Synlett M. Deimling et al. Account

Adventures and Detours in the Synthesis of Hydropentalenes

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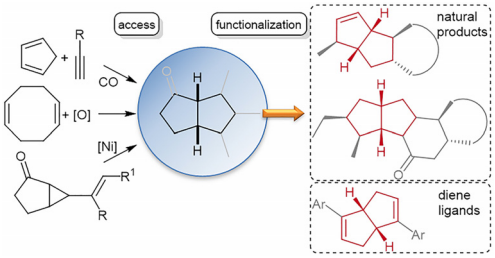

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Abstract Functionalized hydropentalenes (i.e., bicyclo[3.3.0]octanones) constitute important building blocks for natural products and for ligands for asymmetric catalysis. The assembly and tailored functionalization of this *convex* roof-shaped scaffold is challenging and has motivated a variety of synthetic approaches including our own contributions, which will be presented in this account.

Key words bicyclooctanes, diene ligands, hydropentalenes, natural product synthesis

1 Introduction

The bicyclo[3.3.0]octane (hydropentalene) unit is an important constituent of several natural products and biologically active compounds covering a broad range of structural complexity. Selected examples include ptychanolide (**1**; Figure 1), a sesquiterpenoid from the liverwort *Ptychanthus striatus (lehm. et lindenb.)*;[1,2] carbacyclin (**2**) and clinprost (**4**), which are prostaglandin analogues and platelet aggregation inhibitors;[3,4] and the diterpenes silphiperfolene (**5**),[5] (–)-5-oxo-silphiperfolene (**6**),[6] neorogiolane (**8**),[7] hirsutene (**3**),[8] and modhephene (**9**).[9] Other examples include (–)-retigeranic acid A (**10**),[10] an antibacterial sesterterpenoid isolated from a Himalayan lichen and the antibiotic pentalenolactone A (**7**) produced by *Streptomyces* UC5319, which specifically inhibits glyceraldehyde-3-phosphate dehydrogenase in *Trypanosoma brucei*.[11]

We were particularly fascinated by the class of acyltetramic macrolactams, consisting of such structurally related members as the cytotoxin cylindramide A (**11**) from the Pacific sponge *Halichondria cylindrata*,[12] and geodin A (**12**) from the sponge *Geodia sp.*, which shows anthelmintic properties against the nematode *Haemonchus contortus*.[13] Aburatubolactam A (**14**) from the bacterium *Streptomyces sp. SCRC A-20* is an inhibitor of anionic superoxides,[14] and alteramide A (**13**), isolated from the marine bacterium *Altermonas sp.* shows cytotoxic activity.[15]

Therefore, there is a strong interest in the development of methods for synthesizing the bicyclo[3.3.0]octane unit. When we started our work on acyltetramic macrolactams, only few synthetic studies on this unique natural product class had been reported, and therefore we had to struggle in a relatively unexplored land. Another of our motivations was the lack of knowledge on the biological modes of ac-

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Biographical Sketches

(Clockwise from top left) **Sabine Laschat** studied chemistry at the University of Würzburg (1982–1987) and did her Ph.D. studies at the University of Mainz under the supervision of Horst Kunz (1988–1990). After postdoctoral studies with Larry E. Overman at the University of California, Irvine (1990–1991), followed by her habilitation at the University of Münster, she was appointed an associate professor at TU Braunschweig (1997–2002). Since 2002, she has been a full professor of organic chemistry at the University of Stuttgart. She was a speaker of the Collaborative Research Centre SFB 706 'Selective Catalytic Oxidations of C–H Bonds with Molecular Oxygen' (2005–2010), and served as Vice Rector for Research and Technology of the University of Stuttgart (2010–2012) and as speaker of the Project House 'NanoBioMater'. Her research interests include liquid crystals, natural product synthesis, and chemoenzymatic syntheses.

Anna Zens studied chemistry at the University of Stuttgart and received her B.Sc. degree in 2013 and her M.Sc. degree in 2016. Currently she is pursuing her Ph.D. studies at the Institute of Organic Chemistry in the Laschat research group. In her Ph.D. thesis, she focused on the development of new synthetic methods for polyquinanes.

Max Deimling studied chemistry at the University of Stuttgart, where he received his B.Sc. degree in 2015 and M.Sc. degree in 2017. Currently he is pursuing his Ph.D. studies at the Institute of Organic Chemistry in the Laschat research group. His research interests are in the area of diene-ligand design and asymmetric catalysis.

Angelika Baro studied chemistry at the Georg-August-Universität Göttingen (Germany), where she received her Ph.D. degree in clinical biochemistry (1987). Since 1991, she has been responsible for scientific documentation and publication at the Institute of Organic Chemistry of the University of Stuttgart.

Natja Park studied chemistry at the University of Stuttgart and the École de Chimie, Polymères et Matériaux in Strasbourg (2003–2008). After completion of her Ph.D. thesis on the synthesis of tetramic acid macrolactams in the Laschat research group in 2013, she began her career as a research chemist in the field of synthetic rubber (2014–2015), and then moved on to technical project management in the field of chemical anchors (2016 to date).

Christine Hess (née Hofmann) studied chemistry at the University of Stuttgart (2000–2005). Since completing her Ph.D. thesis on the development of synthetic methods on the road to Geodin A in the Laschat research group in 2009, she has taken on various positions in quality management in the pharmaceutical/medical-device industry.

Simon Klenk studied chemistry at the University of Stuttgart (2008–2013). His M.Sc. thesis in the Laschat research group dealt with hydropentalenes. Since completing his Ph.D. thesis (2013–2018) on supramolecular chemistry of proteins at the Leibniz Institute for Molecular Pharmacology (Berlin) under the supervision of Christian Hackenberger, he has been developing RNA assays and analytical methods in the pharmaceutical industry.

Zarfishan Dilruba studied for her M.Chem. degree at the University of Leicester (2016–2020). In her third year of her studies, she joined the Laschat research group (ERASMUS project) and worked on the synthesis of chiral diene ligands (2019). In her final year of study, she produced her M.Chem. thesis on metal processing using iodine in deep eutectic solvents under the supervision of Professor Abbott (2020).

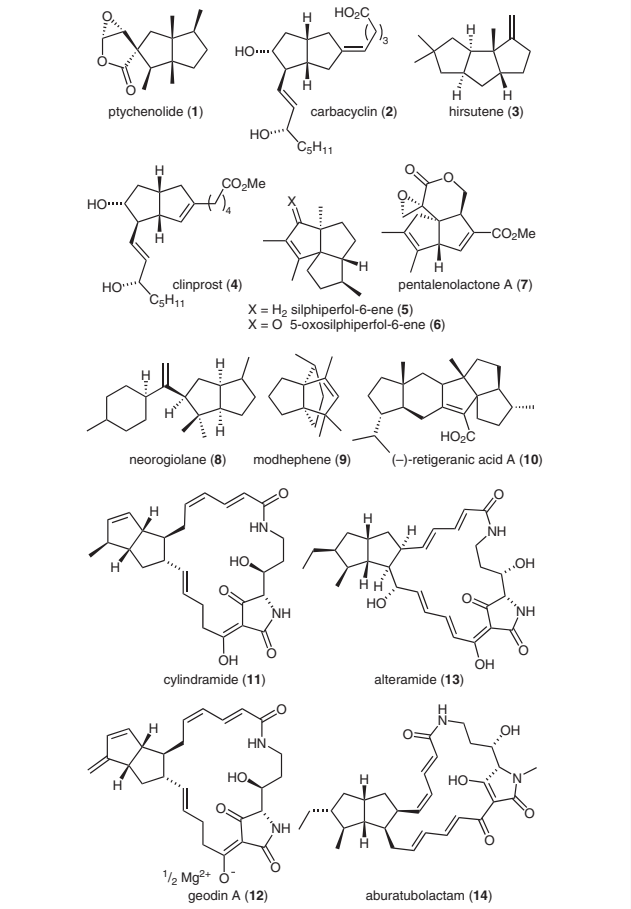


Figure 1 Selected hydropentalene-containing natural products

tion of these compounds. Only limited information was available at that time, despite the wealth of information regarding the chemistry and biology of tetramic acids.[16]

As will be discussed below, these initial endeavors diversified rapidly and brought us a variety of synthetic challenges. On the other hand, new areas were opened, such as asymmetric catalysis with bicyclo[3.3.0]octane-derived diene ligands.

The current account discusses hydropentalene chemistry and applications from our personal perspective. Figure 2 provides an overview of the various retrosynthetic disconnections. Relevant work by other groups has been included whenever appropriate. A more-general overview for interested readers is given in the recommended reviews, which also cover the parent antiaromatic pentalenes and their coordination compounds.[17]

2 Biosynthesis of Hydropentalenes

Early biosynthetic studies by the Du group on the acyltetramic macrolactam heat-stable antifungal factor (HSAF) **15b** (Figure 3), a broad-spectrum antimycotic isolated from *Lysobacter enzymogenes str. C3* that is structurally identical to dihydromaltophilin, identified the genes coding for a hybrid polyketide synthase-nonribosomal peptide synthase (PKS-NRPS), a sterol desaturase, a ferredoxin reductase and an arginase.[18] More recently, Shen, Du, and their co-workers obtained a more detailed insight into the biosynthesis of HSAF **15b**.[19]

As shown in Figure 3, two polyunsaturated hexaketide fragments are linked by an ornithine (Orn) unit, followed by installation of the tetramate subunit through Claisen and Dieckmann condensations.[19] According to Shen and Du, the redox enzyme OX3 takes the role of a gatekeeper and catalyzes a reductive [2+3]-cycloaddition with loose stereospecificity.[19] Only those intermediates with the correct stereochemistry of the first cyclopentane ring are further processed by subsequent redox enzymes OX2 and OX4, forming the second and third ring. Thus, the original hypothesis[18] that the cyclohexane ring is generated before the hydropentalene unit was ruled out by these results.[19] Note that the Clardy[20] and Blodgett[21] groups demonstrated the existence of a common biosynthetic origin for polycyclic acyltetramic macrolactams from phylogenetically diverse bacteria, and discovered novel members of this natural product family, whereas Gulder[22] and Zhang[23] and their respective co-workers reconstructed the biosynthesis of ikarugamycin.

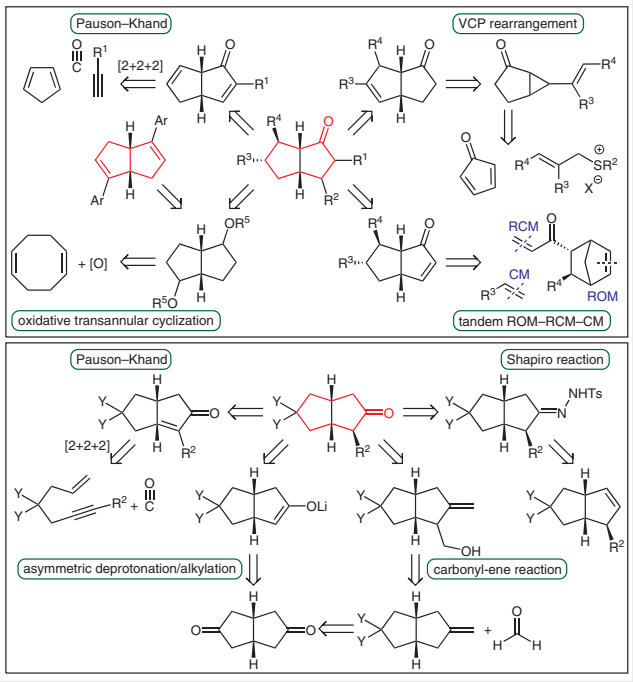


Figure 2 The various retrosynthetic pathways to hydropentalene derivatives described below

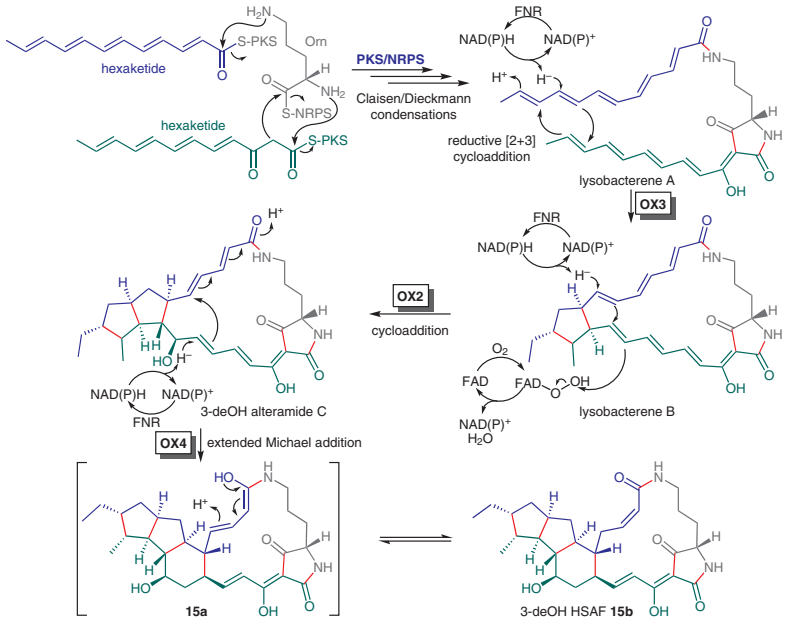
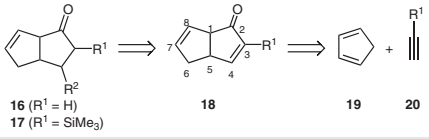


Figure 3 Proposed biosynthesis of the tricyclic system in HSAF **15a**/**15b**[19]

3 Hydropentalenes through the Pauson–Khand Reaction

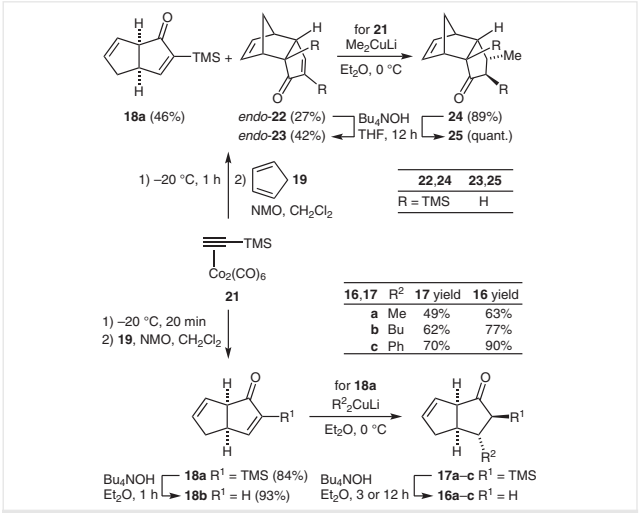
Hydropentalenes **16** and **17** can be synthesized from cyclopentadiene (**19**) and alkynes **20** (R = H, $SiMe_3$) by a Pauson–Khand reaction, followed by functionalization, for example by conjugate addition (Scheme 1).



Scheme 1 Retrosynthetic route through the Pauson–Khand reaction

The Pauson–Khand reaction, i.e. the co-cyclization of an alkyne, an alkene, and carbon monoxide, is a powerful method for accessing cyclopentenones.[24] The original method utilized stoichiometric amounts of $Co_2(CO)_8$ as a metal mediator and a CO source. Much work has been devoted to facilitating the displacement of CO from the cobalt complex by additives to develop catalytic versions of the reaction and to replace CO by surrogates, such as aldehydes.[25]

However, when we stepped into this area, progress was slow and only limited knowledge was available on intermolecular Pauson–Khand reactions, even with simple substrates such as cyclopentadiene.[26] Whereas Becheanu reported only a disappointingly low yield of 9% for the Pauson–Khand reaction of acetylene with cyclopentadiene in the presence of $Co_2(CO)_8$,[27a] we surmised that the use of (trimethylsilyl)acetylene might be beneficial in achieving a cleaner reaction and suppressing multiple co-cyclizations.[27] Gratifyingly, this approach worked quite well (Scheme 2).



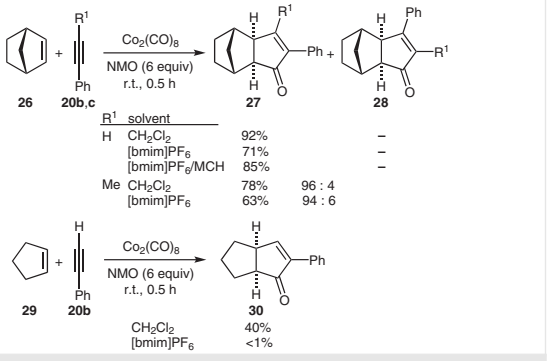
Scheme 2

In particular, after some optimization of the reaction, we found that a brief exposure of the (trimethylsilyl)acetylene cobalt complex **21** with NMO prior to addition of cyclopentadiene **19** at –20 °C improved the yield of bicyclo[3.3.0]octadienone **18a** to 84% without any byproducts. When the reaction time was extended to one hour, the yield of the desired cyclopentenone **18a** decreased considerably to 46%, and competing cobalt-mediated [4+2]-cyc-

loaddition of cyclopentadiene (**19**) to (trimethylsilyl)acetylene, followed by a Pauson–Khand reaction with (trimethylsilyl)acetylene–cobalt complex **21** took place, from which the tricyclic *endo*-product **22** was isolated in 27% yield. The bicyclo[3.3.0]octadienone **18a** could be further elaborated by conjugate addition of cuprate, providing the *trans*-products **17**, which was subsequently desilylated to **16** by treatment with tetrabutylammonium hydroxide (TBAOH) in Et_2O.[28]

More recently, the Riera group demonstrated the utility of trifluoromethyl as a removable steering group that can be released from β-substituted Pauson–Khand products by treatment with DBU in nitromethane/H_2O.[29] Furthermore, Reira reported that ethylene glycol as an additive can significantly accelerate intermolecular Pauson–Khand reactions, doubling the yields, even for challenging combinations such as cyclopentene/(trimethylsilyl)acetylene or cyclopentene/*N*-Boc-propargylamine.[30]

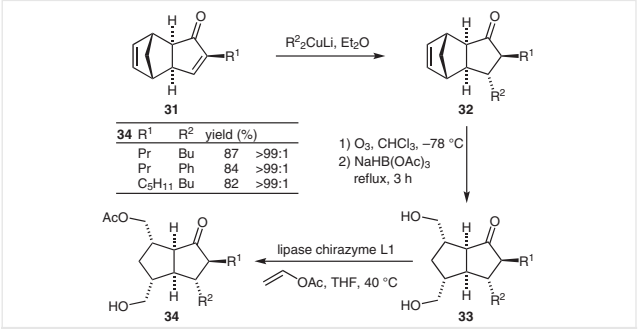
In an earlier work, we found that chlorinated solvents such as CH_2Cl_2 could be replaced by either an ionic liquid such as 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) or a two-phase system such as [bmim]PF_6/methylcyclohexane (MCH) in intermolecular $Co_2(CO)_8$-mediated Pauson–Khand reactions in the presence of NMO at room temperature with good yields and regioselectivities for bicyclic alkenes, such as norbornene (**26**) (Scheme 3).[31]



Scheme 3

However, to our great dismay these conditions completely failed for cyclopentene (**29**), and the corresponding hydropentalene **30** could be detected in trace amounts only.

At first glance, the limitation to bicyclic alkenes seemed to be a serious disadvantage. However, it turned out that tricyclic hydropentalenes such as **31** could be conveniently functionalized by a three-step sequence consisting of conjugate addition of an organocuprate, ozonolysis, and reductive workup with $NaHB(OAc)_3$ to provide the corresponding diols, which were submitted to regioselective acetylation with lipase (Scheme 4).[32] After some experimentation, chirazyme L1 was found to give the best results, providing the



Scheme 4

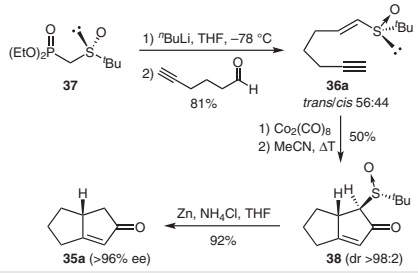
monoacetate **34** in up to 87% yield with excellent regioselectivity (≤99:1).

Note that no satisfactory solution has yet been found to the problem of developing catalytic intermolecular Pauson–Khand reactions.[33] In particular, catalytic asymmetric versions are rare.[34] This is in stark contrast to the various catalytic Pauson–Khand reactions that provide access to enantiomerically enriched bicyclo[3.3.0]octenones **35** from enynes **36** (Scheme 5).[35] In pioneering work, the Buchwald group employed chiral *ansa*-titanocene catalysts,[36] as well as BINOL phosphites and $Co_2(CO)_8$,[37] whereas Narasaka and co-workers used $[RhCl(CO)_2]_2$ and 1 atm of CO,[38] and the Chung group used Ru/Co nanoparticles.[39,40] Croatt and Wender and Lee and Kwong have summarized various modifications of the catalytic intramolecular Pauson–Khand reaction and related [2+2+1]-cycloadditions.[25a,b]

Scheme 5 Retrosynthesis of the intramolecular Pauson–Khand reaction

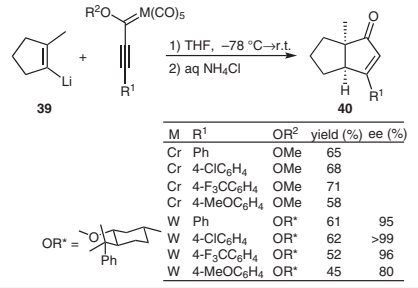
A unique sequential intramolecular co-cyclization/conjugate reduction sequence employing stoichiometric amounts of $Co_4(CO)_{12}$ in *i*-PrOH has been developed by the Krafft group.[41] Presumably, the reaction proceeds via the hydridocobalt species $HCo(CO)_4$, with the hydride delivered from the *i*-PrOH solvent, as shown by deuteration experiments. Although the intramolecular catalytic Pauson–Khand reaction provides efficient access to hydropentalenes **35** in both chiral and achiral fashions (Scheme 5), and the cyclization precursors **36** are conveniently available through reaction of diethyl malonate anion with allylic or propargylic halides, it should be noted that a *geminal*-disubstituted unit is often required in the cyclization precursor to exert a Thorpe–Ingold effect and to drive the co-cyclization to completion. Consequently, unsubstituted derivatives lacking the two electron-withdrawing groups have been described in the literature much less frequently.[42,43,44a] It should be pointed out that the Carretero group has devel-

oped an elegant method for obtaining enantiomerically pure (*S*)-1-*tert*-butylsulfinylenynes such as **36a** (Scheme 6).[44b,45] The required enynes **36** were obtained through a Horner–Wadsworth–Emmons (HWE) olefination from phosphonates **37**. As shown for **36a**, subsequent thermal Pauson–Khand reaction and reductive removal of the sulfoxide auxiliary provided the enantiomerically pure hydropentalene **35a** in excellent yield and with high enantiomeric excess.



Scheme 6

In a complementary approach to the various Pauson–Khand routes, Barluenga et al. used Fischer carbene complexes as precursors for the co-cyclization with vinyllithium reagents, giving rise to bicyclo[3.3.0]octenones **40** in good yields (Scheme 7).[46] Both chromium and tungsten Fischer carbene complexes could be used. In the case of tungsten carbenes carrying menthyl units, high enantioselectivities were obtained.

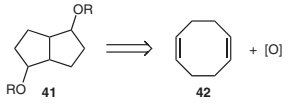


M	R^1	OR^2	yield (%)	ee (%)
Cr	Ph	OMe	65	
Cr	4-ClC_6H_4	OMe	68	
Cr	4-$F_3CC_6H_4$	OMe	71	
Cr	4-$MeOC_6H_4$	OMe	58	
W	Ph	OR*	61	95
W	4-ClC_6H_4	OR*	62	>99
W	4-$F_3CC_6H_4$	OR*	52	96
W	4-$MeOC_6H_4$	OR*	45	80

Scheme 7

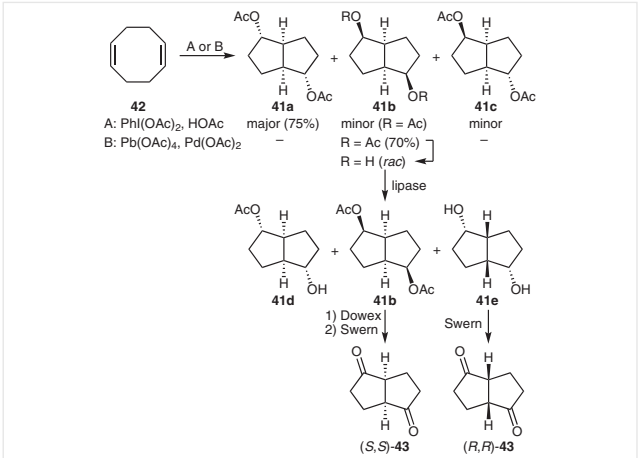
4 Hydropentalenes through Transannular Oxidative Cyclization of Cycloocta-1,4-diene

After struggling with the Pauson–Khand reaction for some time, and bearing in mind that multistep total syntheses of natural products might eventually require multigram amounts of the appropriate hydropentalene building blocks, we turned our attention to the transannular oxidative cyclization of cycloocta-1,4-diene (COD) (**42**; Scheme 8).



Scheme 8 Retrosynthesis of hydropentalene from COD and [O]

At a first glance, the method adopted by the Prakash group seemed advantageous because the oxidation required only a stoichiometric amount of iodosobenzene diacetate (1.3 equiv) (Method A; Scheme 9).[47] However, despite an acceptable yield of 75%, the major diastereomer **41a** could not be separated from the minor diastereomers **41b** and **41c**, and thus this method was not further considered for the synthesis of chiral bicyclo[3.3.0]octanones. On the other hand, the Pd-catalyzed cyclization required 34 mol% of $Pd(OAc)_2$ and 2.3 equivalents of $Pb(OAc)_4$[48] and gave 70% of the racemic diacetate **41b** as a single diastereomer, which could be subjected directly to saponification and lipase-catalyzed optical resolution to give the monoacetate **41d**, diacetate **41b**, and diol **41e** (Method B; Scheme 9).[49,50]

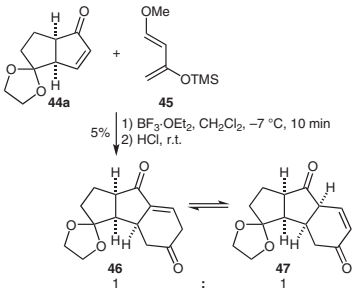


Scheme 9

As chiral diketones **43** were obtainable by Swern oxidation of the diols on a gram scale, this route was used in a total synthesis of cylindramide (**11**), as discussed below.[51]

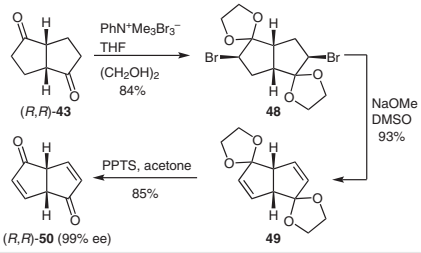
5 Functionalization of Bicyclo[3.3.0]octan-1,4-dione to Dodecahydrocyclopenta[*a*]indenes

A Diels–Alder reaction with electron-rich dienes appeared to provide rapid access to the tricyclic dodecahydrocyclopenta[*a*]indene system. However, this approach was soon discarded because yields of the $BF_3{\cdot}OEt_2$-mediated [4 + 2]-cycloaddition of enone **44a** with Danishefsky diene **45** did not exceed 5%, and the reaction was always compromised by C=C double-bond isomerization, giving a 1:1 mixture of tricyclic compounds **46** and **47** (Scheme 10).[52]



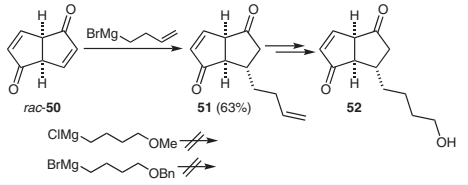
Scheme 10

Dienedione **50** was therefore chosen as an alternative building block. One-pot bromination/acetalization of **43** and base-mediated elimination gave the diene **49**. Cleavage of the diacetal with PPTS gave the dihydropentalenedione **50** in 85% yield and 99% ee (Scheme 11).



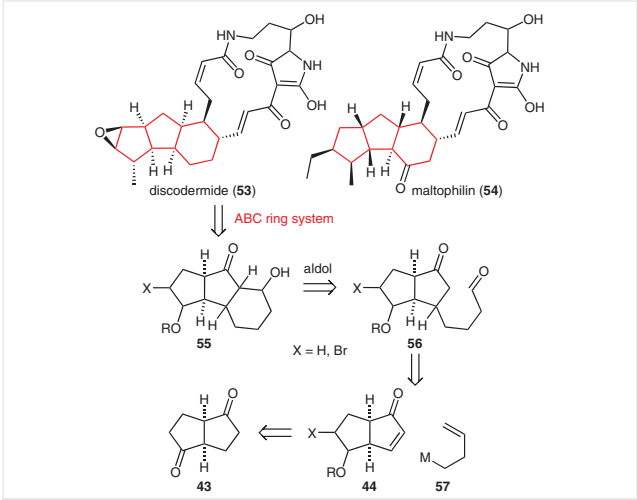
Scheme 11

Unfortunately, further functionalization of this C_2-symmetrical building block **50** by sequential conjugate additions met with difficulties (Scheme 12). Although the addition of a homoallylic Grignard reagent to *rac*-**50** gave the desired mono-1,4-adduct **51** in 63% yield, subsequent hydroboration with either 9-BBN or catecholborane resulted in a competing Weitz–Scheffer epoxidation of the enone and 1,2-reduction to the allylic alcohol. When the corresponding alkoxy-terminated Grignard reagents were employed, no trace of the desired 1,4-adducts were detected.



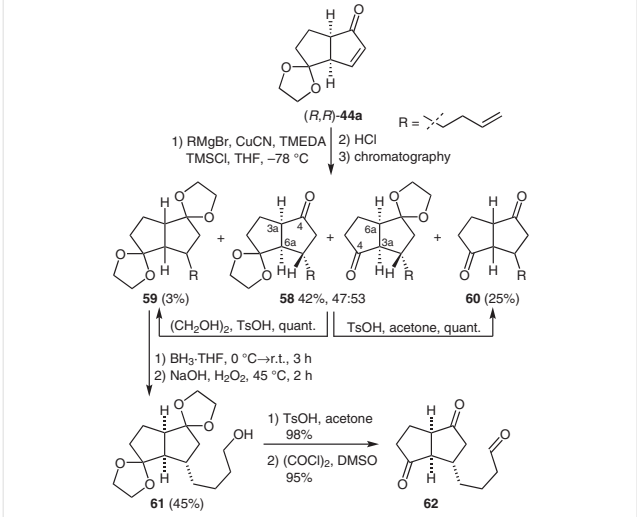
Scheme 12

To gain access to the tricyclic core units of the tetramic acid macrolactams discodermide (**53**),[53] isolated from the sponge *Discodermia dissoluta*,[54,55] and maltophilin (**54**),[56,57] we envisaged the use of the tricyclic hydroxyketone **55** as a synthetic precursor (Scheme 13).[58] We hoped that compound **55** might be obtained from an intramolecular aldol addition of hydropentalene **56**, which could be traced back to the enone **44** and an organometallic reagent **57**, the former being traced back to the C_2-symmetrical diketone **43**.

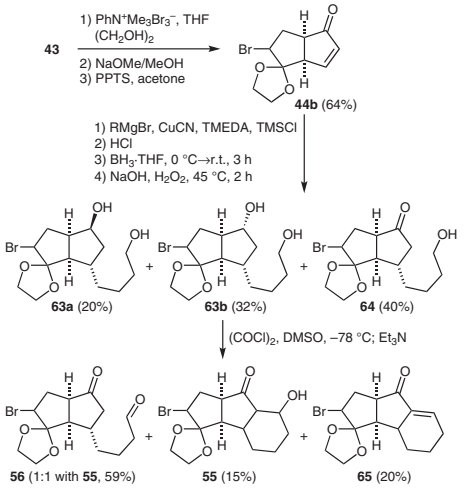


Scheme 13

As shown in Scheme 14, conjugate addition of the unsaturated Grignard reagent to enone **44a** in the presence of CuCN, TMEDA, and TMSCl provided the desired β-substituted ketone **58** as an equimolar mixture (47:53) of two isomers, albeit in a moderate yield of 42%. In addition, diacetal **59** and diketone **60** were isolated in yields of 3 and 25%, respectively. These two byproducts made us suspicious regarding epimerization at the β-carbon. To our great surprise, NMR analysis revealed a completely different story. During acidic workup and chromatography on silica, an acetal migration took place that resulted in racemization rather than epimerization. Despite this serious drawback,



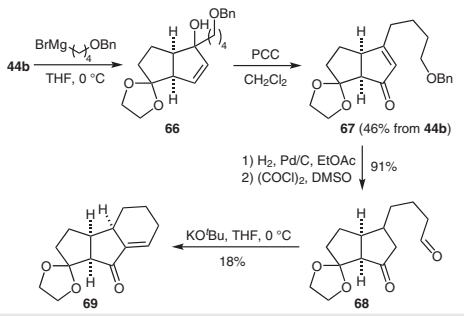
Scheme 14



Scheme 15

the suitability of the aldol strategy was tested. Compounds **58** were converted into the diacetal **59**, which was subjected to hydroboration, acetal cleavage, and Swern oxidation to give the aldehyde **62**. Although treatment with LDA appeared to provide the hydroxy ketone, hydrolytic workup resulted in a retro-aldol reaction, and aldehyde **62** was re-isolated.

This outcome forced us to step back and use the brominated hydropentalenone **44b** as a key intermediate (Scheme 15), available in three steps from diketone **43**. Conjugate addition of the cuprate and subsequent hydroboration gave the diastereomeric alcohols **63a** and **63b** in yields of 20 and 32%, respectively, together with 40% of ketone **64**. This mixture was directly submitted to Swern oxidation to yield a mixture of three products, which gave us some nightmares. Column chromatography provided 59% of a 1:1 mixture of **55**/**56** and **65**. In $CDCl_3$ solution and upon storage in the freezer, a retro-aldol reaction from hydroxy ketone **55** to keto aldehyde **56** was observed, whereas treatment with a base (e.g., *t*-BuOK, KHMDS, LDA) or with silica gel shifted the equilibrium toward the aldol product.



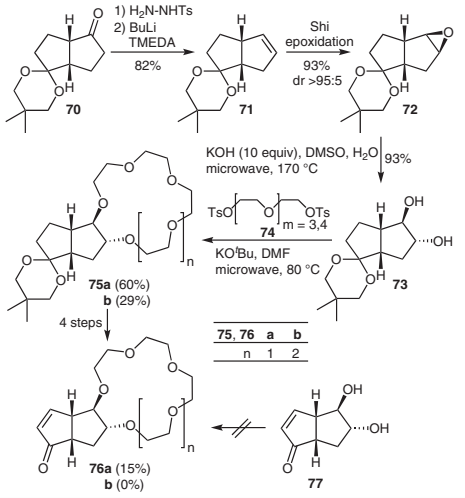
Scheme 16

Hydropentalenone **44b** was treated with a Grignard reagent to obtain the 1,2-addition product **66** (Scheme 16). Oxidative 1,3-transposition of the tertiary allylic alcohol gave the β-substituted ketone **67**, and subsequent hydrogenolysis and Swern oxidation of the terminal hydroxy group gave the bicyclic keto aldehyde **68** in 91% yield. Aldol condensation in the presence of *t*-BuOK gave the tricyclic derivative **69**.[58] Despite the poor yield of 18%, no evidence for a retro-aldol reaction was found.

6 Functionalization of Bicyclo[3.3.0]octan-1,4-diones to Crown Ether Hybrids

Biological studies of cylindramide (**11**) revealed that the cytotoxicity of the natural product was affected by both the hydropentalene unit and by the Ca^{2+} concentration. In other words, the cytotoxicity decreased significantly upon addition of Ca^{2+} salts, suggesting the formation of tetramic acid macrolactam–Ca^{2+} complexes with a concomitant decrease in the intracellular Ca^{2+} concentration. Taking inspiration from Crane and Gademann's concept of truncated natural products,[59,60] we speculated that hybrids consisting of the bioactive hydropentalene unit and a Ca^{2+}-binding crown-ether unit might be able to mimic the action of the natural product **11**. As an additional aim, we hoped to reduce the synthetic effort required to assemble the hydroxyornithine unit and convert it into the final macrocyclic tetramic acid lactam.

Because Ca^{2+} has an ionic radius of 106 pm, which is intermediate between those of Na^+ (98 pm) and K^+ (133 pm), 15-crown-5 (⌀ 170–120 pm) and 18-crown-6 (⌀ 260–330 pm)[61] were chosen as target structures for the hybrid compounds. To access the bicyclo[3.3.0]octan-1,2-diol **73** as a key intermediate for a twofold Williamson etherification, the acetal-protected monoketone **70** was used as starting material (Scheme 17). Conversion of **70** into the tosylhydrazone and subsequent Shapiro reaction gave the alkene **71** in 82% yield over the two steps. Shi epoxidation and basic regioselective epoxide opening with KOH in DMSO–H_2O under microwave conditions delivered the desired *trans*-diol **73** in 93% yield; this was treated with the ditosylate **74** in the presence of *t*-BuOK to give the 15-crown-5 hybrid **75a** in 60% yield, whereas the larger 18-crown-6 hybrid **75b** was obtained in only 29% yield. Acidic hydrolysis of the acetal and a three-step Nicolaou oxidation gave the bicyclo[3.3.0]octaenone–15-crown-5 hybrid **76a** in 15% yield. The larger homologue **76b** could not be isolated. It should be emphasized that the direct twofold Williamson etherification of enone **77** with the ditosylate was not possible.[62]



Scheme 17

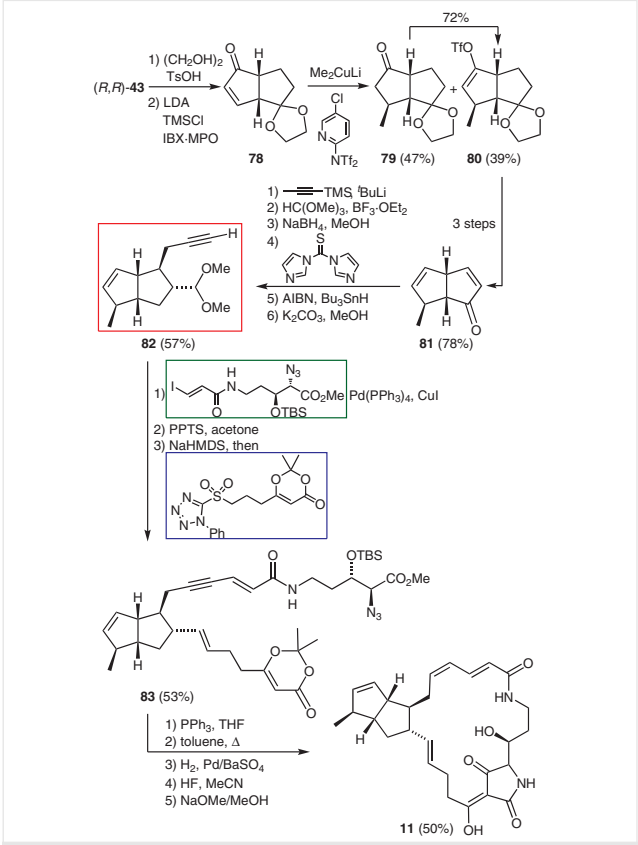
7 Functionalization of Bicyclo[3.3.0]octan-1,4-dione to Cylindramide

Our total synthesis to cylindramide (**11**) is presented in Scheme 18. Starting dione (*R*,*R*)-**43**, which was obtained as shown in Scheme 10, was converted into the enantiomerically pure enone **78**. The latter was submitted to conjugate addition of lithium dimethylcuprate, followed by trapping with (5-chloropyridin-2-yl)triflimide, to provide a mixture of the desired enol triflate **80** together with the ketone **79**, which could be converted into the enol triflate **80** in 72% yield. Pd-catalyzed reduction of **80** with Et_3SiH, acetal cleavage, and Nicolaou oxidation gave the dienone **81**.

Conjugate addition of a propargyl cuprate, trapping with trimethyl orthoformate, Barton–McCombie deoxygenation, and desilylation gave the alkyne building block **82**. The stage was now set for a Sonogashira coupling, removal of the acetal, and Julia olefination to provide the pincer-shaped hydropentalene derivative **83** in 53% yield. The endgame required a Staudinger reduction of the azide, concomitant macrolactamization, Lindlar hydrogenation of the enyne, desilylation with HF in acetonitrile, and Dieckmann condensation, finally delivering cylindramide (**11**) in 29 steps (18 linear steps) and 2.1% overall yield.[49,50]

8 Tandem Ring-Opening Metathesis/Ring-Closing Metathesis/Cross-Metathesis of Bicyclo[2.2.1]heptanes

Parallel to our own synthetic endeavors, Hart and Phillips developed a tandem ring-opening/ring-closing/cross-metathesis (ROM/RCM/CM) approach to the preparation of

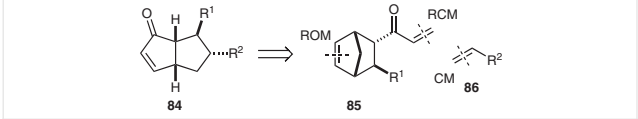


Scheme 18

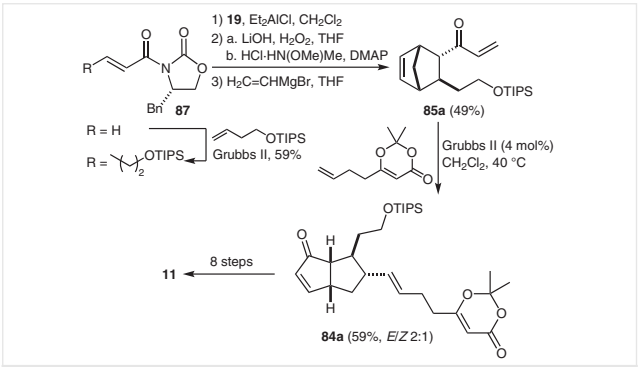
hydropentalenes from norbornenes,[63] based on the seminal work of the groups of Blechert,[64] Hoveyda,[65] Plumet,[66] Hagiwara,[67] Aubé,[68] and Funel[69] (Scheme 19).

Key steps in the Phillips strategy are a chain elongation through cross-metathesis of the α,β-unsaturated *N*-acyloxazolidinone **87**, a subsequent asymmetric Diels–Alder reaction with cyclopentadiene (**19**) utilizing the Evans auxiliary for stereocontrol, removal of the auxiliary, and conversion into the enone **85a** via the Weinreb amide (2 steps), and Grignard reaction. Subsequent ROM/RCM/CM provided the pincer-type compound **84a**, which was then elaborated in eight further steps to the natural product **11** (Scheme 20). Cylindramide (**11**) was isolated in 29 steps and 0.44% overall yield.

The Phillips group further utilized this tandem ROM/RCM strategy in total syntheses of aburatubolactam (**14**)[70] and geodin A (**12**).[71] This time, the synthesis com-

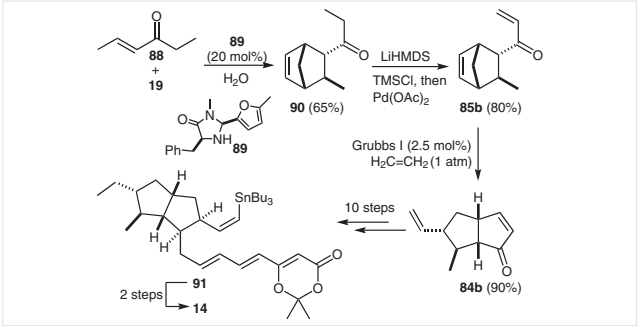


Scheme 19 Retrosynthesis of a ROM/RCM/CM sequence according to Hart and Phillips[63]



Scheme 20

menced with an organocatalytic [4+2]-cycloaddition with but-2-en-3-one (**88**) and cyclopentadiene (**19**) in the presence of MacMillan's catalyst **89** (Scheme 21). A Saegusa oxidation, followed by the tandem ROM/RCM sequence provided hydropentalene **84b**, which was converted in 12 further steps into the natural product **14**. Aburatubolactam (**14**) was isolated in 1.0% overall yield over 23 steps.

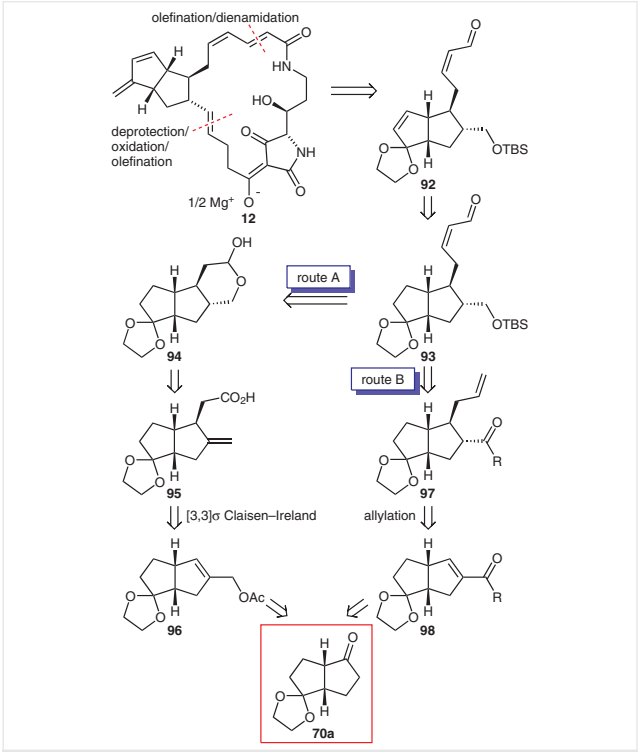


Scheme 21 Aburatubolactam precursor hydropentalene **84b** according to Phillips[70]

Very recently, Kotha et al. used a sequence of Fischer indole synthesis, N-allylation, and ring rearrangement metathesis for the synthesis of azapolyquinanes.[72]

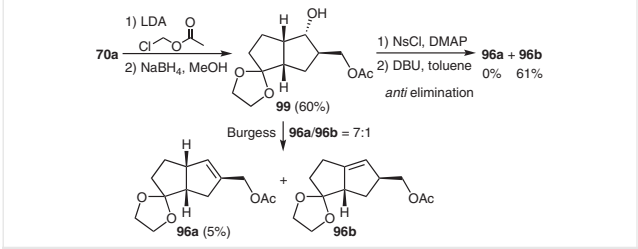
9 Functionalization of Bicyclo[3.3.0]octan-1,4-dione to Geodin A

To access the geodin A target, we envisaged two different synthetic strategies using dienal **92** and the corresponding precursor aldehyde **93** as key intermediates (Scheme 22). Aldehyde **93** could be derived from lactol **94** and its precursor, the carboxylic acid **95** (Route A), which, in turn, should be obtainable by a Claisen–Ireland [3,3]-sigmatropic rearrangement from the allylic acetate **96**. The latter might be derived from keto acetal **70a**. Alternatively, aldehyde **93** might be obtained from the β-allyl-substituted ketone **97**, for which a diastereoselective allylation of enone **98** was planned, the latter again being derived from keto-acetal **70a** (Route B).



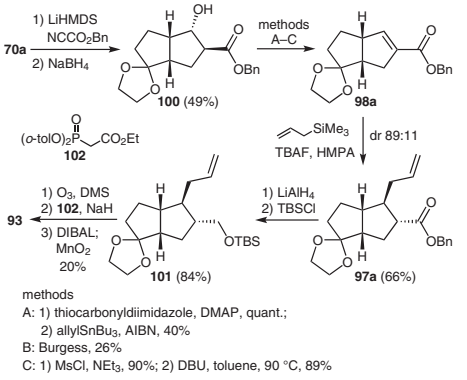
Scheme 22

By Route A, deprotonation of ketoacetal **70a** with LDA and treatment with chloromethyl acetate followed by reduction with $NaBH_4$ gave the secondary alcohol **99**, which was nosylated and treated with DBU in toluene at 90 °C (Scheme 23). Unfortunately, E2 elimination favored an *anti*-orientation of C–H and C–ONs; consequently the undesired regioisomeric alkene **96b** was isolated in 61% yield. When alcohol **99** and the Burgess reagent were used, a 7:1 mixture of the desired regioisomer **96a** and **96b** was formed, albeit in a disappointingly low yield of 5% after HPLC separation. We therefore decided to abandon Route A.



Scheme 23

In accord with Route B, the exocyclic benzyl ester was installed by treatment of ketoacetal **70a** with LiHMDS and benzyl cyanoformate; this was followed by $NaBH_4$ reduction to give the β-hydroxy ester **100** in 49% yield (Scheme 24). Three methods were probed for the elimination toward the benzyl enoate **98a**. A two-step radical elimination via the intermediate thioimidazolide (Method A) gave only 40% of the elimination product **98a**. Treatment of **100** with Burgess reagent proceeded in a disappointingly low yield of 26% (Method B). However, a classical two-step mesylation/base-mediated elimination proceeded uneventfully in 80% yield over the two steps (Method C).[73]



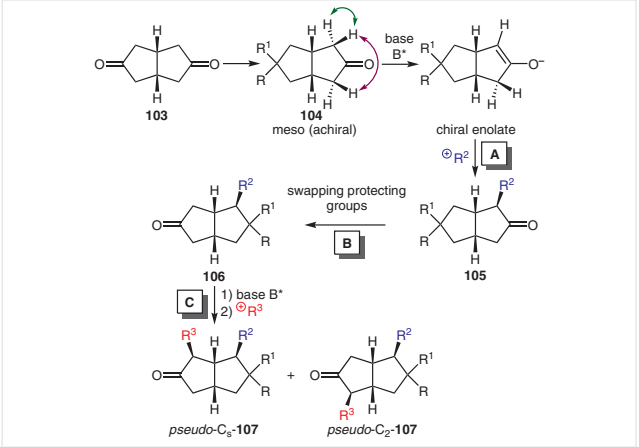
Scheme 24

Considerable experimentation was necessary to get the allylation to run. In the end, diastereoselective allylation was achieved with allyl(trimethyl)silane, HMPA, and TBAF, giving the desired *trans*-1,4-adduct **97a** in 66% yield (dr 89:11).[74]

After reduction of the ester unit, TBS protection of the resulting alcohol, ozonolytic cleavage of the C=C double bond, and reductive workup, the resulting aldehyde was submitted to HWE olefination, DIBAL reduction, and MnO_2 oxidation to give the enal fragment **93**, suitable for further manipulation towards geodin A.

10 Hydropentalenes through Enantioselective Desymmetrization of Weiss Diketones

As discussed above, the oxidative co-cyclization of COD (**42**) provides convenient access to the hydropentalenes. However, from an environmental point of view, the reaction sequence is rather hazardous, requiring 12 g of $Pd(OAc)_2$ and 1 kg of $Pb(OAc)_4$ per 240 mL of **42**. Consequently, an alternative route was sought. Moreover, we hoped that symmetry might be used as a guiding principle to access complex natural product families such as the tetramic acid macrolactams. In that particular case, the hydropentalene core unit of cylindramide (**11**) and geodin A (**12**) can be traced back to the *pseudo*-C_2 symmetrical bicyclo[3.3.0]octane derivative *pseudo*-C_2-**107** (Scheme 25), whereas the corresponding core unit of alteramide A (**13**) and aburatubolactam (**14**) can be traced back to the *pseudo*-C_s symmetrical bicyclo[3.3.0]octane derivative *pseudo*-C_s-**107**. These two scaffolds might come from diastereo- and regioselective functionalization of ketone **106**.



Scheme 25

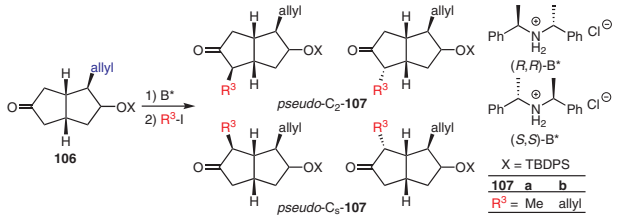
Protective-group swapping leads to the precursor ketone **105**, which can be traced back to Weiss diketone **103**,[75] a commercially available starting material that is easily synthesized on a gram scale. Our approach was inspired by seminal contributions from the groups of Simpkins,[76] Koga,[77] Leonard,[78] and Gais[79] on the enantioselective desymmetrization of *meso* ketones through deprotonation with chiral lithium amide bases and subsequent electrophilic trapping of the chiral enolates.

As illustrated in Scheme 26, an enantioselective desymmetrization employing the phenylethylamine-derived Simpkin's base (*R*,*R*)-B* and subsequent electrophilic quenching worked quite well, giving acceptable yields and good enantiomeric ratios, as long as activated and sterically less-demanding electrophiles were used.[80] Both silyl ethers and acetals were tolerated as protecting groups.

Having established this monofunctionalization, we were interested in whether the newly created stereogenic center would exert any stereocontrol during a second deprotonation/alkylation of the other half of the hydropentalene core.[80] As shown in Table 1, this twofold desymmetrization was indeed successful. The configuration of the chiral base had a strong influence on the regio- and diastereoselectivity. Whereas the (*R*,*R*)-base preferentially gave the *pseudo*-C_2 isomer with a C_2/C_s ratio of 4:1 to 3:1 and a matched diastereoselectivity (>98:2), the pseudo-C_s isomer was favored in the presence of the (*S*,*S*)-base in a C_2/C_s ratio of 1:4 and with a matched diastereoselectivity of >99:1 (Table 1).

As discussed in Section 6, our aim was to produce truncated cylindramide derivatives carrying the hydropentalene unit and a crown ether or flexible oligoethylene chain

Table 1 Asymmetric Deprotonation/Alkylation of Ketone **106**[a]



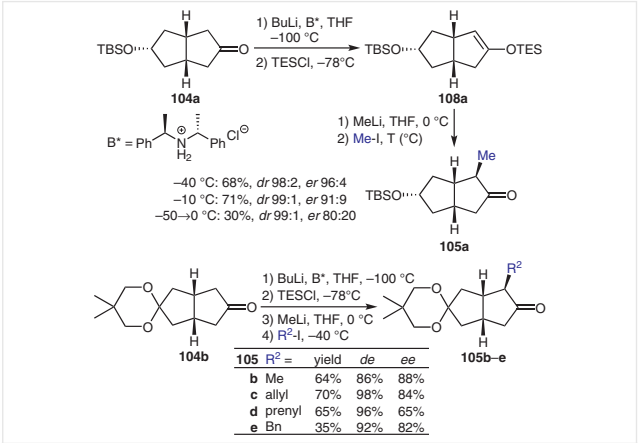
		pseudo-C_2				*pseudo*-C_s		
107	B*	C_2/C_s	yield (%)	dr		yield (%)	dr	
a	(*R*,*R*)	79:21	58	99.5:0.5	matched	15	65:35	mismatched
b	(*R*,*R*)	76:24	28	98:2	matched	9	52:48	mismatched
a	(*S*,*S*)	21:79	16	13:87	mismatched	60	100:0	matched
b	(*S*,*S*)	20:80	17	29:71	mismatched	68	1:99	matched

[a] Ketone **106** derived from **105** after protective-group swapping (see Scheme 25).

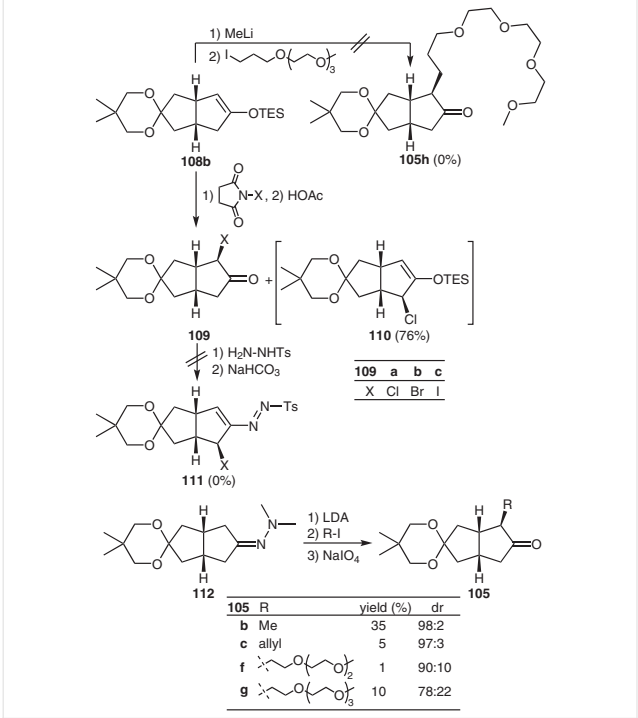
that would mimic the Ca^{2+}-binding hydroxyornithine unit in the natural product.[81] As shown in Scheme 27, in a first attempt the chiral silylenol ether **108b** was treated sequentially with MeLi and the triethylene glycol iodide (TEG-I), but no trace of the desired TEG hydropentalene **105h** could be isolated.

In an alternative attempt, the synthesis of chiral *N*-tosyl azoenes from silylenol ether **108b** was investigated. Treatment with NBS or NIS provided the α-substituted ketones **109b** and **109c**. However, when NCS was employed, diastereoselective chlorination of the silylenolether took place, yielding **110** in 76% yield with no trace of the ketone **109a**. Unfortunately, this approach was another dead end, and the α-halo ketones **109** could not be converted into the azoenes **111** (Scheme 27).

Both *N*,*N*-dimethylhydrazine (**112**) and the corresponding *N*-tosylhydrazine were reluctant reactants in the asymmetric deprotonation/alkylation sequence when alkyllithium reagents were used for deprotonation. In contrast, deprotonation of **112** with LDA and subsequent electrophilic trapping with methyl, allyl, or TEG iodides provided the desired α-substituted ketones **105** after oxidative cleavage of the hydrazone unit with $NaIO_4$, albeit in low yields (Scheme 27).



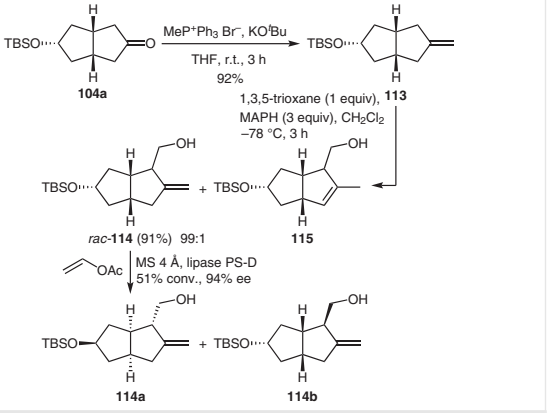
Scheme 26



Scheme 27

11 Functionalization of Weiss Diketones by Carbonyl Ene Reactions

To obtain building blocks with the 1,2-disubstitution pattern required for acyltetramic macrolactams, a desymmetrization through a carbonyl-ene reaction and subsequent enzymatic resolution was probed by using the OTBS-protected ketone **104a** as a starting material (Scheme 28).[82]

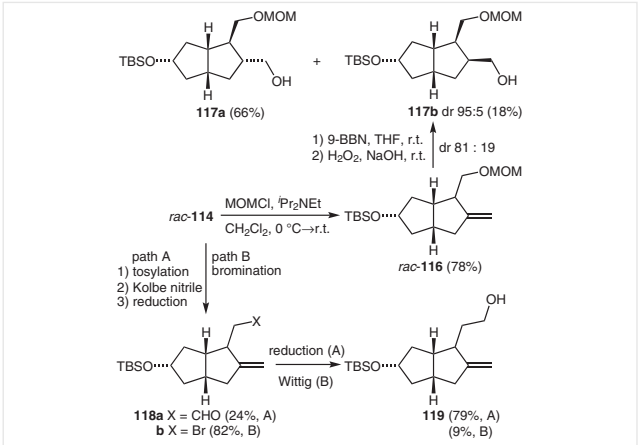


Scheme 28

Wittig olefination provided the starting exocyclic alkene **113**. After considerable experimentation with various Lewis acids, we found that Maruoka's methylaluminum bis(2,6-diphenylphenoxide) (MAPH; 3 equiv) mediated the carbonyl-ene reaction of trioxane with alkene **113** to give the regioisomeric product **114** in 91% yield (dr 99:1). Optical resolution was then achieved through lipase-catalyzed acylation to give the homoallylic alcohol with 94% ee at 51% conversion.

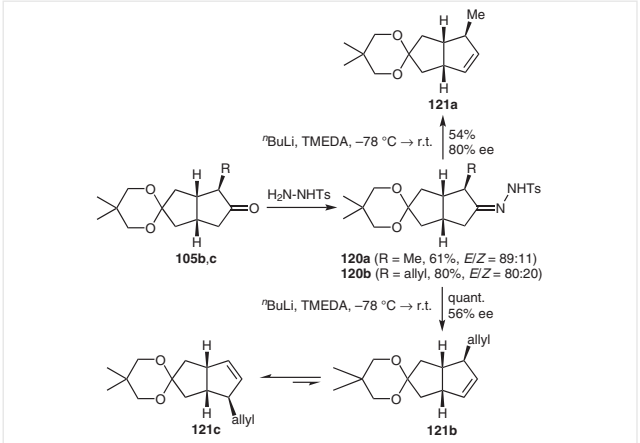
Carbonyl-ene product *rac*-**114** was further manipulated by MOM-protection and hydroboration to give the two MOM-protected diols **117a** and **117b** in yields of 66 and 18% (dr 95:5), respectively (Scheme 29).

Alternatively, chain extension was possible through tosylation, Kolbe nitrile synthesis, reduction to aldehyde **118a**, and finally reduction to alcohol **119** (Scheme 29, Path A). On the other hand, bromination of *rac*-**114** and Grignard reaction of **118b** with formaldehyde gave alcohol **119** in a poor yield (Path B).



Scheme 29

Luckily, initial experiments with α-methyl and α-allyl bicyclo[3.3.0]octanone tosylhydrazones **120a** and **120b**, respectively, revealed an excellent regioselectivity in favor of the less-substituted C=C double bond (Scheme 30).[84] However, for the α-allyl-substituted elimination product **121b**, a significant degree of racemization was observed (56% ee) in contrast to the corresponding methyl-substituted product **121a**, where the stereochemistry was almost retained (80% ee). Presumably, the erosion of optical purity of **121b** was due to a thermal [3,3]-sigmatropic Cope rearrangement of the alkene.



Scheme 30

12 Functionalization of the Weiss Diketone to Cylindramide and Geodin A Core Units

Introduction of a C=C double bond through a Shapiro reaction was probed as means of accessing the core units of the acyltetramic macrolactams **11** and **12**. We were particularly worried regarding the regioselectivity of the Shapiro protocol.[83]

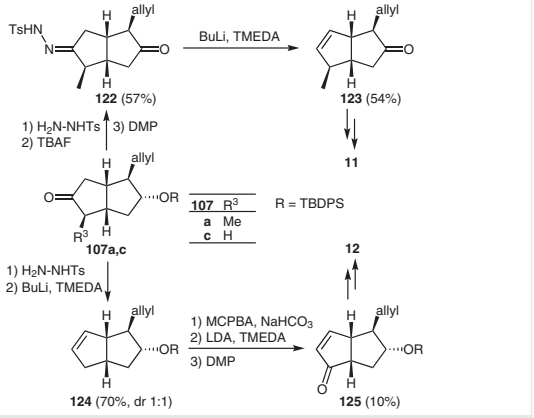
Taking this limitation into consideration, we decided to keep the allylic moiety in the 'other half' of the bicyclo[3.3.0]octane unit, which is not prone to sigmatropic rearrangement. As shown in Scheme 31, ketone **107a** was converted into the *N*-tosylhydrazone, followed by deprotection of the silyl ether and oxidation to the α-allyl ketone **122**, which was subjected to the Shapiro reaction to provide the desired alkene **123** in 54% yield.

The α-unsubstituted ketone **107c** was directly submitted to Shapiro reaction to give the alkene **124** in 70% yield as a 1:1 diastereomeric mixture. Further elaboration in three steps gave the target compound **125**, albeit in a disappointingly low yield of 10%. Despite these drawbacks, the core units **123** and **125** of cylindramide (**11**) and geodin A (**12**) were successfully prepared.

13 Biological Properties of Bicyclo[3.3.0]octanes

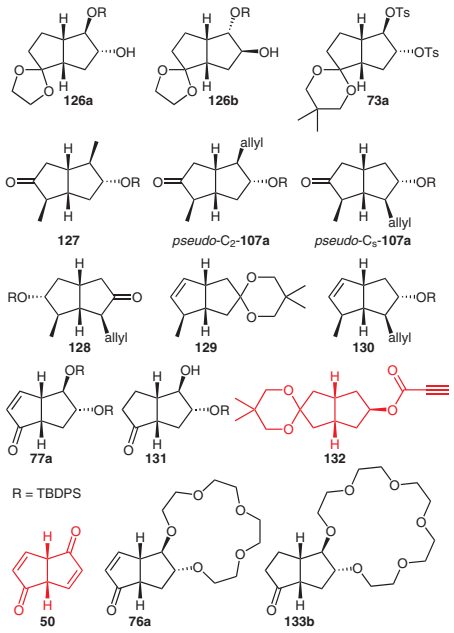
Biological studies on cylindramide (**11**) revealed a pronounced cytotoxicity against various cancer cell lines[85] that was Ca^{2+} dependent. A closer examination of derivatives differing in both the macrocyclic unit and in the bicyclo[3.3.0]octane unit showed that both parts contribute to the pharmacophore. For example, when the bicyclo[3.3.0] unit was replaced by cyclopentanes, the IC_{50} values decreased to 3% of the original value. This result motivated us to perform further structure–activity studies on a library of hydropentalenes [Table 2 and Table S1 (SI)].[86] From this screening, two derivatives **50** and **132** with the highest activity were selected for a cluster analysis employing natural products with a known mode of action. Clustering was found with tubulysin B, griseofulvin, and nocodazol, which are compounds that interfere with microtubule polymerization and spindle formation. We therefore proposed a microtubuli-affecting mode of action. Tubulin and F-actin were identified by target-fishing experiments.

Moreover, the dihydropentalenedione **50** induced actin and tubulin polymerization. It was also evident from the biological-screening data that the bicyclo[3.3.0]octanone–crown ether hybrids **76a** and **76b** did not meet our expectations, displaying little or no cytotoxicity compared with the most active hydropentalenes **50** and **132**.



Scheme 31

Table 2 Cytotoxicity of Pentalene Derivatives against Two Cell Lines Determined by the MTT test[a,b]

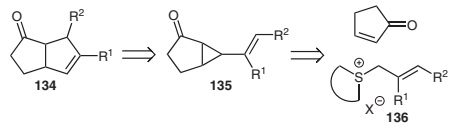


Entry	Compound	L-929 mouse fibroblast IC_{50} [μg/mL]	KB-3-1 IC_{50} [μg/mL]
1	**126a**	18	–
2	**126b**	17	–
3	**73a**	>40	11
4	**127**	3	–
5	***C*$_2$-107a**	10	–
6	***C*$_s$-107a**	7	–
7	**128**	2.2	–
8	**129**	>40	–
9	**130**	3	–
10	**77a**	10	>40
11	**131**	15	11
12	**132**	0.6	6
13	**50**	0.4	–
14	**76a**	20	26
15	**133b**	35	30

[a] MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide.
[b] For further derivatives, see Table S1 (Supporting Information).

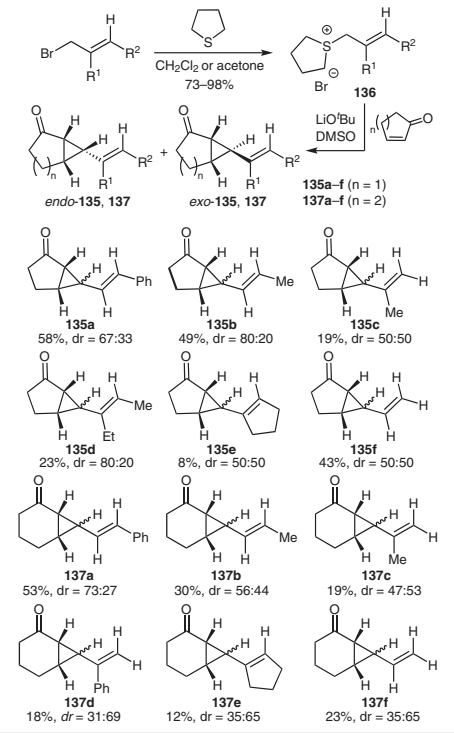
14 Hydropentalenes through Vinylcyclopropane Cyclopentene Rearrangement

Inspired by Hudlicky's seminal contributions[87] and by the more recent work of Zou and Louie on the transition-metal-catalyzed vinylcyclopropane–cyclopentene rear-



Scheme 32

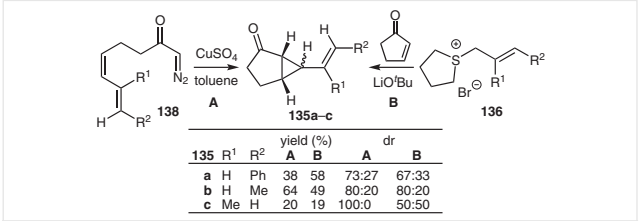
rangement,[88] we surmised that partially activated vinylcyclopropanes carrying only one nearby carbonyl group might be suitable precursors to access hydropentalenes (Scheme 32).



Scheme 33 Synthesis of vinylcyclopropanes **135** and **137**. Compounds **135d** and **135e** were prepared by Route A (Scheme 34).[89]

The required vinylcyclopropanes **135** might come from cyclopentenone and allylsulfonium salts **136** (Scheme 33).[89,90] The synthesis of the vinylcyclopropanes was found to be strongly dependent on the substitution pattern. For example, terminally substituted sulfonium salts ($R^2 \neq H$) gave higher yields than vicinally substituted salts ($R^1 \neq H$). In addition, the base, solvent, and counterion affected the yield and selectivity. The most annoying side reaction was the [2,3]-sigmatropic rearrangement, resulting in the formation of α-allyl sulfides rather than vinylcyclopropanes.[89,90]

Despite these disadvantages this approach delivered the desired vinylcyclopropanes **135** in two steps (Route B, Scheme 34), whereas the corresponding Cu-catalyzed

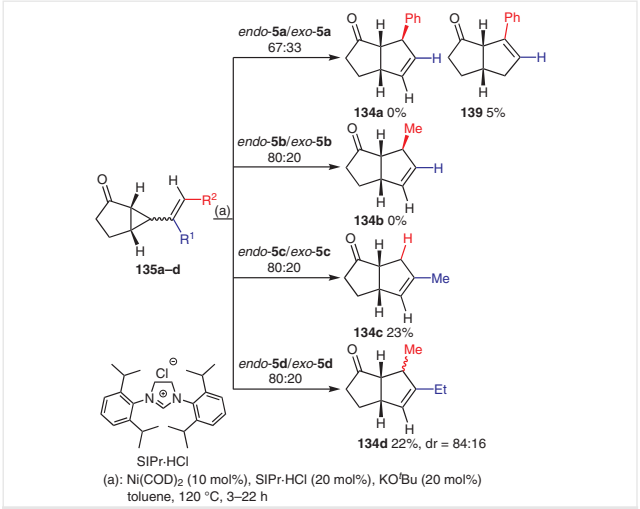


135	R^1	R^2	yield (%) A	yield (%) B	dr A	dr B
a	H	Ph	38	58	73:27	67:33
b	H	Me	64	49	80:20	80:20
c	Me	H	20	19	100:0	50:50

Scheme 34

[2+1]-annulation of unsaturated α-diazo ketones **138** required six steps from commercially available starting materials (Route A, Scheme 34).[89]

Having solved this issue, it took us endless optimizations to figure out the proper conditions for the Ni-catalyzed vinylcyclopropane rearrangement. Among the various tested Ni N-heterocyclic carbene catalysts $Ni(SIPr)_2$ [SI = 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene], prepared in situ from SIPr·HCl, *t*-BuOK, and $Ni(COD)_2$, gave the best results, although ring opening always compromised the yields. To our great dismay, the vinylcyclopropanes, which were hardest to make, i.e. the *vicinal*-substituted compounds **135c** and **135d** were much more prone to undergo the desired vinylcyclopropane rearrangement. On the other hand, vinylcyclopropanes **135a** and **135b** with a terminal substituted C=C double bond were obtained in decent yields, but unfortunately reacted only sluggishly to give the bicyclo[3.3.0]octenes **134** (Scheme 35).[90]



Scheme 35

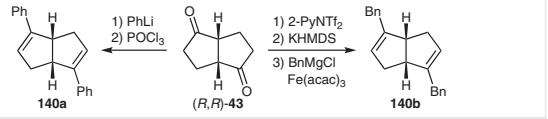
Computational studies confirmed the experimental results. Note that only *endo*-vinylcyclopropanes *endo*-**135c** and *endo*-**135d** were reactive in the Ni catalysis, whereas the *exo*-vinylcyclopropanes *exo*-**135c** and *exo*-**135d** remained completely unreactive. This behavior could be rationalized by means of DFT calculations which showed that the catalytic intermediate arising from *endo*-**135c** with *vici-*

nal substitution had short half-lives of the order of seconds or minutes, whereas intermediates derived from *exo*-**135b** with terminal substituent at the C=C bond had half-lives of the order of days.

15 Functionalization of Bicyclo[3.3.0]octanes toward Chiral Dienes

Chiral dienes have entered the field of asymmetric catalysis as a result of the seminal discoveries of the groups of Hayashi,[91] Carreira,[92] and Grützmacher[93] that a diene can exert efficient stereocontrol in asymmetric transition-metal catalysis.[94]

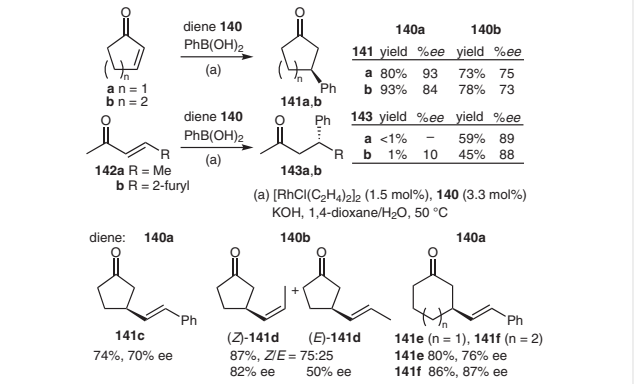
As mentioned above in Sections 9 and 10, symmetry arguments fascinated and puzzled us for quite a while. Having obtained gram quantities of the chiral bicyclo[3.3.0]octan-1,4-dione **43** as a key intermediate during the cylindramide total synthesis, we hoped that this compound and its optical antipode might be valuable precursors for chiral diene ligands. The synthesis of the diene ligands **140** commenced with (3a*R*,6a*R*)-bicyclo[3.3.0]octan-1,4-dione (*R*,*R*)-**43**, which was treated with phenyllithium followed by elimination with $POCl_3$ to give the 1,4-diphenyldiene **140a** (Scheme 36).[95] Alternatively, the dione (*R*,*R*)-**43** was converted into a bisenol triflate and submitted to Fe-catalyzed Negishi cross-coupling to yield the 1,4-dibenzyldiene **140b**.



Scheme 36

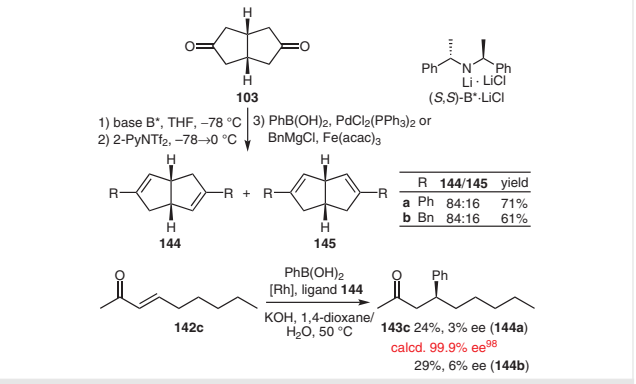
The two ligands displayed complementary activities in the Rh-catalyzed 1,4-additions of arylboronic acids to enones. Whereas the 1,4-diphenyldiene **140a** gave higher yields and enantioselectivities of cyclic enones than did the 1,4-dibenzyldiene **140b**, the former was completely inactive upon employment of acyclic enones. In contrast, 1,4-dibenzyldiene **140b** provided the corresponding 1,4-addition products in decent yields and good ee values (Scheme 37). The scope of substrates and reagents could be further extended to seven-membered rings and vinylboronates.[96] Note that the Lin group published almost simultaneous reports on the same ligand.[97]

Motivated by a series of papers by the Kantchev group[98] dealing with *in silico* catalysis through DFT methods, we became interested in the C_2-symmetrical 2,5-disubstituted bicyclo[3.3.0]octan-1,4-diene **144a**. Despite the much larger distance of the substituents R from the Rh center (compared with the diene ligand **140a**), a high ee value was expected for the 1,4-addition products derived from aliphatic enones (Scheme 38).[99]



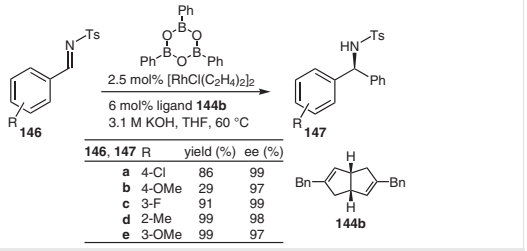
Scheme 37

When we used a strategy similar to that shown in Scheme 36 for the synthesis of dienes **144** from Weiss diketone **103**, we noticed that, depending on the base, considerable amounts of the undesired C_s-symmetrical (achiral) diene **145** were formed (Scheme 38). For example, treatment of Weiss diketone **103** with a chiral Simpkins base, trapping with triflimide, and subsequent Suzuki cross-coupling with phenylboronic acid delivered the dienes **144a** and **145a** in 71% yield as an 84:16 regioisomeric mixture.[100] For ligands with other substituents, similar results were obtained, requiring laborious preparative HPLC separations to gain access to the pure C_2-symmetrical dienes **144**. Attempts to solve the purification issue by selective formation of Pd–diene complexes were only partially successful. It should be emphasized that Strand recently solved this problem of *racemic* and *meso* ligands in an elegant way[101] by selective complexation of the *rac*-diene with $[Rh(ethene)_2Cl]_2$, while the *meso*-diene did not form a stable Rh complex, in agreement with our own observations.[100] Strand was able to obtain diastereomerically pure monomeric Rh diene binaphthylamine complexes by treatment of the *rac*-Rh diene complex with (*R*)-binaphthyldiamine.[101] The enantiomerically pure diene was finally isolated after decomplexation with COD.



Scheme 38

After making all these efforts to obtain regioisomerically and enantiomerically pure ligands, we were very disappointed in their poor catalytic performance in 1,4-additions. Fortunately, it turned out that dienes **144** were suitable catalysts for Rh-catalyzed 1,2-addition of phenylboroxine to *N*-tosylimines **146**. After some optimization, *N*-tosylimines **146** with various substitution patterns were converted into the secondary amines **147**, in most cases in high yields and with excellent enantioselectivities (Scheme 39).

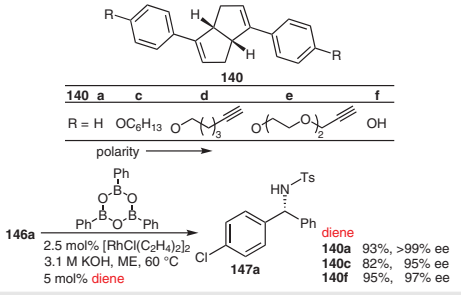


146, 147	R	yield (%)	ee (%)
a	4-Cl	86	99
b	4-OMe	29	97
c	3-F	91	99
d	2-Me	99	98
e	3-OMe	99	97

Scheme 39

We were curious as to whether the HPLC separation of *rac*- and *meso*-dienes **144** and **145** is really necessary, and we speculated that mixtures rather than isolated dienes might be used in the catalysis. In comparing the catalytic 1,2-addition of the pure (*R*,*R*)-dibenzyl-diene **144b** with that of a 67:38 mixture of the C_2 and C_s forms, the latter provided the product **147a** in similar yield but with reduced enantioselectivity. Presumably, this resulted either from diluted stereocontrol in the case of the 'innocent' C_s diene **145b** or a racemic background catalysis in the case of C_2/C_s interconversion through C=C bond isomerization. The latter possibility came to our mind, because attempts to obtain crystals from a Rh(C_s diene) complex resulted in the exclusive crystallization of the Rh(C_2 diene) complex. Such a Rh-catalyzed C=C isomerization is much more likely, according to DFT calculations, and agrees well with experimental findings obtained by the Strand group.[101]

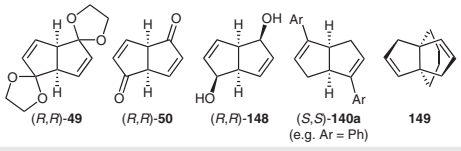
More recently, bicyclo[3.3.0]octadienes and the resulting Rh complexes were probed in microemulsions (MEs) as nonconventional solvents.[102] MEs are stable single-phase emulsions of a hydrophobic solvent (oil), a polar solvent



Scheme 40

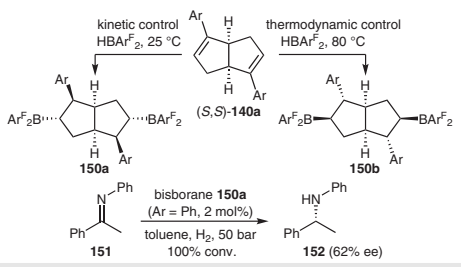
(e.g., H_2O), and a surfactant, such as a sugar amphiphile C_8G_1.[103] These MEs have a sponge-like nanostructure with channels measuring 55 Å that provide excellent liquid confinement, in particular for multicomponent reactions involving substrates, catalysts, additives, and products with various polarities. We were able to demonstrate, for the first time, that such MEs permit the Rh-catalyzed 1,2-addition even when dienes **140** of different polarities were employed (Scheme 40). Furthermore, preliminary kinetic experiments revealed a rate increase in the ME as compared with conventional solvent mixtures such as 1,4-dioxane–H_2O.[102]

The promising results of the roof-shaped bicyclo[3.3.0]octadienes in asymmetric catalysis motivated several groups worldwide to step into this area and to develop novel hydropentalene-derived ligands.[104–106] A brief overview is given in Scheme 41.[106]



Scheme 41

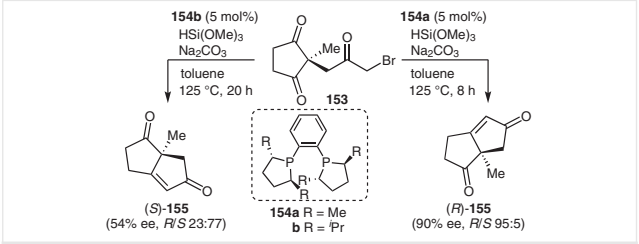
Very recently, Peng and Wang reported the conversion of chiral diene (*S*,*S*)-**140a** through hydroboration into the bicyclic bisboranes **150a** and **150b**, which were employed as organocatalysts for the hydrogenation of imines **151** (Scheme 42).[107]



Scheme 42

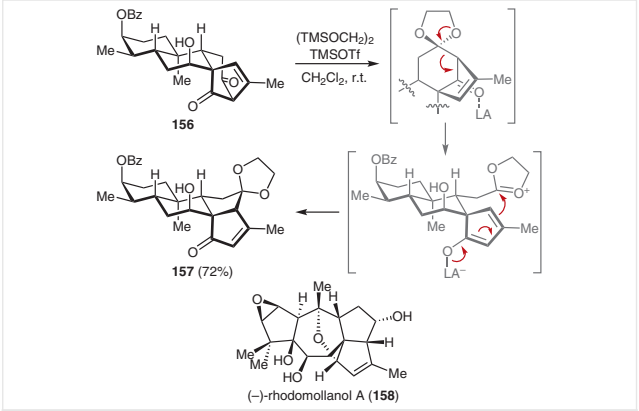
16 Miscellaneous Syntheses of Hydropentalenes

In this section, we would like to draw the reader's attention to some recent synthetic approaches towards hydropentalenes. An organocatalytic enantioselective Wittig reaction of *meso*-triketone **153** using chiral phosphines (*S*,*S*)-MeDuPhos (**154a**) and (*S*,*S*)-*i*PrDuPhos (**154b**) was developed by the Werner group, providing the (*R*)- and (*S*)-bicyclo[3.3.0]octenediones **155** in 90 and 54% ee, respectively (Scheme 43).[108]



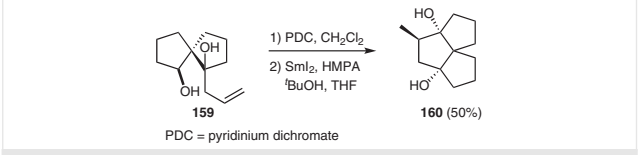
Scheme 43

The Ding group disclosed an unprecedented Lewis acid mediated retro-Dieckmann fragmentation/vinylogous Dieckmann cyclization cascade of tetracyclic ketone **156** to enone **157** for the installation of a bicyclo[3.3.0]octane unit in a total synthesis of the diterpenoid (–)-rhodomollanol A (**158**; Scheme 44).[109]



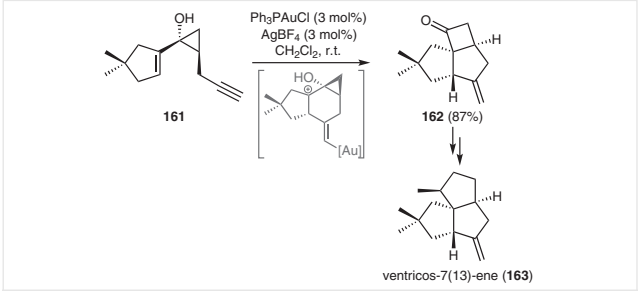
Scheme 44

Oxidation of the spirocyclic homoallylic alcohol **159**, followed by SmI_2-mediated cyclization, gave the triquinane **160**, as reported by the Tu group (Scheme 45).[110] SmI_2-mediated radical cascade cyclizations were utilized by Procter and co-workers for the construction of quaternary stereocenters.[111]



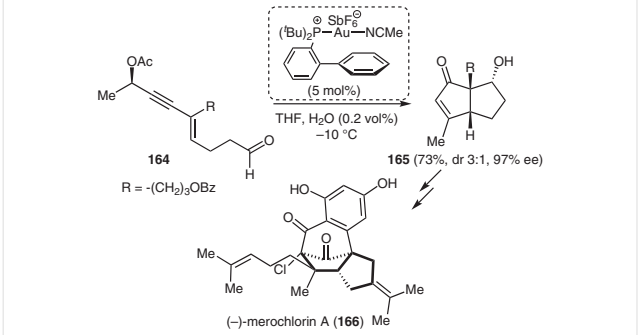
Scheme 45

Gold-catalyzed ring expansions have been successfully employed for a variety of hydropentalene-containing natural products.[112] For example, the Toste group reported an Au-catalyzed ring expansion of cyclopropanol **161**, followed by a semipinacol shift, to give the hydropentalene subunit of the angular triquinane ventricos-7(13)-ene (**163**; Scheme 46).[113]



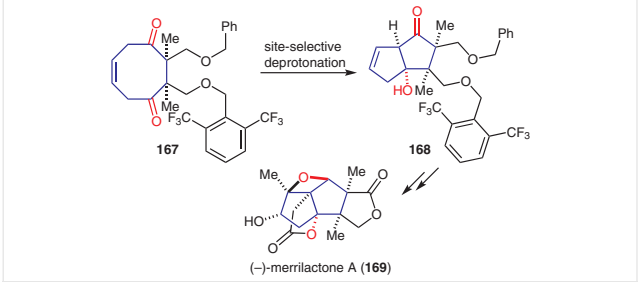
Scheme 46

As already mentioned in Section 14, the laborious synthesis of starting materials containing small rings often compromises the efficiency of subsequent catalytic steps. This problem was elegantly circumvented by Carreira and co-workers in their total synthesis of (–)-merochlorin A (**166**; Scheme 47).[114] The key bicyclo[3.3.0]octenone intermediate **165** was obtained by enantiospecific Au-catalyzed tandem 1,3-acyloxy migration/Nazarov/aldol reaction from acyclic precursor **164**.



Scheme 47

The asymmetric total synthesis of (–)-merrilactone A (**169**) was accomplished by a site-selective deprotonation of the cyclooctenedione **167** with a subsequent transannular aldol reaction to give hydropentalene **168** as a key step (Scheme 48).[115]



Scheme 48

17 Conclusion and Outlook

The current account summarizes our efforts in the synthesis and applications of bicyclo[3.3.0]octanes over the last 20 years. This demonstrated the value of the hydropentalene scaffold in relation to natural product chemistry and biologically active compounds. One lesson learned was that key intermediates from natural product chemistry can fertilize new directions in catalysis, and vice versa. On the other hand, it should be kept in mind that small molecules often cause nightmares for the preparative organic chemist. This is particularly true for the bicyclo[3.3.0]octanes. There are several reasons for this challenging chemistry. The *convex* roof-shape of the bicyclo[3.3.0]octane unit results in a spherical shape, leading to high volatility of many members of this compound family. Therefore, special care has to be taken during workup and purification to avoid product loss. Furthermore, the roof-shape causes a severe steric bias toward *endo*-attack compared with *exo*-attack of incoming reagents. Often, even standard transformations fail or give low yields due to steric restrictions caused by neighboring groups. In addition, even simple functionalizations or functional-group interconversions, such as addition or removal of a single hydroxy group, can change the polarity in a much more pronounced way as compared with the introduction of a hydroxy group onto a larger molecule (e.g., MW 800 or above). Thus, polarity and solubility issues play an important role in the chemistry of hydropentalenes. The old saying 'Every magic comes with price tag' also apply to hydropentalenes. Nevertheless, the field is certainly not closed, and applications in the direction of materials science are on the horizon, awaiting to be discovered.

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Generous financial support by the Deutsche Forschungsgemeinschaft (DFG, project number 358283783 - SFB 1333, subproject B3), the Ministerium für Wissenschaft, Forschung und Kunst des Landes Baden-Württemberg, the Fonds der Chemischen Industrie and the European Commission (ERASMUS fellowship for Z.D.) is gratefully acknowledged.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707226.

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