Review

Methodology for the Construction of the Bicyclo[4.3.0]nonane Core

Nicholas A. Eddy * and Pranjali Ichalkaranje

Department of Chemistry, University of Connecticut, Storrs, CT 06269 USA; pranjali.ichalkaranje@uconn.edu
* Correspondence: nicholas.eddy@uconn.edu; Tel.: +1-860-486-6394

Academic Editor: Vassilios Roussis
Received: 31 July 2016; Accepted: 3 October 2016; Published: 12 October 2016

Abstract: The bicyclo[4.3.0]nonane scaffold, commonly known as a hydrindane, is a common structural motif found in many terpenoid structures and one that remains a challenge for synthetic chemists to elaborate with appropriate regio- and stereo-selectivity. Over the course of the study of terpene natural products, the elaboration of the hydrindane structure has seen progress on the utilization of both old and newer methods to achieve the desired outcomes. This review seeks to serve as a general overview of these methods, and detail specific examples.

Keywords: triterpenes; triterpenoids; Diels-Alder; metathesis; Michael additions

1. Introduction

Throughout the vast array of structures that polyterpenes and polyterpenoids can exist in, a common motif that appears regularly has been the bicyclo[4.3.0]nonane (also called hydrindane) scaffold [1]. Notably, the hydrindane moiety often contains a significant portion of the stereochemistry contained in the natural product; thus presenting a wealth of opportunity for method development and posing a synthetic challenge [2]. Over the past forty years, different strategies have been employed to showcase the utility of reaction sequences leading to the hydrindane nucleus, with most targeting the thermodynamically unfavorable trans isomer. This review will focus on the general classes of reactions used for the synthesis of hydrindane cores, as well as examples of strategies employed.

Natural products play a predominant role in medicine and nature, and often bear complex structural elements, e.g., fused ring systems, bridged structures, and contiguous stereocenters. Of particular interest is the hydrindane nucleus, which bears significant amounts of stereocenters in a broad range of bioactive natural products. Naturally occurring terpenoids, functionalized terpene derivatives, are not just a structural curiosity, but play a central role in medicinal chemistry [1,3]. Their biological activity can range from anti-tumor activity to effects on cardiovascular systems (cardiac glycosides) to anti-inflammation [4–9]. Due to these far ranging biological activities, the hydrindane scaffolds often become the target for development into drug-like molecules for the treatment of disease [10,11]. As the reader will note, the hydrindane scaffold is present throughout the examples shown in Figure 1. In light of the prevalence of this scaffold, it should be apparent that no small effort is made in the synthesis and utilization of this common structure across multiple targets.

The cedrelone limonids, isolated from Trichilia P. Br. (Meliacae), possesses bioactivity against cancerous cell lines for leukemia (HL-60), hepatocellular carcinoma (SMMC-7721), lung cancer (A-549), breast cancer (MCF-7), and colon cancer (SW480) [9]. The isolated compounds from this study ranged in IC₅₀ from 1 to 15.9 µM. Panthogenin A and B, isolated from Dioscorea panthaica, causes 100% insulin sensitization at 10 µg/mL [12]. Physaminimin acts an antibiotic and anti-inflammatory compound isolated from Physalis minima in southeastern China, and tested for nitric oxide synthase (NOS) activity in multiple cell lines [4]. Huangqiyegenin V also possess anti-inflammatory activity and has been tested for NOS inhibition [13]. Kadcoccinone F and its congeners have exhibited anticancer bioactivity against
HL-60, SMMC-7221, A-549, MCF-7, and SW480 cell lines [14]. Ultimately, these are a small subset of the diverse scaffolds that triterpenes and triterpenoids may exist in, but serve as a representative set for the purpose of this review. Herein, this review will point to multiple methods of derivation and focus on the synthesis and use of the hydrindane system for biologically active, medicinally relevant, natural product synthesis.

![Examples of naturally occurring triterpenoids.](image)

**Figure 1.** Examples of naturally occurring triterpenoids.

### 2. Synthetic Strategies

#### 2.1. Hajos–Parrish Dione

When considering the structures of the natural products shown in Figure 1, the reader should note that a large portion of the molecules’ stereochemistry is contained in the hydrindane scaffold, giving it a range of structural complexity that can be challenging to synthesize. This prompted the development of the Hajos–Parrish dione (1) and its 6,6-fused analog, the Wieland–Miescher diketone (2), shown in Figure 2. The present section will detail the development, use, and elaboration of scaffolds stemming from 1 for natural product synthesis.

![Structure of Hajos–Parrish dione (1) and Wieland–Miescher dione (2).](image)

**Figure 2.** Structure of Hajos–Parrish dione (1) and Wieland–Miescher dione (2).

In 1974, Hajos and Parrish described the synthesis of 1 in an effort to enantioselectively synthesize the trans-hydrindane present in steroids (see Scheme 1) [15]. Here it was found that Michael addition of 2-methyl-1,3-cyclopentadione with but-3-ene-2-one afforded the intermediate 3, which was subsequently transformed into 1 through the action of proline. A benefit to this sequence is that either enantiomer of 1 can be synthesized efficiently. Further treatment of 1 with NaBH₄ in cold ethanol
selectively reduced the more sterically free ketone to 4, which was then protected as the tert-butyl ether 5 through acid catalyzed reaction with isobutylene [16]. Upon reduction of 5 with mild reduction conditions for palladium catalyzed hydrogenation, it was found that the cis-hydrindane (cis-6) was formed in preference to the trans isomer (trans-6). In consideration of 5’s structure, the authors attributed the reaction preference to the more open β-face being presented over the α during the reduction [17]. Under the best conditions, only 34.5% of trans-6 was found from palladium catalyzed reduction in cyclohexane. Derivatization of 5 with methyl magnesium carbonate (MMC), followed by the same reduction conditions was able to selectively produce trans-6, which upon treatment with 2 M HCl undergoes hydrolysis and decarboxylation to afford trans-6. The isolated trans-hydrindane was carried forward through a series of Michael additions and annulations to yield the desired 19-nor-steroid systems for study.

Scheme 1. Synthesis and reduction of 1 to trans-hydrindane derivative 6.

Other terpenoid systems benefit from 1. 7-epi-Pinguisone (epi-7) exhibits insect anti-feedant activity and was synthesized in 1981 by Jommi (see Scheme 2) [18]. In this work, the authors relied upon the nature of the open β-face to selectively add a second methyl group in the cis configuration, giving 8. Treatment of 8 with an excess of bromine in acetic acid, and further elimination provided 9. Exposure to an excess of lithium dimethylcuprate allowed for 10 with four contiguous stereocenters formed with the appropriate stereochemistry. The authors attribute the high level of induction for 10 to stem from the Drieding model of 9, where the steric hindrance of the α- and β-face of the molecule are similarly hindered, and thus the selectivity of the reaction is governed by the steric bulk of the cuprate. Compound 10, isolated during exploratory reactions, was acylated through its enolate directly after cuprate addition, and spontaneously cyclized to form dione 11 without isolation of the intermediate dione. Reduction with 9-BBN on 11 afforded epi-7.

Unnatural A-19-nor-steroids provide another class of biologically active molecules. Anordrin, an androstane like molecule, has been used for contraception (see Scheme 3). Work done in 1983 by Crabbe on an analogous system, dinordrin (12), showcased further use of 1 in synthesis [19]. Beginning with 1, the reaction was sulfonated to afford 13, and then reduced to 14 with H2 and Pd/C. Condensation with 15, formed by ethyl acetooacetate and ethylene glycol, afforded 16 after annelation. Subsequent deprotection and aldol condensation led to androstane core 17. Ethynylation and trapping with propionic anhydride led to dinordrin 12.
Photolysis was attempted, and found to give the improper stereochemistry, thus prompting epimerization with NaOCH₃. The epimerized product gave the desired cycloadduct, which was then deprotected and oxidized to yield 25. Further steps led to punctatins A and D.

Paquette followed with a synthesis of punctatins A and D (see Scheme 4) [20]. Using 1, reduction of the more hindered ketone followed by protection with tributyl chloromethylstannane (SEM-Cl) led to 18. Treatment with LiAlH₄, followed by protection of the resulting alcohol with SEM-Cl led to the distannyl 19. Lithiation at −78 °C with warming allowed for Still’s [2,3]-Wittig rearrangement, which was protected as the methoxyethoxymethyl (MEM) ether (20). Hydroboration followed by oxidative cleavage leading to 21 found issues with regioselectivity from 1, typically giving a mix with 22. In an effort to increase the regioselectivity of the latter steps, 18 was derivatized with isobutyl bromide, giving 23. Under the same sequence of reduction and protection as prior, the authors were able to generate 24. Further elaboration through their conditions for Still’s [2,3]-Wittig rearrangement and hydroboration/oxidation sequence found better regioselectivity for the resulting ketone. Photolysis was attempted, and found to give the improper stereochemistry, thus prompting epimerization with NaOCH₃. The epimerized product gave the desired cycloadduct, which was then deprotected and oxidized to yield 25. Further steps led to punctatins A and D.
Until this point, Hajos and Parrish’s work for generating the trans-hydrindane was used as a standard methodology, with little further development on the reduction of the enone moiety. In 1988, the use of DIBAL-H with tert-butyllcopper was found to selectively and in good yield reduce the enone to the trans-hydrindane (see Scheme 5) [21]. In 2001, this was investigated again using silyl copper systems, finding that phenyldimethylsilylcopper is more efficient at producing the trans-hydrindane [22]. A separate method for introducing the trans-ring juncture came from 26 [23]. Then, transformation of 26 through hydroboration/oxidation to ketone 27, then trapping of the HMDS generated enolate with TMS-I allowed for treatment of the enol ether with PhSeCl, and subsequent oxidation by mCPBA afforded enone 28. Luche reduction with NaBH₄/CeCl₃ comes from the β-face of the hydrindane, and the resulting alcohol acts as a directing group for reduction with Wilkinson’s catalyst to give trans-hydrindane 29. The authors note here that Crabtree’s catalyst for this system leads to the cis isomer [23].

Hydrindane 1 again found use in the total synthesis of austalides, meroterpenoids from Aspergillus ustus (see Scheme 6) [24, 25]. In this work, protection of 1 followed by Birch reduction in the presence of MeI gave 30, which was then treated with acid and 4-chlorobutan-2-one to give 31 as a single diastereomer. Polymethylation under the action of MeI in tert-BuOK/tert-BuOH afforded the dimethylated system 32. Dihydroxylation with OsO₄/NMO, and protection with SEM-Cl gave 33.
Baeyer–Villiger oxidation with mCPBA was found to occur in the A ring first, and allowed for trapping of the ortho-ester with Me\(_3\)O\(^+\) BF\(_4\)\(^-\) to afford 34, after a second Baeyer–Villiger. Further steps finalized the synthesis of austalide B.

Scheme 6. Synthesis of austalide B core from 1.

Terpene and terpenoid derivatives are well known to hold significant bioactivity, thus it should be no surprise that the bicyclo[4.3.0]nonane scaffold should also possess some selectivity relevant for medical applications. Indeed, this is true, and more surprisingly, selectivity in some cases is driven by substitution of the hydrindane [10,11,26,27]. Progesterone analogues were discovered to inhibit angiogenesis in conjunction with heparin (see Scheme 7) [11]. Here, it was found that the C-17 α-hydroxy functionality was important for the anti-angiogenic activity. Even when using the hydrindane moiety alone, it was found that the anti-angiogenic activity was retained. In this work, trans-6 was protected as dithiane, and oxidized via Swern’s conditions to give 35. Cyanohydrin formation led to attack on the β face, giving 36. Transformation of the cyanide into methyl ketone 37, followed by complete removal of the dithiane with Raney nickel and reoxidation led to structural derivatives of the progesterone C/D rings. Vitamin D\(_3\) analogues have also been utilized in structure-activity relationship (SAR) studies [28]. Hydrindane 1 was protected as the dithiane, 40, then olefinated through Horner–Wadsworth–Emmons conditions to give α,β-unsaturated ester 41. Tandem reduction steps led to the removal of the dithiane and conjugated alkene, leaving the isolated alkene untouched (42). Hydroboration/oxidation led to β-hydroxy 43, and further transformed into the Inhoffen–Lythgoe diol, 44. Later, formulation of an ethenyl substitution for application to (+)-estradiol was found to be higher yielding than the previous sequence [29]. Following previously published conditions, this work took 1 on to form 45, and further into 46. Enolate formation with LHMDS and trapping with N-phenyltriflimide led to the enol triflate precursor for Stille coupling with vinyl tributylstannane, generating 47. Isolated 47 was proposed as a short sequence leading to Diels–Alder diene precursors primed for formation of triterpene and triterpenoid B rings.

Solanopyrones, potent inhibitors of DNA polymerase β and λ, have been synthesized utilizing a Beckmann fragmentation of the hydrindane core to reveal the proper stereochemistry necessary for the pyranone moiety (see Scheme 8) [30]. Under known conditions, 1 was transformed into 48, and deprotected to reveal the hydroxyl 49. Protection with concomitant reduction of the α,β-unsaturated ketone led to 50, which was oxidized and transformed into oxime 51. Beckmann fragmentation followed by deprotection of the dioxolane led to 52 as the desired intermediate.

As another approach to the vitamin D\(_3\) hydrindane intermediate, an approach utilizing the α,β-unsaturated ketone as a directing group was explored in two accounts (see Scheme 9) [31,32]. Luche reduction of the ketone, 5, with NaBH\(_4\)/CeCl\(_3\) afforded the allylic alcohol with good diastereoselectivity, giving 53 [31]. Upon epoxidation with mCPBA (54), and reduction with Hutchin’s conditions of NaBH\(_3\)CN–BF\(_3\)·OEt\(_2\), the trans-hydrindanediol 55 was produced. Further reaction
with thionocarbonyl diimidazole (TCDI), methyl iodide, and reduction by LAH allowed for selective reduction of the less hindered side of the diol to afford the trans-hydridanol 56. In a subsequent account [32], Wicha showed that acylation with Ac₂O of 55 along with selective removal of the less hindered ester by K₂CO₃ gave 57, which was treated with TCDI and reduced with Bu₃SnH/AIBN to afford 58 in six steps with an overall yield of 63% from 5.

Scheme 7. Derivatizations of 1 and trans-6 for SAR studies.

1 found use in the synthesis of the methyl ester of globostellatic acid X, a selective inhibitor of human endothelial umbilical vein cell proliferation (see Scheme 10) [33]. Treatment of 1 with tert-butyllcopper and DIBAL-H in HMPA/THF at −78 °C allowed for the generation of trans-6, which was protected as the dioxolane and then olefinated with ethyl 2,2-dibromopropanoate/tert-butyllithium. Quenching the reaction mixture with MeI afforded 59. Reduction/oxidation using DIBAL-H followed by Swern’s conditions for oxidation provided α,β-unsaturated aldehyde 60, which was transformed...
into the alkenyl iodide 61 through the action of iodoform and chromium (II) chloride followed by oxidation with CrO3. Acidic deprotection of the dioxolane, and Stille coupling with 62 led to globostellatic acid derivative 63 which were used for SAR studies.

Scheme 9. Rapid entry to calcitriol (vitamin D₃) hydridane.

Scheme 10. Globostellatic acid SAR derivative synthesis.

Cortistatins, belonging to the triterpene alkaloids class, pose a particular synthetic challenge. Recent routes have been attempted, with two being successful (see Scheme 11) [34–36]. In 2008, Hirama proposed using 1 to undergo a Knovenagel condensation/electrocyclization/radical cyclization strategy to afford cortistatin A—the most potent cortistatin [34]. Hydridane 1 was transformed into 64 by NaBH₄ reduction, protection of the alcohol with TBS-Cl, and alkylation. Reduction of 64 with NaBH₄/NiCl₂ allowed for production of the trans-hydridane 65, and further treated with HMDS in the presence of TMS-Cl and NaI to afford the trimethylsilyl enol which was oxidized to α,β-unsaturated ketone 66. Triflation and palladium catalyzed carbonylation in methanol afforded ester 67, which underwent reduction with DIBAL-H and oxidation with DMP to afford aldehyde 68. Knovenagel condensation of 68 with 1,3-cyclohexanedione afforded 69, which was able to be turned into key intermediate 70 for cortistatins in relatively few steps. Sorensen also put forth an approach to the cortistatin framework utilizing 1 and envisioned phenolic oxidation to form the furan bicyclic fusion [35]. Hydridane 1 was transformed into the TBS ether, 71, and reacted with methyl magnesium carbonate. A series of hydrogenation with Pd/BaSO₄ yielded the trans-hydridane, which was exposed to Eschenmoser’s salt to afford the exocyclic alkene with loss of CO₂. Under thermal conditions, 1,3-dipolar cycloaddition with the nitrone led to the formation of 1,2-isooxazolidine, 72. Triffilation of the ketone followed by palladium catalyzed carbonylation led to a methyl ester. A short sequence led to pendant alcohol system 73, which was oxidized to allow for formation of the spiro-tetrahydrofuran moiety through phenolic oxidation. Nicolau also proposed a route to the eastern portion of cortistatin A, using 1 [36].
Cyathane and cyanthiwigin diterpenoids have also been synthesized via 1 through a parallel kinetic resolution strategy (see Scheme 12) [37]. Hydrindane 1 was transformed into the MOM ether 75 through reduction and protection. Further transformation by Rubottom oxidation conditions and protection of the resulting alcohol with TBS-Cl, allowed for hydrogenation with Adam’s catalyst to give the formation of 76. Triflation and Stille coupling gave the dienol 77, which went exposed to Simmons–Smith cyclopropanation yielded the vinylcyclopropane 78. Swern oxidation and Wittig olefination led to the cycloheptadiene scaffold, 79, via a Cope rearrangement.

Xenibellol, another diterpenoid found to be cytotoxic to P-388 cells, has been synthesized from 1 (see Scheme 13) [38]. Reduction and protection led to TBS ether 80. Treatment with MMC and LAH reduction led to a diol, which was selectively protected as the MOM ether to generate 81. Formation of the SEM ether allowed for 2,3-Wittig rearrangement with n-BuLi to give 82. Tosylation, followed by TBAF deprotection and etherification led to the advanced intermediate 83.
A methanol moiety was installed via paraformaldehyde/boron trifluoride, then oxidized to reveal the aldehyde. Grignard addition with isobutylmagnesium bromide and reoxidation generated intermediate for OSW-1. Deprotection, followed by reduction and protection led to the formation of the desired trans-hydrindane core, for OSW-1.

In the last decade, other modifications to hydridane cores have been explored. In the synthesis of dictyoxetane’s hydrindane, ent-1 was transformed into 84, then dihydroxylated with OsO₄/NMO to give a diol (see Scheme 14) [39]. Here the authors found a unique method for formation of the trans-hydrindane core by treating the diol with PPh₃, C₂Cl₆, and Hunig’s base in acetonitrile to afford 85. Putatively, the transient phosphinite ether, undergoes pinacol rearrangement to yield the desired hydridane. Similarly, a unified approach to trans-hydrindanes common to an array of sesterterpenoids was put forth by Trauner [40]. In this work, 1 was transformed into the tert-butyl ether, then further into the trans-hydrindane, along the path outlined by Hajos and Parrish. Protection of the ketone, and removal of the tert-butyl ether followed by oxidation allowed for a ketone to be established for subsequent installation of the α,β-unsaturated system, 87. Cuprate addition led to formation of 88, which holds the appropriate substitution for further synthesis of natural products. This unified approach was later shown in the synthesis of (+)-nitidasin [41].

OSW-1, a steroidal glycoside, has been found to possess potent anti-cancer effects (see Scheme 15) [42]. The des-AB aglycone have been also found to possess potent inhibitory effects. Hydridane 1 was reduced with DIBAL/tert-butylcopper, then protected as the dioxolane, and olefinated to give 89. Deprotection, followed by reduction and protection led to the TBS ether, 90. A methanol moiety was installed via paraformaldehyde/boron trifluoride, then oxidized to reveal the aldehyde. Grignard addition with isobutylmagnesium bromide and reoxidation generated intermediate 91. Under acidic deprotection, removal of the TBS group was found along with production of the dioxolane, which was protected with TBS-OTf to form the desired product. A sequence of dihydroxylation, oxidation, and reduction led to the formation of the desired trans-hydrindane core, for OSW-1.
1 has also been transformed into the core of shiartane type 1 nortriterpenoids (see Scheme 16) [43]. Utilizing the known transformation to 80, sodium hydride and bromide 93 were used to generate scaffold 94. LAH reduction followed by hydroxy directed epoxidation with mCPBA led to a chiral epoxide, which was further oxidized with IBX to give 95. Wacker-Tsuji oxidation gave a diketone, which allowed for cyclization with L-proline to afford 96. Grignard addition of vinylmagnesium bromide followed by cross metathesis with methyl acrylate allowed for elaboration of the western portion of the shiartane scaffold. Further reduction and esterification completed the western portion, giving 97.

Scheme 16. Synthesis of shiartane scaffold from 80.

The work done with 1 has provided a great benefit to total synthesis, but is not without its limitations. As shown, the trans-hydrindane, trans-6, is complicated by the open β-face of 5, giving a more facile reduction to lead to the cis-isomer. Above, the published results have shown that reactions are available to circumvent this preferred pathway, while allowing for further elaboration of the core structures necessary for the desired target. However, the length of these sequences can be deleterious to yield, and thus other methods have been explored for more rapid, efficient, and higher yielding syntheses. These reactions are presented below.

2.2. Cyclization Strategies to Hydrindane Cores

As functionalization of 1 often requires lengthy steps with protection and deprotection steps in order to achieve selective reaction, as well as having problems directly accessing a trans-hydrindane scaffold. A common strategy for negating the deleterious effect of the fused 6,5-bicyclic structure is to directly form it in a single step through cycloaddition methodology; Diels-Alder reactions, metathesis reactions, and Michael additions.

The Diels-Alder reaction, which has been reviewed extensively [44–48], provides a systematic way of introducing contiguous stereocenters with relative ease. One of the main advantages of the Diels-Alder cycloaddition is the overall understanding of its reactivity, selectivity, and methods for
chiral induction. Using vinylallene sulfoxides in the synthesis of sterpurene [49,50], chiral alcohol 99 was coupled to cyclobutenyl iodide 98, then transformed into intermediate 101 through the action of PhSCI (see Scheme 17). This intermediate underwent a facile cyclization to afford the desired core, and after treatment with MeMgBr/Ni(dppp)Cl and Na/NH₃, sterpurene (103) was isolated. A second example of the intramolecular Diels-Alder is the use of chiral 1,3-butadiene-2-carboxylates bearing a pendant chiral modifier [51]. Here, when using oxazolidinone 104, 105 was obtained in good yield with high diastereoselectivity (ca. 17:1). Likewise, advanced intermediate 108 was proposed from the combination of iodide 106 and alkyne 107 after coupling, Lindlar reduction, and cycloaddition [52]. Of note, the chromium carbene 110 can also be used to simultaneously form B and C rings in steroidal systems when treated with 109. [53] Similar methodology was applied to the synthesis of galliellalactone, which inhibits IL-6 signaling implicated in oncogenic pathways [54].

Scheme 17. Cycloaddition strategy to hydrindane scaffolds.
A benefit to the Diels-Alder is that it requires so little to effect cyclization, and can be used in combination with other reactions (see Scheme 18). An approach to the bakkane skeleton through successive alkylations of dimethylmalonate led to Diels-Alder precursor 112, which provided a cis-hydridane 113 for further elaboration [55,56]. More recent work has expounded upon this route to utilize 118 and α,β-unsaturated aldehydes to provide adducts similar in nature to 114, and has been applied to the synthesis of nootakone [57]. In addition to these ideas, a diene can be generated through photoenolization of benzaldehyde derivatives [58]. This idea has been applied to the hamigeran series, where an advanced intermediate 121 was exposed to light to catalyze the photoenolization and allowed to undergo resulting cycloaddition to 122. A Diels-Alder/carbocyclization has also been shown to give cis-hydridane products through the action of zinc salts [59]. Here, dieneyne 123 reacts with acrolein to undergo a primary Diels-Alder, and spontaneously cyclizes to hydrindane 124. Across a range of substrates, up to 96% yield was obtained with excellent diastereoselectivities (ca. 17:1).

![Scheme 18. Diels-Alder cascades for hydrindane synthesis.](image)

The use of the intramolecular Diels-Alder in natural product synthesis has been found valuable in the synthesis of polycyclic structures. Stork showed that naturally occurring cytochalasins were amenable to a targeted intramolecular Diels-Alder (see Scheme 19, 125 to 126) [60]. In 1989, Hudlicky approached the total synthesis of (−)-retigeranic acid with similar methodology [61]. In Hudlicky’s synthesis, 127 was converted through the intramolecular Diels-Alder to a set of regioisomers, 128. Five steps resolved the regioisomeric mixture into the desired natural product, 129. Uenishi later followed by generating the requisite [4+2] diene–dienophile pair, 130 and 131, through nickel–chromium catalyzed bond formation to give intermediate 132 that spontaneously cyclized to 133 for the synthesis of ircinianin and wistarin [62]. Evans and Johnson in the same year utilized a chiral copper reagent to effect an efficient intramolecular Diels-Alder cycloaddition to afford trans-hydridane 135 in 91% from 134 for use in the synthesis of (−)-isopulo’upone [63].
Sorenson in 2002 utilized a set of tandem intramolecular Diels-Alder reactions for (+)-FR182877 (see Scheme 20) [64]. In this work, the tetrene 136 was synthesized, then went through a macrocyclization reaction under the action of Pd2dba3. A subsequent sequence of five reactions following the proposed biosynthetic route led to completion of the molecule. Heckrodt in 2003 showed a similar intramolecular Diels-Alder inspired by biomimetic conditions of elisabethinin A [65]. Here, the authors built aryl triene 138, and the sequence of deprotection via TBAF and phenolic oxidation of FeCl3 allowed for generation of an intermediate benzoquinone that underwent spontaneous trapping with the pendant diene to afford the final product in 91%.

Scheme 19. Utilization of intramolecular Diels-Alder reactions in natural product synthesis.

Scheme 20. Synthesis of (+)-FR182877 and elisabethinin A.
Shiina and Nishiyama applied the intramolecular Diels-Alder to deriving tricyclic derivatives of the trans-hydrindane core (see Scheme 21) [66]. Tethered diene 141 under sealed tube conditions in toluene led to the tricyclic core 142, which was later utilized as derivative 143 in the racemic synthesis of chloroscephone (145) and isochiloscyphone [67]. Akai et al. showed that lipase resolution allowed for tandem dynamic kinetic resolution of racemic alcohols, 146. Subsequent trapping with an intramolecular Diels-Alder reaction led to the formation of complex tricycles with four contiguous stereocenters set with high levels of enantioinduction [68].

Scheme 21. Examples of intramolecular Diels-Alder reactions leading to tricyclic cores.

Other notable examples of intramolecular Diels-Alder reactions that are able to form hydrindane cores have appeared in the literature, but have yet to show direct use (see Scheme 22). Sorensen utilized polyene 149 in a route toward the synthesis of abyssomicin C, ultimately forming the spiro[6.5] ring juncture through an intramolecular Diels-Alder reaction [69]. Crimmins and Brown utilized an approach with 151 as an intermediate to synthesize ophirin B [70]. Lastly, Stoltz applied an intramolecular Diels-Alder utilizing pyrone 153 as a key intermediate in the progress to basiliolides and transtaganolides [71].

Scheme 22. Intramolecular Diels-Alders potentially applicable to hydrindane synthesis.
Metathesis as a cyclization tactic has become a notable method for ring forming reactions. The use of Grubbs or Grubbs–Hoveyda catalysts has often been the choice of catalyst used for these reactions, and their involvement in the synthesis of hydrindanes has become documented (see Scheme 23) [72,73]. Bicyclo[2.2.2]octenes are useful substrates for these reactions because they are readily synthesized from Diels-Alder cycloadditions, and can be utilized to give hydrindane scaffolds with a variety of functionalizations. Derivative 155 was derivatized with vinylmagnesium bromide and then exposed to Grubbs second generation catalyst to yield hydrindane 157 in 93% [74]. Later explorations led to the derivative 159 to undergo ROM/RCM cleavage to give alkenyl substituted hydrindane 160 [75]. Dialdehyde 161 was transformed into 162 and exposed to Grubbs second generation to give [7.6.5]tricycle 163 [76]. Enyne metathesis coupled to Diels-Alder cycloaddition has also been applied to this type of methodology [77]. Further, a sequential ring closing metathesis followed by Heck coupling was shown in 2010, giving a trans-hydrindane core for the C/D ring juncture [78]. This methodology has been applied to the synthesis of norrisolide [79].

![Scheme 23. Metathesis strategies for hydrindane formation.](image)

Enyne metathesis has found an increasing interest in the synthesis of natural products (see Scheme 24) [80–84]. It has found significant use in the synthesis of larger ring systems [85–89] and heterocyclic systems [90–95], but only occasionally in the synthesis of hydrindanes [96–99]. Palladium, platinum, gold, and ruthenium have been found to be the catalysts of choice for this class of reactions. Grubbs has shown that his catalyst was able to efficiently form triterpenoid system 165 from 164 [100]. Cyclohexenyl system 166 forms hydrindone 167 when exposed to triphenylphosphinegold triflate in modest yield [98]. Dienyne 168 has been shown on three accounts to form substituted hydrindadiene 169 in good yields utilizing gold catalysts [86,87,91]. Cyclopentane system 170 under the action of Grubbs I allowed for hydrindane 171 to be formed [97].

![Scheme 24. Enyne metathesis reactions leading to hydrindane cores.](image)
Cycloaddition and metathesis reactions give rapid entry into the hydrindane core, but are not the only pathway available to their synthesis. Along with Michael additions, as in the synthesis of 1, Morita–Baylis–Hillman reactions and radical reactions can be used to form the bicyclic core (see Scheme 25). Their use, however, does add to a sequence’s number of steps in order to judiciously choose substrates that provide the desired stereochemical outcome. Oxidation of the trimethylsilyl ether 172 with mCPBA affords the Rubottom product, 173 [101]. Further oxidation by lead tetraacetate and Horner–Wadsworth–Emmons olefination led to ketoester 174. A reduction-oxidation sequence to garner the requisite dialdehyde ultimately provided trans-hydrindene 175 after treatment with sodium methoxide in methanol. Similarly, utilization of cyclopentanone 176 with ketone 177 led to formation of hydrindene 178 in 78% [102]. Other examples have appeared in the literature [103–106].

In a similar vein as the Michael additions, the Morita–Bayliss–Hillman under phosphine or transition metal catalysis has been shown to provide similar results to Michael addition strategies (see Scheme 26). Using enyne 179 with tri-n-butylphosphine, cis-hydrindane 180 was generated [107]. Likewise, the cis-hydrindane 182 was found to be formed from a full equivalent of tri-n-butylphosphine with triketone 181 [108]. Lastly, the titanium variant of the Morita–Bayliss–Hillman using 181 gives 182, stemming from the thermodynamic Z-titanium enolate that forms as an intermediate [109].

3. Summary and Outlook

Here, we have presented methodology that has been used for the production of the hydrindane core. The difficulty associated in the generation of this scaffold lies not in the difficulty of the reactions leading to the core, but rather lies in the thermodynamic nature of the cis-hydrindane core’s stability. This has been alleviated through judicious choice of substrates, either through derivatization to change thermodynamic stability or through development of scaffolds prone to react in the desired
manner. With the propensity of natural products bearing this moiety, it becomes necessary to discuss the synthesis of the hydrindane because of its inherent bioactivity (vide supra) and the number of stereocenters distributed over the scaffold. Thus, the hydrindane motif serves a dual purpose: (1) a synthetic challenge; and (2) a lead compound for drug development. As shown in this review, there has been a large volume of work done representing a broad range of reactions and elaborations of the hydrindane nucleus that greatly benefit natural product synthesis, as well as medicinal chemistry.

Acknowledgments: The authors would like to thank Christian Brueckner (UConn) for his support with this manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

References
1. Jankowski, P.; Marczak, S.; Wicha, J. Methods for the construction of trans-hydrindane rings and their origins in steroid chemistry. Vitamin D total synthesis. Tetrahedron 1998, 54, 12071–12150.
2. Hong, B.-C.; Sarshar, S. Recent advances in the synthesis of indan systems: A review. Org. Prep. Proced. Int. 1999, 31, 1–86. [CrossRef]
3. Chapelon, A.-S.; Moraleda, D.; Rodriguez, R.; Ollivier, C.; Santelli, M. Enantioselective synthesis of steroids. Tetrahedron 2007, 2007, 11511–11616. [CrossRef]
4. Xu, X.-M.; Guan, Y.-Z.; Shi, H.-L.; Wang, X.-L.; Zou, L.-Y. Withaphysalin-type withanolides from Physalis minima. Phytochem. Lett. 2016, 15, 1–6. [CrossRef]
5. Xiang, L.; Wang, Y.; Yi, X.; Feng, J.; He, X. Furopsisterol and spirostanol saponins from the rhizome of Tupistra chinesis and their cytotoxic and anti-inflammatory activities. Tetrahedron 2016, 72, 134–141.
6. Srivastava, P.K.; Gupta, M.R.; Khare, N.K. Two novel steroidal derivatives from chloroform-soluble extract of hoya longifolia. Nat. Prod. Res. 2016, 30, 199–205. [CrossRef] [PubMed]
7. Yan, Y.-X.; Lin, J.-Q.; Wang, H.-W.; Chen, J.-X.; Chen, J.-C.; Chen, L.; Zhou, L.; Qiu, M.-H. Identification and antifeedant activities of limonoids from azadirachta indica. Chem. Biodivers. 2015, 12, 1040–1046. [CrossRef] [PubMed]
8. Ling, Y.; Fu, Z.; Zhang, Q.; Xu, L.; Liao, L. Identification and structural elucidation of steroidal saponins from the root of Paris polyphylla by HPLC-ESI-QTOF-MS/MS. Nat. Prod. Res. 2015, 29, 1798–1803. [CrossRef] [PubMed]
9. Li, K.-L.; Zhang, P.; Li, X.-N.; Guo, J.; Hu, H.-B.; Xiao, C.-F.; Xie, X.-Q.; Xu, Y.-K. Cyotoxic limonoids from Trichilia americana leaves. Phytochemistry 2015, 118, 61–67.
10. Sevillano, L.G.; Melero, C.P.; Boya, M.; Lopez, J.L.; Tome, F.; Caballero, E.; Carron, R.; Montero, M.J.; Medarde, M.; San Feliciano, A. Synthesis an inotropic activity of hydrindene derivatives. Bioorg. Med. Chem. 1999, 7, 2991–3001. [CrossRef]
11. Schweiger, E.J.; Joullie, M.M.; Weiss, P.B. Synthesis of a C,D-ring analog of 17-a-hydroxyprogesterone. Tetrahedron Lett. 1997, 38, 6127–6130. [CrossRef]
12. Shan, X.-Q.; Peng, S.-L.; Shi, H.-L.; Wang, X.-L.; Ding, L.-S.; Liao, X. Panthogensins A and B, two novel norergostanol steroids from Dioscorea panthaica. Chin. Chem. Lett. 2014, 25, 1256–1258. [CrossRef]
13. Wang, Z.-B.; Zhai, Y.-D.; Ma, Z.-P.; Yang, C.-J.; Pan, R.; Yu, J.-L.; Wang, Q.-H.; Yang, B.-Y.; Kuang, H.-X. Triterpenoids and Flavonoids from the leaves of astragalus membranaceus and their inhibitory effects on nitric oxide production. Chem. Biodivers. 2015, 12, 1575–1574. [CrossRef] [PubMed]
14. Hu, Z.-X.; Shi, Y.-M.; Wang, W.-G.; Li, X.-N.; Du, X.; Liu, M.; Li, Y.; Xue, Y.-B.; Zhang, Y.-H.; Pu, J.-X.; et al. Kadcoccinones A–F, new biogenetically related lanostane-type triterpenoids with diverse skeletons from kadsura coccinea. Org. Lett. 2015, 17, 4616–4619. [CrossRef] [PubMed]
15. Hajos, Z.G.; Parrish, D.R. Asymmetric synthesis of bicyclic intermediates of natural product chemistry. J. Org. Chem. 1974, 39, 1615–1621. [CrossRef]
16. Micheli, R.A.; Hajos, Z.G.; Cohen, N.; Parrish, D.R.; Portland, L.A.; Sciamanna, W.; Scott, M.A.; Wehrli, P.A. Total synthesis of optically active 19-norsteroids. (+)-Estr-4-ene-3,17-dione and (+)-13b-ethylgon-4-ene-3,17-dione. J. Org. Chem. 1974, 40, 675–681. [CrossRef]
17. Hajos, Z.G.; Parrish, D.R. The stereocontrolled synthesis of trans-hydrindan steroidal intermediates. J. Org. Chem. 1973, 38, 3239–3243. [CrossRef] [PubMed]

18. Bernasconi, S.; Ferrari, M.; Gariboldi, P.; Jommi, G.; Sisti, M.; Destro, R. Synthetic study of pinguisane terpenoids. J. Chem. Soc. Perkin Trans. 1 1981. [CrossRef]

19. Nassim, B.; Schlemper, E.O.; Crabbe, P. Total synthesis of dinordrin and analogues. J. Chem. Soc. Perkin Trans. 1 1983. [CrossRef]

20. Paquette, L.A.; Sugimura, T. Enantiospecific total synthesis and absolute configurational assignment of (−)-punctatin A (antibiotic M95464). J. Am. Chem. Soc. 1986, 108, 3841–3842. [CrossRef]

21. Daniewski, A.R.; Liu, W. A novel silyl-copper catalyst for the reduction bromination of Hajos dione. Improved preparation of a CD synthon for the synthesis of vitamin D. J. Org. Chem. 2001, 66, 626–628. [CrossRef]

22. Daniewski, A.R.; Liu, W. A novel silyl-copper catalyst for the reduction bromination of Hajos dione. Improved preparation of a CD synthon for the synthesis of vitamin D. J. Org. Chem. 2001, 66, 626–628. [CrossRef]

23. Fernandez, B.; Perez, J.A.M.; Granja, J.R.; Castedo, L.; Mourino, A. Synthesis of hydrindan derivatives related to vitamin D. J. Org. Chem. 1992, 57, 3173–3178. [CrossRef]

24. Paquette, L.A.; Wang, T.-Z.; Sivik, M.R. Enantioselective synthesis of natural (−)-austalide B, an unusual ortho ester metabolite produced by toxigenic cultures of aspergillus ustus. J. Am. Chem. Soc. 1994, 116, 2665–2666. [CrossRef]

25. Lugar, C.W.; Magee, D.; Adrian, M.D.; Shetler, P.; Bryant, H.U.; Dodge, J.A. B-ring unsaturated estrogens: Biological evaluation of 17α-dihydroequilenin and novel b-nor-6-thiaequilenins as tissue selective estrogens. Bioorg. Med. Chem. Lett. 2003, 13, 4281–4284. [CrossRef] [PubMed]

26. Wright, J.S.; Sadnia, H.; Anderson, J.M.; Durst, T.; Asim, M.; El-Salfiti, M.; Choueiri, C.; Pratt, M.A.C.; Ruddy, S.C.; Lau, R.; et al. A-CD estrogens. I. Substituent effects, hormone, potency, and receptor subtype selectivity in a new family of flexible estrogenic compounds. J. Med. Chem. 2011, 54, 433–448. [CrossRef] [PubMed]

27. Van Gool, M.; Zhao, X.; Sabbe, K.; Vandewalle, M. Synthesis of 14,20-bis-epi-1α,25-dihydroxy-19-norvitamin D3 and analogues. Eur. J. Org. Chem. 1999, 1999, 2241–2248. [CrossRef]

28. Di Filippo, M.; Izzo, I.; Vece, A.; De Riccardis, F.; Sodano, G. Enantioselective synthesis of a trans-ethenyl-hydrindene, a useful steroid CD-ring diene precursor. Tetrahedron Lett. 2001, 42, 1155–1157. [CrossRef]

29. Shi, H. Facile method for stereoselective synthesis of new chiral (1R,4aR,8aR)-trans-3,5,7,8,9,10-hexahydro-3-methylene-naphthalene-6-one, an important precursor for solanapyrones. Synth. Commun. 2006, 36, 237–248. [CrossRef]

30. Chochrek, P.; Wicha, J. A new expedited approach to a vitamin D ring C/D building block from the Hajos dione, involving epoxide opening at the more substituted carbon atom. Tetrahedron Lett. 2006, 47, 6017–6020. [CrossRef]

31. Kotoku, N.; Tamada, N.; Hayashi, A.; Kobayashi, M. Synthesis of BC-ring model of globostellatic acid X methyl ester, an anti-angiogenic substance from marine sponge. Bioorg. Med. Chem. Lett. 2008, 18, 3532–3535. [CrossRef] [PubMed]
37. Miller, L.C.; Ndungu, J.M.; Sarpong, R. Parallel kinetic resolution approach to the cyathane and cyanthiwigin diterpenes using a cyclopropanation/Cope rearrangement. *Angew. Chem. Int. Ed.* 2008, 48, 2398–2402. [CrossRef] [PubMed]

38. Kim, W.H.; Angeles, A.R.; Lee, J.H.; Danishefsky, S.J. Concise synthesis of the xenibellols core. *Tetrahedron Lett.* 2009, 50, 6440–6441. [CrossRef] [PubMed]

39. Defaut, B.; Parsons, T.B.; Spencer, N.; Male, L.; Kariuki, B.M.; Grainger, R.S. Synthesis of the trans-hydrindane core of dictyoxetane. *Org. Biomol. Chem.* 2012, 10, 4926–4932. [CrossRef] [PubMed]

40. Hog, D.T.; Mayer, P.; Trauner, D. A unified approach to trans-hydrindane sesterterpenoids. *J. Org. Chem.* 2012, 77, 5838–5843. [CrossRef] [PubMed]

41. Hog, D.T.; Huber, F.M.E.; Jimenez-Oses, G.; Mayer, P.; Houk, K.N.; Trauner, D. Evolution of a unified strategy for complex sesterterpenoids: Progress toward astellatol and the total synthesis of (−)-nitidasin. *Chem. Eur. J.* 2015, 21, 13646–13665. [CrossRef] [PubMed]

42. Minato, D.; Li, B.; Zhou, D.; Shigeta, Y.; Toyooka, N.; Sakurai, H.; Sugimoto, K.; Nemoto, H.; Matsuya, Y. Synthesis and antitumor activity of des-AB analogue of steroidal saponin OSW-1. *Tetrahedron* 2013, 69, 8019–8024. [CrossRef]

43. Mehta, G.; Yaragorla, S. A concise, enantiospecific, Hajos–Parrish ketone based model approach toward the tetracyclic core of complex shiartane-type nortriterpenoid natural products. *Tetrahedron Lett.* 2013, 54, 549–552. [CrossRef]

44. Fallis, A.G. The intramolecular Diels-Alder reaction: Recent advances and synthetic applications. *Can. J. Chem.* 1984, 62, 183–234. [CrossRef]

45. Takao, K.; Munakata, R.; Tadano, K. Recent advances in natural product synthesis by using intramolecular Diels-Alder reactions. *Chem. Rev.* 2005, 105, 4779–4807. [CrossRef] [PubMed]

46. Bear, B.R.; Sparks, S.M.; Shea, K.J. The type 2 intramolecular Diels-Alder reaction: Synthesis and chemistry of bridgehead alkenes. *Angew. Chem. Int. Ed.* 2001, 40, 820–849. [CrossRef]

47. Juhl, M.; Tanner, D. Recent applications of intramolecular Diels-Alder reactions to natural products. *Chem. Soc. Rev.* 2009, 38, 2983–2992. [CrossRef] [PubMed]

48. Reber, K.P.; Tilley, S.D.; Sorenson, E.J. Bond formations by intermolecular and intramolecular trappings of acetylketenes and their application to organic synthesis. *Chem. Soc. Rev.* 2009, 38, 3022–3034. [CrossRef] [PubMed]

49. Gibbs, R.A.; Okamura, W.H. A short enantioselective synthesis of (+)-sterpurene: Complete intramolecular transfer of central to axial to central chiral elements. *J. Am. Chem. Soc.* 1988, 110, 4062–4063. [CrossRef]

50. Gibbs, R.A.; Bartles, K.; Lee, R.W.K.; Okamura, W.H. An enantioselective central-axial-central chiral element transfer process leading to a concise synthesis of (+)-sterpurene: Intramolecular Diels-Alder reactions of vinylallene sulfoxides. *J. Am. Chem. Soc.* 1989, 111, 3717–3725. [CrossRef]

51. Urabe, H.; Kusaka, K.; Suzuki, D.; Sato, F. Chiral 1,3-butadiene-2-carboxylates for an efficient asymmetric Diels-Alder reaction. *Tetrahedron Lett.* 2002, 43, 285–289. [CrossRef]

52. Chang, J.; Paquette, L.A. Studies aimed at the total synthesis of the antitumor antibiotic cochleamycin A. An enantioselective biosynthesis-based pathway to the AB cyclic core. *Org. Lett.* 2002, 4, 253–256. [CrossRef] [PubMed]

53. Ghoriai, B.K.; Herrndon, J.W.; Lam, Y.-F. One-step convergent synthesis of the steroid ring system via the coupling of g,d-unsaturated Fischer carbene complexes with o-ethynylbenzaldehyde. *Org. Lett.* 2001, 3, 3535–3538. [CrossRef] [PubMed]

54. Hossain, M.F.; Yadav, R.N.; Mondal, S.; Jana, A.; Ghosh, S. Intramolecular Diels-Alder route to angularly oxygenated hydrindanes. Synthesis of the functionalized bicyclic skeleton present in galiellalactone. *Tetrahedron* 2013, 69, 7956–7963. [CrossRef]

55. Constantino, M.G.; de Oliveira, K.T.; Polo, E.C.; da Silva, G.V.J.; Brocksom, T.J. Core structure of eremophilanes and bakkanes through niobium catalyzed Diels-Alder reaction: Synthesis of (±/-)-bakkenolide. *A J. Org. Chem. 2006, 71*, 9880–9883. [CrossRef] [PubMed]

56. Back, T.G.; Nava-Salgado, V.O.; Payne, J.E. Synthesis of (±/-)-bakkenolide A and its C-7, C-10, and C-7,10 epimers by means of an intramolecular Diels-Alder reaction. *J. Org. Chem.* 2001, 66, 4361–4368. [CrossRef] [PubMed]
57. Handore, K.L.; Seetharamsingh, B.; Reddy, D.S. Ready access to functionally embellished cis-hydrindanes and cis-decalins: Protecting group-free total syntheses of (+/−)-nootkatone and (+/−)-noreremophilane. J. Org. Chem. 2013, 78, 8149–8154. [CrossRef] [PubMed]

58. Nicolau, K.C.; Gray, D.L.F.; Tae, J. Total synthesis of Hamigerans and analogues thereof. Photochemical generation and Diels-Alder trapping of hydroxy-o-quinodimethanes. J. Am. Chem. Soc. 2004, 126, 613–627. [CrossRef] [PubMed]

59. Han, Y.; Zhu, L.; Gao, Y.; Lee, C.-S. A highly convergent cascade cyclization to cis-hydrindanes with all-carbon quaternary centers and its application in the synthesis of the aglycon of dendronobiloside. A Org. Lett. 2011, 13, 588–591. [CrossRef] [PubMed]

60. Stork, G.; Nakamura, E. A simplified total synthesis of cytochalasins via an intramolecular Diels-Alder reaction. J. Am. Chem. Soc. 1983, 105, 5510–5512. [CrossRef]

61. Hudlicky, T.; Fleming, A.; Radesca, L. [2+3] and [3+4] Annulation of enones. Enantiocontrolled total synthesis of (−)-retigeranic acid. J. Am. Chem. Soc. 1989, 111, 6691–6707. [CrossRef]

62. Uenishi, J.; Kawahara, R.; Yonemitsu, O. Total synthesis of (−)-ircinianin and (+)-wistarin. J. Org. Chem. 1997, 62, 1691–1701. [CrossRef]

63. Evans, D.A.; Johnson, J.S. Chiral C2 symmetric Cu(II) complexes as catalysts for enantioselective intramolecular Diels-Alder reactions. Asymmetric synthesis of (−)-isopulo’upone. J. Org. Chem. 1997, 62, 786–787. [CrossRef]

64. Vosburg, D.A.; Vanderwal, C.D.; Sorenson, E.J. A synthesis of (+)-FR182877, featuring tandem transannular Diels-Alder reactions inspired by a postulated biogenesis. J. Am. Chem. Soc. 2002, 124, 4552–4553. [CrossRef] [PubMed]

65. Heckrodt, T.J.; Mulzer, J. Total synthesis of elisabethinin A: Intramolecular Diels-Alder reaction under biomimetic conditions. J. Am. Chem. Soc. 2003, 125, 4680–4681. [CrossRef] [PubMed]

66. Shiina, J.; Nishiyama, S. Intramolecular Diels-Alder reaction leading to tricyclic derivatives as intermediates of natural product synthesis. Tetrahedron 2003, 59, 6039–6044. [CrossRef]

67. Shiina, J.; Nishiyama, S. A new approach to the bicyclo[4.3.0] ring system of natural products from the liverwort: Total synthesis of (+/−)-chiloscyphone and (+/−)-isoschiloscyphone. Tetrahedron Lett. 2004, 45, 9033–9036. [CrossRef] [PubMed]

68. Akai, S.; Tanimoto, K.; Kita, Y. Lipase-catalyzed domino kinetic resolution of racemic 3-vinylcyclohex-2-en-1-ols/intramolecular Diels-Alder reaction: One-pot synthesis of optically active polysubstituted decalins. Angew. Chem. 2004, 116, 1431–1434. [CrossRef]

69. Zapf, C.W.; Harrison, B.A.; Drahil, C.; Sorenson, E.J. A Diels-Alder macrocyclization enables an efficient asymmetric synthesis of the antibacterial natural product abyssomicin C. Angew. Chem. 2005, 117, 6691–6695. [CrossRef]

70. Crimmins, M.T.; Brown, B.H. An intramolecular Diels-Alder approach to the eunicelins: Enantioselective total synthesis of ophirin B. J. Am. Chem. Soc. 2004, 126, 10264–10266. [CrossRef] [PubMed]

71. Nelson, H.M.; Stoltz, B.M. Progress toward the synthesis of the basiliolides and transtaganolides: An intramolecular pyrone Diels-Alder entry into a novel class of natural products. Org. Lett. 2008, 10, 25–28. [CrossRef] [PubMed]

72. Bose, S.; Ghosh, S. Olefin metathesis—Application in the synthesis of natural products and related organic compounds. Proc. Indian Nat. Sci. Acad. 2014, 80, 37–54. [CrossRef]

73. Kureeva, V.B.; Afonso, C.A.M. Synthesis of cyclopentitols by ring-closing approaches. Chem. Rev. 2009, 109, 6809–6857. [CrossRef] [PubMed]

74. Minger, T.L.; Phillips, A.J. Ring-opening-ring-closing metathesis of bicyclo[2.2.2]octenes: A novel synthesis of decalins and hydrindanes. Tetrahedron Lett. 2002, 43, 5357–5359. [CrossRef]

75. Holtyslaw, J.; Koreeda, M. A ring-rearrangement metathesis approach toward the synthesis of cyclopentane and cyclohexa[c]indene systems. Org. Lett. 2004, 6, 3719–3722. [CrossRef] [PubMed]

76. Pfeiffer, M.W.B.; Phillips, A.J. Total synthesis of (+)-cyanthiwigin U. J. Am. Chem. Soc. 2005, 127, 5334–5335. [CrossRef] [PubMed]

77. Ramharter, J.; Mulzer, J. Total synthesis of valerenic acid, a potent GABA receptor modulator. Org. Lett. 2009, 11, 1151–1153. [CrossRef] [PubMed]
78. Foucher, V.; Guizzardi, B.; Groen, M.B.; Light, M.; Linclau, B. A novel, versatile D → BCD steroid construction strategy, illustrated by the enantioselective total synthesis of estrone. Org. Lett. 2010, 12, 680–683. [CrossRef] [PubMed]

79. Granger, K.; Snapper, M.L. Concise synthesis of norrisolide. Eur. J. Org. Chem. 2012. [CrossRef]

80. Trost, B.M.; Krische, M.J. Transition metal catalyzed cycloisomerizations. Synlett 1998. [CrossRef]

81. Semeril, D.; Bruneau, C.; Dixneuf, P.H. Imidazolium and imidazolinium salts as carbene precursors or solvent for ruthenium catalyzed diene and enyne metathesis. Adv. Synth. Catal. 2002, 344, 585–595. [CrossRef]

82. Poulsen, C.S.; Madsen, R. Enyne metathesis catalyzed by ruthenium carbene complexes. Synthesis 2003. [CrossRef]

83. Diver, S.T.; Giessert, A.J. Enyne metathesis (enyne bond reorganization). Chem. Rev. 2004, 104, 1317–1382. [CrossRef] [PubMed]

84. Mori, M. Synthesis of natural products and related compounds using enyne metathesis. Adv. Synth. Catal. 2007, 349, 121–135. [CrossRef]

85. Hato, Y.; Oonishi, Y.; Yamamoto, Y.; Nakajima, K.; Sato, Y. Stereselective construction of spiro-fused tricyclic frameworks by sequential reaction of enynes, imines, and diazoalkenes with Rh(I) and Rh(II) catalysts. J. Org. Chem. 2016, 81, 7847–7854. [CrossRef] [PubMed]

86. Nieto-Oberhuber, C.; Perez-Galan, P.; Herrero-Gomez, E.; Lauterbach, T.; Rodriguez, C.; Lopez, S.; Bour, C.; Rosellon, A.; Cardenas, D.J.; Echavarren, A.M. Gold(I)-catalyzed intramolecular [4+2] cycloadditions of 1,3-enynes or alkenes: Scope and mechanism. J. Am. Chem. Soc. 2008, 130, 269–279. [CrossRef] [PubMed]

87. Trost, B.M.; Yanai, M.; Hoogsteen, K. A Pd-catalyzed [2+2] cycloaddition. Mechanism of a Pd-catalyzed enyne metathesis. J. Am. Chem. Soc. 1993, 115, 5294–5295. [CrossRef]

88. Monnier, F.; Bray, C.V.-L.; Castillo, D.; Aubert, V.; Derien, S.; Dixneuf, P.H.; Toupet, L.; Ienco, A.; Mealli, C. Selective ruthenium-catalyzed transformations of enynes with diazoalkanes into alkénylbicyclo[3.1.0]hexanes. J. Am. Chem. Soc. 2007, 129, 6037–6049. [CrossRef] [PubMed]

89. Ma, S.; Yu, S.; Gu, Z. Gold-catalyzed cyclization of enynes. Angew. Chem. Int. Ed. 2006, 45, 200–203. [CrossRef] [PubMed]

90. Mendez, M.; Munoz, M.P.; Nevada, C.; Cardenas, D.J.; Echavarren, A.M. Cyclizations of enynes catalyzed by PtCl₂ or other transition metal chlorides: Divergent reaction pathways. J. Am. Chem. Soc. 2001, 123, 10511–10520. [CrossRef] [PubMed]

91. Furstner, A.; Szillat, H.; Gabor, B.; Mynott, R. Platinum- and acid-catalyzed enyne metathesis reactions: Mechanistic studies and applications to the syntheses of streptorubin B and metacycloprodigiosin. J. Am. Chem. Soc. 1998, 120, 8305–8314. [CrossRef]

92. Kinoshita, A.; Mori, M. Remarkable effect of ethylene gas in the intramolecular enyne metathesis of terminal alkynes. J. Org. Chem. 1998, 63, 6082–6083. [CrossRef] [PubMed]

93. Kaliappan, K.P.; Panda, S.; Betkekar, V.V.; Gagosz, F. Phosphine gold(I)-bis-(trifluoromethanesulfonyl)iminate complexes as new highly efficient and air-stable catalysts for the cycloisomerization of enynes. Org. Lett. 2005, 7, 4133–4136. [CrossRef] [PubMed]

94. Mezailles, N.; Ricard, L.; Gagosz, F. Phosphine gold(I)-bis-(trifluoromethanesulfonyl)iminate complexes as new highly efficient and air-stable catalysts for the cycloisomerization of enynes. Org. Lett. 2005, 7, 4133–4136. [CrossRef] [PubMed]

95. Schramm, M.P.; Reddy, D.S.; Kozmin, S.A. Siloxyalkyne-alkene metathesis: Rapid access to highly functionalized enones. Angew. Chem. Int. Ed. 2001, 40, 4274–4277. [CrossRef]

96. Mezailles, N.; Ricard, L.; Gagosz, F. Phosphine gold(I)-bis-(trifluoromethanesulfonyl)iminate complexes as new highly efficient and air-stable catalysts for the cycloisomerization of enynes. Org. Lett. 2005, 7, 4133–4136. [CrossRef] [PubMed]

97. Betkekar, V.V.; Panda, S.; Kaliappan, K.P. A tandem enyne/ring closing metathesis approach to 4-methylene-2-cyclohexenols: An efficient entry to oteiliones and loloanolides. Org. Lett. 2012, 14, 193–201. [CrossRef] [PubMed]
100. Zuercher, W.J.; Scholl, M.; Grubbs, R.H. Ruthenium-catalyzed polycyclization reactions. *J. Org. Chem.* **1998**, *63*, 4291–4298. [CrossRef]

101. Stork, G.; Shiner, C.S.; Winkler, J.D. Stereochemical control of the internal Michael reaction. A new construction of trans-hydrindane systems. *J. Am. Chem. Soc.* **1982**, *104*, 310–312. [CrossRef]

102. Taber, D.F.; Malcolm, S.C. Synthesis of (−)-astrogorgiadiol. *J. Org. Chem.* **2001**, *66*, 944–953. [CrossRef] [PubMed]

103. Gorobets, E.; Stepanenko, V.; Wicha, J. Enantioselective total synthesis of a trans-hydrindane rings/side-chain building-block of vitamin D—Asymmetric induction an an acid-catalyzed conjugate-addition reaction. *Eur. J. Org. Chem.* **2004**. [CrossRef]

104. Danheiser, R.L.; Carini, D.J.; Basak, A. (Trimethylsilyl)cyclopentene annulation: A regiocontrolled approach to the synthesis of five-membered rings. *J. Am. Chem. Soc.* **1981**, *103*, 1604–1606. [CrossRef]

105. Fleming, F.F.; Vu, V.A.; Shook, B.C.; Rahman, M.; Steward, O.W. Metalated nitriles: Chelation-controlled cyclizations to cis and trans-hydrindanes and decalins. *J. Org. Chem.* **2007**, *72*, 1431–1436. [CrossRef] [PubMed]

106. Fleming, F.F.; Zhang, Z.; Wang, Q.; Steward, O.W. Cyclic alkenenitriles: Synthesis, conjugate addition, and stereoselective annulation. *J. Org. Chem.* **2003**, *68*, 7646–7650. [CrossRef] [PubMed]

107. Wilson, J.E.; Sun, J.; Fu, G.C. Stereoselective phosphine-catalyzed synthesis of highly functionalized diquinanes. *Angew. Chem. Int. Ed.* **2010**, *49*, 161–163. [CrossRef] [PubMed]

108. Wang, Y.; Jaunet, A.; Geoffroy, P.; Miesch, M. Phosphine-catalyzed reactions of activated olefins tethered to cycloalkanones. Substrate- and solvent-controlled synthesis of bicyclo[3.2.1]octanones, mixed acetals, and Morita-Baylis-Hillman products. *Org. Lett.* **2015**, *17*, 6198–6201. [CrossRef] [PubMed]

109. Ressault, B.; Jaunet, A.; Geoffroy, P.; Goudedranche, S.; Miesch, M. Access to polyfunctionalized diquinanes, hyrindanes, and decalines via TiCl4 promoted Michael-Aldol and Baylis-Hillman reactions. *Org. Lett.* **2012**, *14*, 366–369. [CrossRef] [PubMed]

© 2016 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC-BY) license (http://creativecommons.org/licenses/by/4.0/).