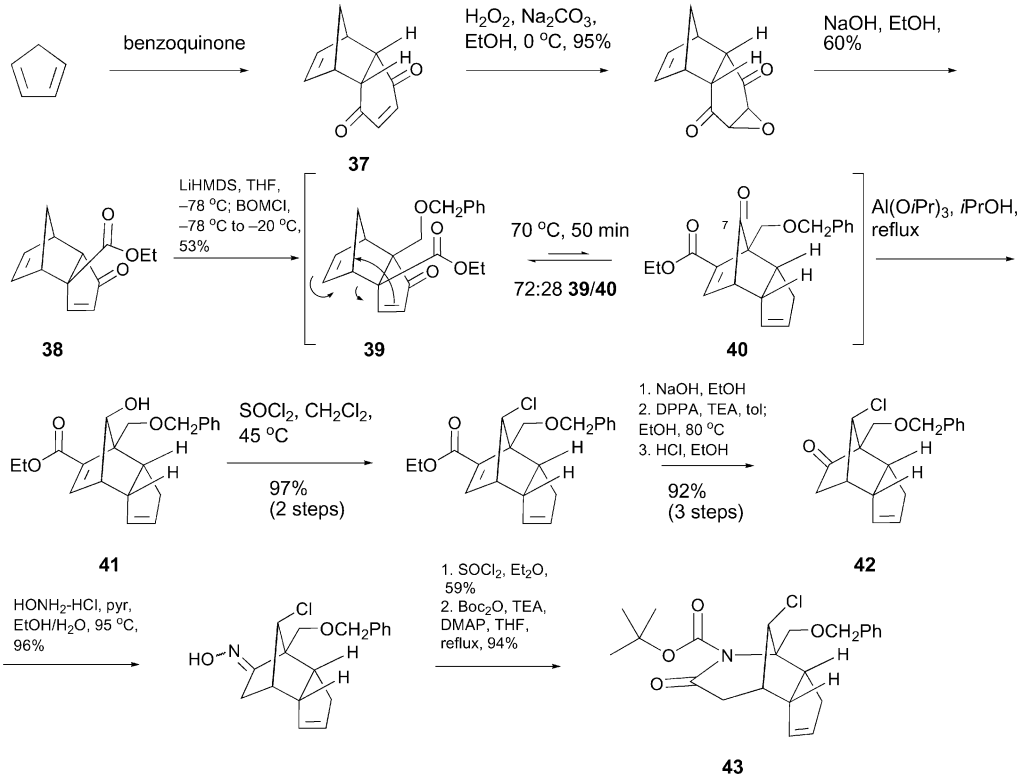
clopentane precursor and then to manipulate functionality at the C7 position (norbornene numbering) in a chemo- and diastereoselective manner followed by oxidative cleavage of the olefin. The sequence (Scheme 3)[8b] commences with a diastereoselective cycloaddition of 5-(trimethysilyl)cyclopentadiene with a chiral fumarate to provide the bicyclo[2.2.1]heptane efficiently. The C7 position is then oxygenated by a remarkable sequence wherein bromo-lactonization of **20** is followed by an Ag^{I}-mediated rearrangement of the C7-silane to generate the inverted alcohol **22** via methanolysis of the putative lactone intermediate **21**. The authors report that the process is reliable on >50 gram scale. The alcohol is then advanced in a straight-forward way to ketone **23**.

A Strecker reaction on ketone **23** produced a single amino-nitrile isomer **24**. The exquisite diastereoselectivity was attributed to steric shielding of one iminium diastereoface by the bulky *exo*-oriented benzyloxymethylene. The azidonitrile **25**, generated by Cu^{II}-catalyzed diazotransfer could be successfully reduced and elaborated to the silyl ether **26**. Oddly, attempts at reduction of variously protected amino-nitrile substrates led to decomposition. At this stage, an ambitious oxidative ring cleavage was postulated to strategically differentiate between the carbon atoms of the norbornene double bond. In the event (Scheme 4, A), ozonolysis provided regioselectively the ester/aldehyde **29** in excellent yield. The authors invoke anchimeric participation of one benzyloxy group in the rearrangement of the primary ozonide to generate the putative oxonium species **28** followed by methanolysis and dehydration to **29**. A similar neighbouring group participation-regioselectivity phenomenon has been observed during ozonolotic ring opening of norbornene **34** (Scheme 4, B).[10] In this case the proximal *endo*-disposed carboxylate distinguishes between the two sp^2-hybridized carbon atoms of the double bond by giving rise to a fused tricyclic acetal-hemiacetal ring system **35** that can be reduced to the differentiated bicyclic lactone **36**.

"Carboxy-inversion" (**30**→**31**, Scheme 4, A)[11] was realized by generation of the unsymmetrical diacyl peroxide from carboxylic acid **30** using DCC and peracid. This intermediate was heated to promote rearrangement to the mixed carbonate and subsequent methanolysis afforded the alcohol **31**. An inconsequential diastereomeric mixture of diazides **32** was obtained in four additional steps. Tandem acetate saponification/ester epimerization with Cs_2CO_3 provided the massadine core fragment **33** in an enantioselective fashion (24 linear steps). Notably, carboxylic acid **30** *may* be poised for a Barton/Hunsdiecker-type decarboxylative chlorination[8a] that would provide access to a chlorocyclopentane scaffold which maps directly onto the revised structure of palau'amine (**4**).



Scheme 4. A: Completion of a D-ring-core fragment of massadine featuring end-group differentiation through ozonolotic olefin cleavage.[8b] B: A related norbornene ozonolysis resulting in regioselectivity due to neighboring group participation.[10]



Scheme 5. Gin's synthesis of bridged lactam intermediate **43**.[12]

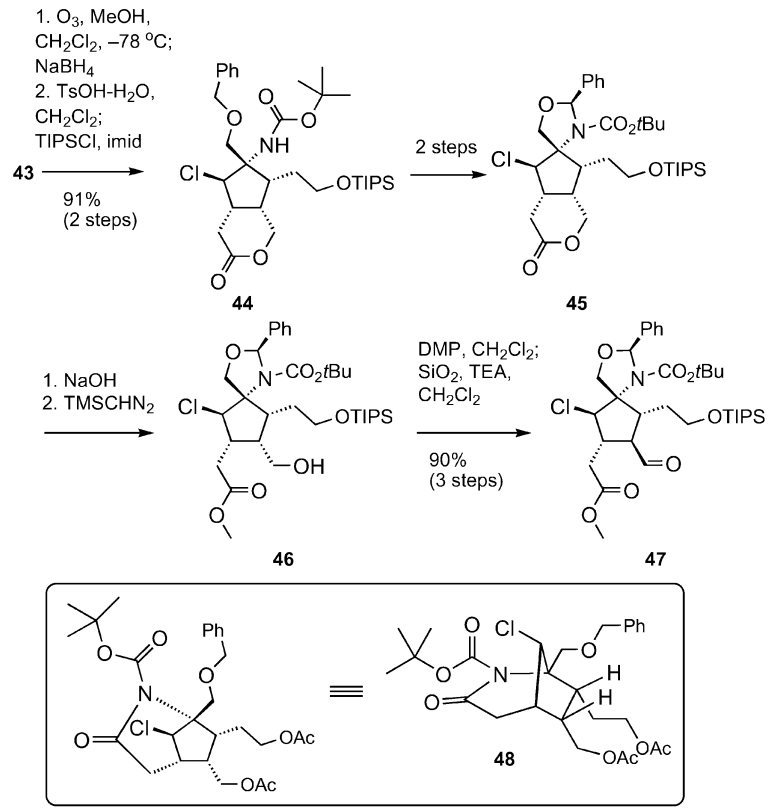
2.3. Gin's Synthesis of Chlorocyclopentane Oroidin Cores

Gin and co-workers have employed a long known [3,3]-sigmatropic rearrangement (vida infra) of bridged tricyclodecadienes (e.g. **39**, Scheme 5)[12] in order to obtain a C7-functionalized norbornene intermediate suitable for elaboration to the chlorocyclopentane core of **4**. Chemoselective nucleophilic epoxidation of the racemic Diels–Alder adduct **37** provides a keto-epoxide which can be subjected to a Favorskii-type ring-contraction rearrangement. This step proceeds by enolization followed by intramolecular oxirane ring-opening and finally dehydrative ring-contraction to provide the enone/ester **35** in good yield. Subsequent α-alkylation affords the ketone **39** that bears a 1,5-diene system susceptible to equilibration via a [3,3]-sigmatropic rearrangement (**39**→**40**) as first described by Woodward.[13] This process provides a latent chloride functionality at C7 of norbornene **40** in the form of a ketone thereby rendering relatively simple Diels–Alder adducts such as **34** useful as synthons for the preparation of complex cyclopentanes. The **39/40** mixture in a thermodynamic ratio of 72:28 was reduced under Meerwein–Verley–Pondorf conditions, advancing selectively intermediate **40** through rearrangement and reduction. The notable efficiency of this process relies on Curtin–Hammett chemical kinetics of the dynamic **39/40** system. The alcohol **41** can be chlorinated with net retention of configuration and the ketone **42** is generated through the intermediacy of an ene-carbamate Curtius rearrangement product. A thionyl chloride mediated Beckmann ring expansion of the oxime was completely regioselective resulting from migration of the more substituted alkyl group to provide the lactam **43** after Boc protection.

Reductive ozonolysis (Scheme 6) of the cyclopentene in **43** and subsequent intramolecular alcoholysis of the imide (TsOH) gave **44** after silyl ether protection. Oxazoline **45**, generated in two additional steps, could then be chemoselectively hydrolyzed and esterified to afford **46**. Finally, oxidation of the alcohol was accompanied by a fortuitous epimerization resulting in formation of aldehyde **47** (19 operations from cyclopentadiene) as a single diastereomer. Chlorocyclopentane **47** bears a differentially functionalized stereopentad corresponding to the revised palau'amine E-ring stereochemical configuration,[7] albeit in racemic form. The diastereomeric bridged cyclopentane **48**, prepared by a related sequence from the **39/40** mixture, maps directly onto the originally proposed structure of palau'amine.[6] Thus, stereoselective access to both chlorocyclopentane oroidin cores was accomplished from a common intermediate.

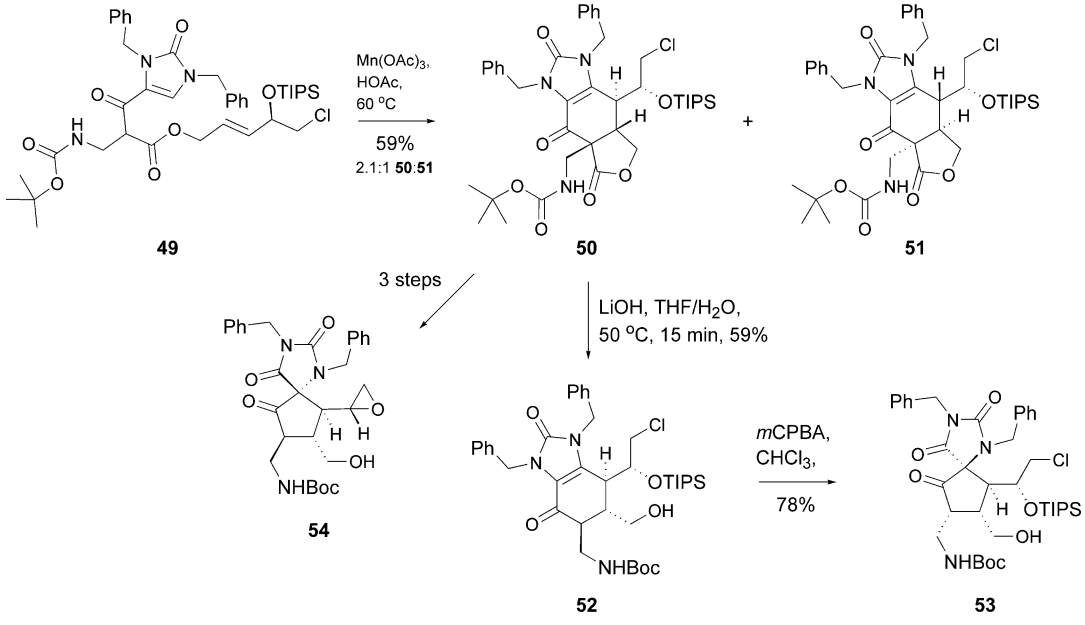
2.4. Chen's Mn^{III}-Enolate Oxidation Strategy

Chen has developed a $Mn(OAc)_3$-promoted oxidative radical heterobicyclization of β-keto esters tethered to unsaturated N-heterocyclic ring systems (Scheme 7).[14] When **49** is treated with Mn^{III} in warm acetic acid the resulting enolate undergoes single electron oxidation to an electrophilic α-radical[15] that cyclizes by a 5-*exo*/6-*endo* pathway to generate **50** and **51** in a cascade bicyclization reaction.



Scheme 6. Gin's completion of diastereomeric oroidin chlorocyclopentane core synthons.[12]

Two C–C bonds and three contiguous stereocenters are established in this step; as only two of a possible eight diastereomers are obtained, this strategy may be well-suited for the synthesis of complex natural product substructures. The ester functionality of lactone **50** is then excised under decarboxylative conditions to afford the alcohol **52**. This intermediate can be oxidatively rearranged to the spirocyclic cyclopentanone-hydantoin **53** with concomitant epimerization of the methylene amino-bearing stereocenter. Diastereomeric cyclopentanone **54** can also be prepared from **50** in three high-yielding and stereoselective synthetic operations.



Scheme 7. Chen's Mn^{III}-mediated oxidative radical heterobicyclization strategy to access the core skeleton of oroidin alkaloids.[14]

While the relative stereochemistry of **54** is epimeric to the massadine/palau'amine core-ring fragment at two stereogenic centers and the problem of stereoselective introduction of the chlorine substituent has not been addressed, this work represents an elegant application of Mn^{III}-enolate oxidation to complex cyclopentane synthesis and the route is extremely concise relative to contemporary approaches to similar carbocycles.

2.5. Romo's Synthesis of the D-E *trans*-Fused 5–5 Ring System of Revised Palau'amine

Chen's oxidative ring-contraction strategy borrows from the pioneering work of Lovely[16] and Romo[17] who have demonstrated that Diels–Alder adducts such as **55** (Scheme 8) can be converted into the palau'amine core skeleton by a two-step oxidation/chlorination/ring-contraction sequence.[17a,17b] The unsaturated imidazolone **55** is first subjected to DMDO oxidation at low temperature providing the allylic alcohol **56** in excellent yield as a single diastereomer. Treatment of the cup-shaped **56** with an electrophilic chlorinating agent results in halogenation on the convex face of the tricyclic system. This generates an iminium species that is susceptible to a 1,2-alkyl migration to yield the ring-contracted spirocycle **57** in good yield on gram scale.[17b] The use of cyclohexene as a HOCl buffer suppresses formation of aromatized over-oxidation by-products. The lactam was cleaved with concomitant epimerization of the methoxycarbonyl-containing stereocenter to provide the *all-trans* relative stereochemistry common to oroidin alkaloids **4** and **5**. The relative configuration of this *anti*-chlorocyclopentane **58** was verified crystallographically.[17c] Cyclization to the *trans*-fused 5–5 system was realized under mild Mitsunobu conditions at room temperature to provide the azabicyclooctane **60** in 74% yield.[17c] Notably, the coupling constants of several key protons in this core substructure correlate well with palau'amine. Demonstration of the feasibility of this intramolecular cyclization to obtain the D–E *trans*-fused 5–5 ring system of the revised palau'amine structure is a critical achievement toward an eventual total synthesis of **4**.

3. Trehazolin Aminocyclopentane Core[18]

An established retrosynthetic analysis[18d] of trehazolin is depicted in Figure 3. The fused aminooxazoline system is

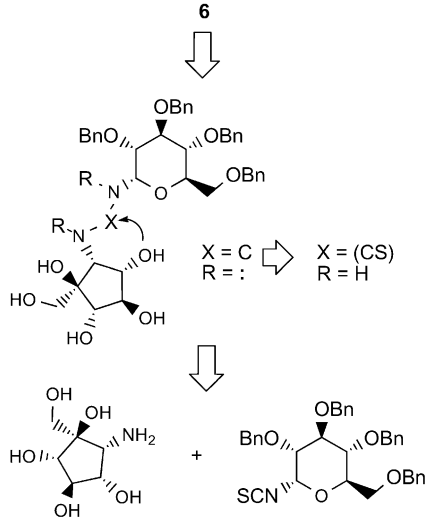
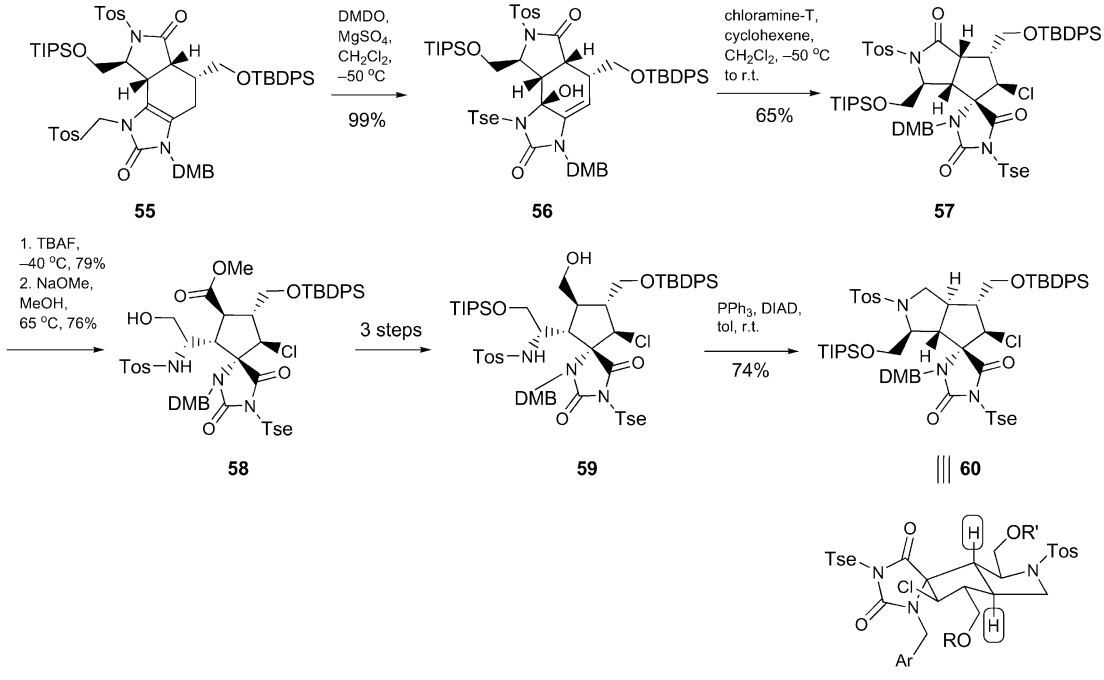


Figure 3. Retrosynthetic disconnection of the glycosidic C–N bond of trehazolin (**6**) generates the aminocyclitol ring fragment and a glycosyl isothiocyanate.[18d]



Scheme 8. Romo's Diels–Alder/oxidation/tandem chlorination-1,2-alkyl shift sequence delivers densely functionalized spirocycles for elaboration to the *trans*-fused bicyclic core substructure of palau'amine.[17]

often envisioned to arise from a thiourea precursor via the intermediacy of a carbodiimide. Glycosidic C–N bond disconnection then gives rise to the densely functionalized aminocyclopentitol ring fragment and a glucopyranosyl derivative. Section 3 will focus on creative and efficient approaches to the aminocyclopentane core of **6**.

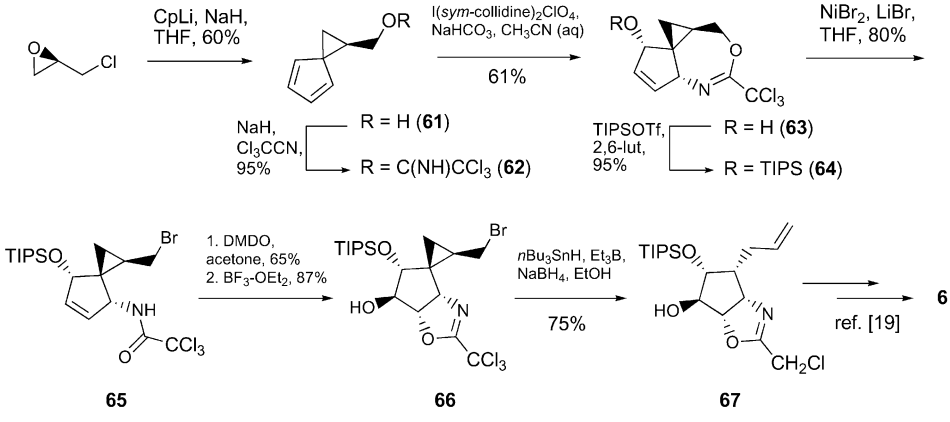
3.1. Carreira's Total Synthesis of Trehazolin

Carreira's innovative total synthesis of trehazolin (**6**)[19] relied on a key spirocyclic intermediate, whose asymmetric synthesis was without precedent. Preparation of the nonracemic spirocycloheptadiene (Scheme 9, **61**) called for exquisite regioselectivity and chemoselectivity in the condensation of a metal cyclopentadienide with epichlorohydrin, as initial S_N2 displacement vs. epoxide opening would lead to enantiomeric products. Therefore, the relative reaction rates would govern the enantioselectivity of the transformation with initial epoxide opening followed by spirocyclization affording the desired optically active (*R*)-**61**. The authors found that treatment of lithium cyclopentadienide with enantiopure (*R*)-epichlorohydrin in the presence of NaH delivered **61** in good yield and excellent enantioselectivity (91% *ee*).[19] Remarkably, the requisite 1,4-amino alcohol functionality could then be obtained directly from trichloroacetimidate **62** by treatment with an electrophilic iodinating agent in aqueous acetonitrile. This outcome is mechanistically consistent with iodonium complexation followed by *N*-cyclization to generate an allylic iodide that is subsequently hydrolyzed under the reaction conditions, giving rise to the 1,4-amino carbinol **63**. Nucleophilic opening of the imidate is followed by diastereoselective epoxidation from the less hindered face of the molecule. Next, Lewis acidic conditions promote epoxide ring opening by the vicinal trichloroamide to efficiently provide the bicyclic oxazoline **66**. The spiro-fused cyclopropyl moiety was then fragmented under free-radical conditions affording the terminal alkene with concomitant partial reduction of the trichloromethyl group. Penta-substituted cyclopentane **67** was eventually advanced to synthetic trehazolin in a successful total synthesis campaign.[19]

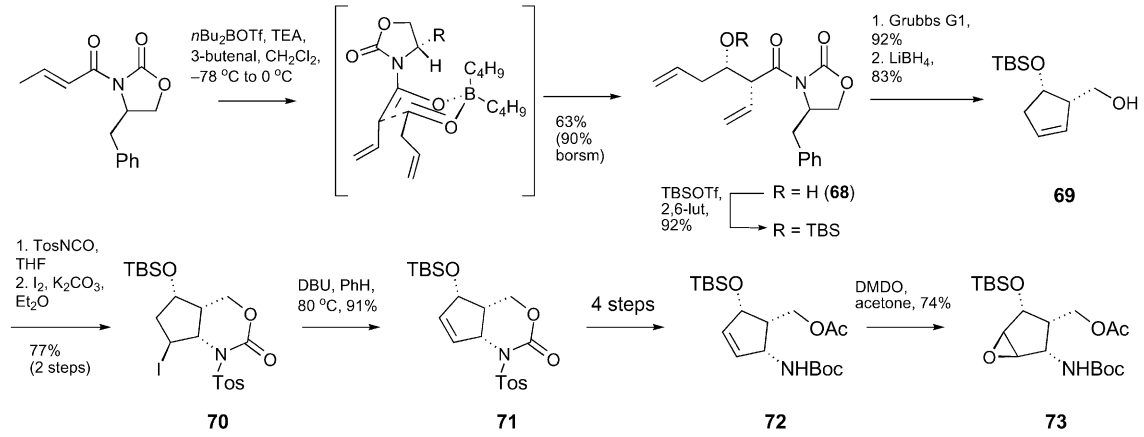
3.2. Crimmins' Formal Total Synthesis of Trehazolin

Crimmins' recent synthesis of the hexa-substituted aminocyclopentitol core of trehazolin (**6**) is notable for its complete stereocontrol.[20] The Evans dialkyl boron triflate protocol (Scheme 10) generates the (*Z*)-boron enolate which reacts with 3-butenal to yield the *syn*-aldol product in good yield. Diastereofacial selectivity in this example is governed by minimization of 1,3-diaxial interactions in the chairlike Zimmerman–Traxler transition state (as shown). Protection of **68** followed by ring-closing metathesis (RCM) generated a cyclopentene from which the chiral oxazolidine auxiliary was reductively removed. The alcohol **69** was then converted into the *N*-sulfonyl carbamate by treatment with *p*-toluenesulfonyl isocyanate and subsequent iodo-amination was affected by complexing the olefin from the less-hindered face with iodine followed by electrophilic cyclization to generate the iodide **70** in good yield on multi-gram scale. Elimination provided the trisubstituted cyclopentene **71** that was elaborated to **72** by four protecting group manipulations. DMDO epoxidation of the less hindered face of the alkene gave epoxide **73** as a single isomer.

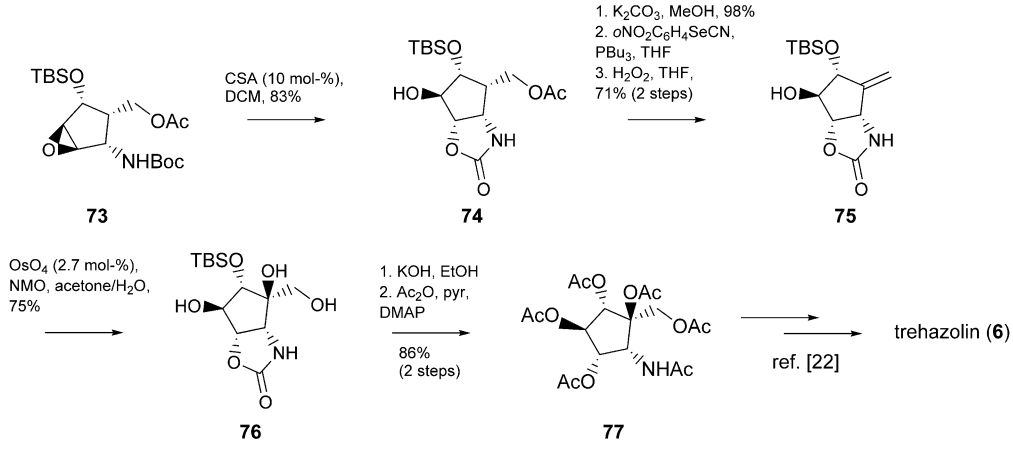
As shown in Scheme 11, mildly acidic conditions promote the nucleophilic opening of the epoxide by the proximal carbamate carbonyl oxygen to generate efficiently the oxazolidinone **74** and a Grieco elimination protocol[21] was used to convert the primary acetate into the exocyclic olefin **75**. Dihydroxylation under Upjohn conditions was completely stereoselective, affording a single triol **76** in 75% yield. The heavily functionalized cyclopentane **76** could be successfully progressed to the advanced trehazolin synthon **77** in two additional steps (18 linear operations from 3-butenal). The fully substituted peracetylated cyclopentane intermediate **77** intersects with Shiozaki's synthetic route[22] to the glycosidase inhibitor trehazolin, thus constituting a formal total synthesis.



Scheme 9. Carreira's total synthesis of trehazolin from an optically active spirocycloheptadiene **61**.[19]



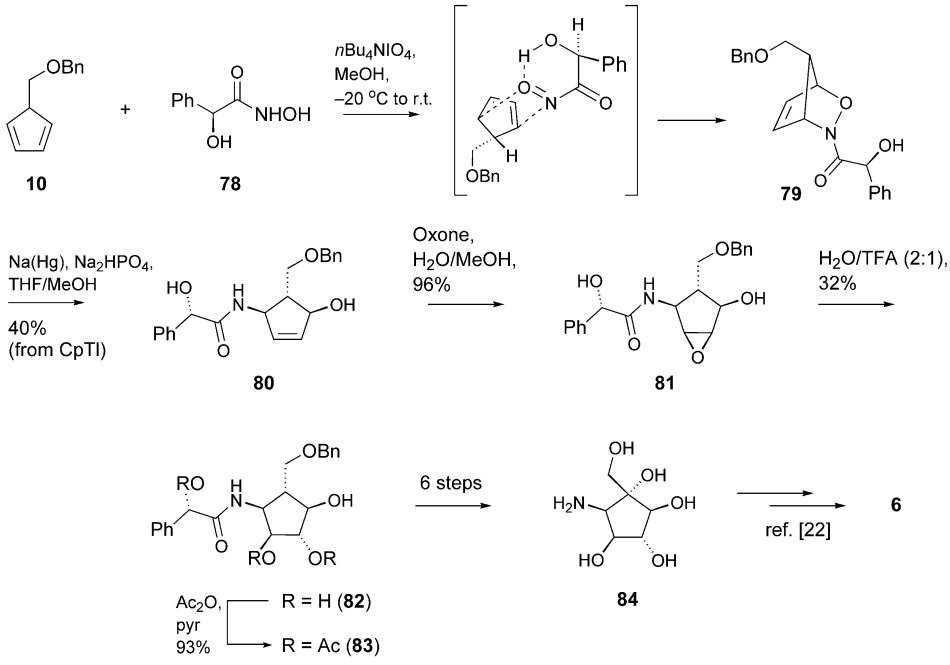
Scheme 10. Crimmins' RCM/electrophilic cyclization–elimination sequence to access the fully substituted cyclopentane intermediate **73** en route to a formal synthesis of trehazolin.[20]



Scheme 11. Crimmins' synthesis of the carbocyclic sugar of trehazolin.[20]

3.3. Ganem's Formal Total Synthesis of Trehazolin

Ganem's synthetic approach to trehazolin (**6**)[23] was to craft an *N*,*O*-heteronorbornene intermediate by a diastereoselective heterocycloaddition whereby reductive *N*,*O*-bond cleavage of the cycloadduct would furnish a 3,4,5-trisubstituted cyclopentene that could be further functionalized by osmylation or epoxidation. The route (Scheme 12) begins with a hetero-Diels–Alder reaction between 5-alkylcyclopentadiene **10** and a chiral acyl nitroso species, generated by in-situ oxidation of the hydroxamic acid **78**. Relative and absolute stereocontrol in the formation of the three contiguous chiral centers is mitigated by approach of the heterodienophile from the face opposite to the 5-benzyloxymethyl group as well as intramolecular hydrogen bonding in the acyl nitroso species (as shown), which directs *endo* cycloaddition *anti* to phenyl group. In this way, the mandelate-derived hydroxy stereocenter provides an acceptable level of diastereofacial selectivity (*dr* ≈ 4:1) such that multi-gram quantities of the purified trisubstituted cyclopentene **80** were accessible following reduction with sodium amalgam.[23] Epoxidation proceeded from the face opposite the bulky benzyloxy methyl substituent to provide epoxide **81** in excellent yield. Unfortunately, the epoxide was resistant to hydrolysis under acidic conditions and only after prolonged exposure to aqueous TFA was ring-opened unselectively to a 1:1.6 mixture of desired triol **82** and its isomer (not shown) in modest yield. The benzyloxy methyl substituent was then converted into the required tertiary hydroxy quaternary center by a sequence involving hydrogenolysis, Grieco elimination[21] and OsO_4-mediated dihydroxylation, which, upon global deprotection, afforded the unprotected aminocyclopentitol core of **6** in good yield. As this intermediate has been previously converted to trehazolin,[22] a formal total synthesis was achieved.

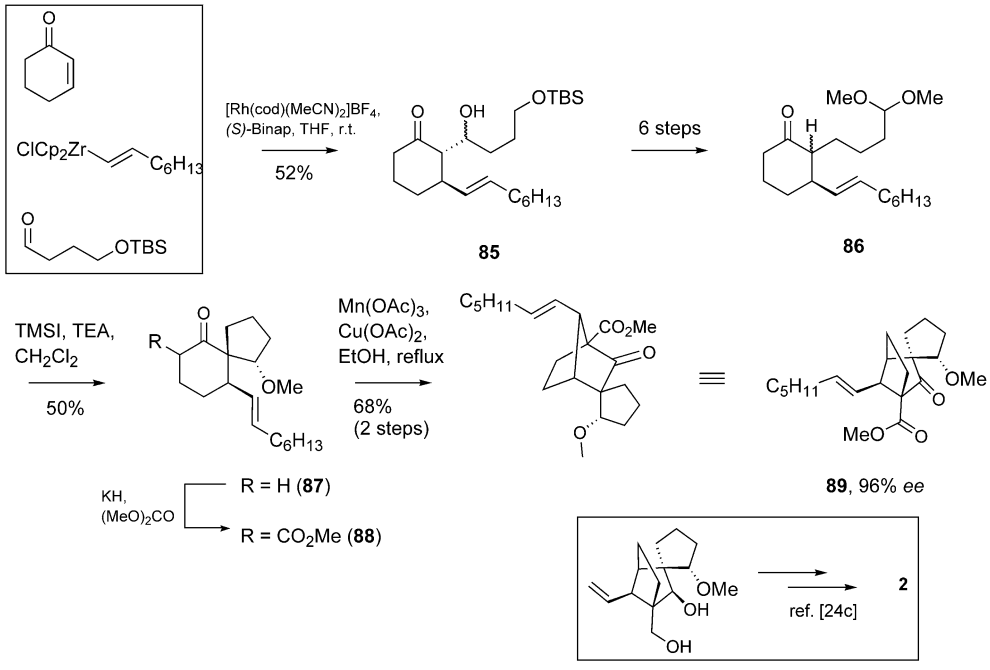


Scheme 12. Ganem's synthesis of trehazolin precursor **84** featuring a creative acyl nitroso heterocycloaddition reaction (**10**→**79**).[23]

4. Vannusal B

4.1. Nicolaou's Expedient Entry into the Fused Polycyclic Skeleton of the Vannusals

Nicolaou's enantioselective total synthesis of the originally assigned structure of vannusal B (**2**)[24c] commences with a catalytic asymmetric three-component 1,4-addition/aldol reaction (Scheme 13). Treatment of cyclohexenone and an aliphatic aldehyde with a vinyl zirconium species in the presence of a chiral rhodium catalyst provides aldol product **85** as a mixture of diastereomers (*dr* ≈ 1.4:1) in good yield. The rhodium catalyst serves a number of functions in a proposed catalytic cycle[24b] that is initiated by transmetallation of the alkenyl zirconium and π complexation of the newly generated olefin-appended rhodium with the cyclic enone. Asymmetric transfer of the alkenyl group



Scheme 13. Nicolaou's expedient entry into the bicyclo[2.2.1]heptane framework of the vannusals featuring a highly convergent catalytic asymmetric three-component reaction.[24]

onto C4 of the enone then gives rise to a chiral rhodium enolate capable of engaging the aldehyde in an aldol reaction. A critical feature of this multicomponent reaction is chemoselectivity of the in situ generated rhodium alkenyl species in differentiating between enone and aldehyde, thereby allowing sequential cascading events in a one-pot transformation. Cyclohexanone **85** was then advanced to acetal **86** by a short series of oxidation state adjustments and functional group manipulations. Intramolecular spirocyclization via a Mukaiyama-type aldol reaction was affected by exposure to TMSI in the presence of base to afford the methoxy spiroketone **87** in acceptable yield. The β-keto ester was subsequently obtained by KH-mediated methoxycarbonylation. Finally, the remaining quaternary center of the desired bicyclo[2.2.1]heptane substructure was fashioned by a Mn^{III}-enolate oxidation/5-*exo* radical cyclization pathway according to the Snider synthetic protocol.[25] This key vannusal building block **89** was obtained with high optical purity (96% *ee*) and a related intermediate (Scheme 13, lower right box) was successfully advanced to the originally assigned structure of vannusal B.[24c] Intriguingly, the spectroscopic data of the synthetic compound did not match those reported for the naturally occurring vannusal B, thus underscoring the bewildering question as to the true molecular identity of this natural product.

5. Outlook and Conclusion

Stereochemically intricate cyclopentanes decorated with contiguous arrays of heteroatoms at the periphery of the carbocycle and/or fused to heterocyclic ring systems encompass some of the more daunting challenges for modern synthetic chemistry. Given the exciting advances outlined above[26] and the recent arrival of completed total syntheses of complex oroidin dimers,[27] a creative solution to the synthetic problem posed by palau'amine amid other captivating and coveted natural products should be forthcoming in the near future.

Acknowledgments

Dr. Ahmed Mamai is acknowledged for helpful discussions.

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Received: December 11, 2008
Published Online: February 11, 2009

