General Enantioselective and Stereochemically Divergent Four-Stage Approach to Fused Tetracyclic Terpenoid Systems

Joshua M. Nicholson[†],

Adam B. Millham[†],

Andrea R. Bucknam,

Lauren E. Markham,

Xenia Ivanna Sailors,

Glenn C. Micalizio

Department of Chemistry, Dartmouth College, Burke Laboratory, Hanover, New Hampshire 03755, United States

Abstract

Tetracyclic terpenoid-derived natural products are a broad class of medically relevant agents that include well-known steroid hormones and related structures, as well as more synthetically challenging congeners such as limonoids, cardenolides, lanostanes, and cucurbitanes, among others. These structurally related compound classes present synthetically disparate challenges based, in part, on the position and stereochemistry of the numerous quaternary carbon centers that are common to their tetracyclic skeletons. While de novo syntheses of such targets have been a topic of great interest for over 50 years, semisynthesis is often how synthetic variants of these natural products are explored as biologically relevant materials and how such agents are further matured as therapeutics. Here, focus was directed at establishing an efficient, stereoselective, and molecularly flexible de novo synthetic approach that could offer what semisynthetic approaches do not. In short, a unified strategy to access common molecular features of these natural product families is described that proceeds in four stages: (1) conversion of epichlorohydrin to stereodefined enynes, (2) metallacycle-mediated annulative cross-coupling to generate highly substituted hydrindanes, (3) tetracycle formation by stereoselective forging of the C9–C10 bond, and (4) group-selective oxidative rearrangement that repositions a quaternary center from C9 to C10. These studies have defined the structural features required for highly stereoselective C9–C10 bond formation and document the generality of this four-stage synthetic strategy to access a range of unique stereodefined systems, many of which bear stereochemistry/substitution/functionality not readily accessible from semisynthesis.

Graphical Abstract

C9/C13 stereochemistry typical of cucurbitanes and *ent*-9α-estranes

C10/C13 stereochemistry common in androstanes, pregnanes, cardenolides, lanostanes, euphanes, and limonoids

/ = key bond forged
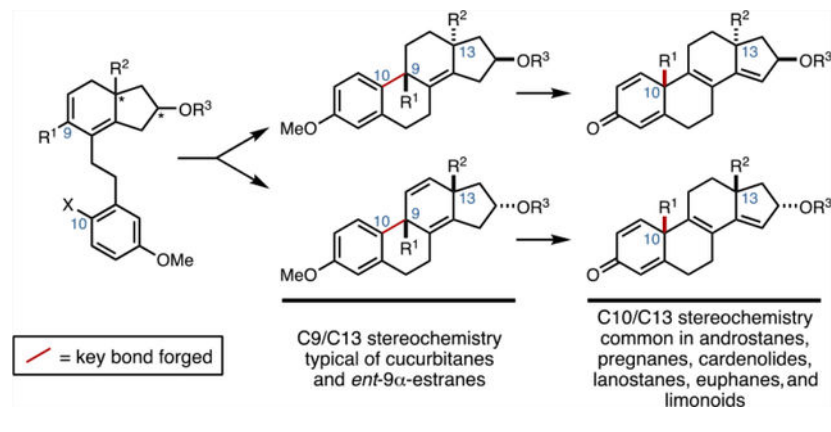
INTRODUCTION

Steroid hormones and related compounds are the most successful class of natural product-inspired pharmaceuticals, with >140 FDA-approved examples.[1] As such, the compounds in this class can be considered as pharmaceutically privileged and viable molecular platforms for drug discovery and development.[2] The vast majority of medically relevant agents among this group are based on estrane-, androstane-, pregnane-, or cardenolide skeletons, although a vast array of more complex tetracyclic terpenoid systems are well known (Figure 1A).[3] Historically, the recognition that such molecules have profound impacts in human biology led to substantial advances in synthetic organic chemistry throughout the middle of the 20th century. In fact, while numerous advances in "de novo" synthesis (commonly referred to as "total" synthesis) have been described that pave a path to these steroidal systems that contain one or two quaternary carbon stereocenters at the ring fusions of their tetracyclic skeleton (e.g., C10 and C13), modern medicinal exploration in the area is predominantly driven by natural product functionalization or "semisynthesis". [4] This reality is likely due to the current superiority of semisynthetic approaches that do not require enantioselective assembly of the stereochemically complex fused carbocyclic core skeletons of members of this natural product class. This dependency on semisynthesis is further amplified when considering medicinal exploration of tetracyclic terpenoid-inspired systems based on lanostane,[5] euphane,[6] limonoid,[7] and cucurbitane[8] natural product families. These latter examples are significantly more challenging synthetic targets owing to their unique patterns of substitution at ring-fusion carbons (e.g., additional quaternary centers at C8, C9, and C14) and the variation in relative stereochemistry at some of these centers (i.e., C10,C13-*anti* and C10,C13-*syn*; Figure 1A). These structural differences weigh heavily on the synthesis design[9] and can be reasoned to result in retrosynthetic strategies that rely on disparate sequences of chemical transformations, exploit structurally distinct starting materials, and proceed with varying levels of step economy. Here, we describe a common asymmetric four-stage synthetic strategy of high step economy that can be employed to access a range of stereodefined tetracyclic terpenoid-related systems. The process is inherently flexible with respect to absolute and relative stereochemistry, is capable of producing substituted tetracyclic systems not easily accessible from semisynthesis, and proceeds

in a highly convergent manner. A key feature of this advance is based on establishing stereodivergent means to forge the steroidal C9–C10 bond to generate tetracyclic systems that have either a *syn*- or *anti*-stereochemical relationship between C9 and C13 (Figure 1B). In short, double asymmetric Friedel–Crafts cyclization has been established as a general and highly stereoselective means to access C9a-substituted estranes (**1** → **2**), while cyclization by an intramolecular Heck reaction has been revealed to be highly selective for the formation of C9β-substituted estranes (**4** → **5**; Figure 1B). The value of this stereodivergent bond construction is further amplified by the ability of each stereodefined system (**2** and **5**) to undergo a unique oxidative dearomatization/group-selective Wagner–Meerwein rearrangement that stereospecifically repositions the quaternary center from C9 to C10 in each system (**2** → **3**, and **5** → **6**). These latter transformations provide a general synthetic entry to steroidal systems that bear either C10,C13-*anti* stereochemistry (e.g., limonoids and euphanes), or C10,C13-*syn* stereochemistry (e.g., androstanes, pregnanes, and cardenolides).[10] This advance is distinct from the existing technology for forging the steroidal C9–C10 bond that proceeds either without the generation of a quaternary center at C9 (**7** → **8**; Figure 1C)[11] or employs Pd-catalyzed coupling technology that requires the use of a complex chiral ligand to generate systems bearing a quaternary center at C10 (**9** → **10**).[12]

RESULTS AND DISCUSSION

This "unified" synthetic pathway (vide infra) to structurally diverse tetracyclic terpenoid systems (**2**, **3**, **5**, and **6**), which proceeds through sequential C9–C10 bond formation followed by rearrangement, has grown from our previously reported metallacycle-mediated annulative cross-coupling reaction that enables the union of readily available chiral enynes with trimethylsilyl (TMS)-alkynes and produces stereodefined polyunsaturated hydrindanes (**11** → **12**; Figure 2A).[10,13] This annulation reaction, along with subsequent cyclization chemistry, is successful on a multigram scale and has played a prominent role in recent natural product synthesis efforts (**13–15**; Figure 2B);[14] consideration of state-of-the-art strategies for asymmetric de novo synthesis of tetracyclic terpenoid systems led us to contemplate the potential value of this annulative process for the construction of a range of such stereodefined carbocyclic systems.

As illustrated in Figure 2C, it was imagined that the hydrindane product of annulation (**17**) may serve as a useful intermediate for the construction of steroidal tetracycles (**18**) if it were possible to achieve stereoselective C9–C10 bond formation. The products of this reaction were not only recognized to be potentially valuable C9-substituted estranes that contained structural motifs observed within the cucurbitane family of natural products but they were also thought to be valuable precursors to families of tetracyclic terpenoids that contain a C10 quaternary center (**18** → **19**). Although not previously reported, it was imagined that oxidative dearomatization could result in termination by group-selective Wagner–Meerwein rearrangement that relocates C9 substitution to C10. These transformations that proceed after metallacycle-mediated hydrindane formation (**17** → **18** → **19**) are the subject of the following discussion.

Tandem Protodesilylation/Friedel–Crafts Cyclization.

Early efforts to accomplish C9–C10 bond formation were based on the goal of achieving acid-mediated tandem protodesilylation and stereoselective Friedel–Crafts cyclization. Lewis acid-complexed phenols soon emerged as particularly well-suited Brønsted acids that, at low temperature, induce protodesilylation, subsequent site-selective protonation at C11, and regioselective and stereoselective Friedel–Crafts cyclization.[15] As illustrated in Figure 3A, the complex formed from o,o'-dihydroxybiphenyl and $SnCl_4$ smoothly converted the silylated hydrindane **20** to **21** in 55% yield. Interestingly, this cyclization proceeded with good levels of stereoselection in favor of the C9,C13-*anti* isomer (ds = 9:1).

In an effort to perturb the inherent selectivity of this reaction, to both enhance the substrate's bias to form the *anti*-product and potentially reverse the sense of stereocontrol to selectively deliver the *syn*-isomer, attention was directed toward exploring double asymmetric[16] variants of this process. Lewis acid-complexed 1,1'-bi-2-naphthol (BINOL) systems originally popularized by Yamamoto as a means to achieve chiral Brønsted acid-mediated enantioselective polyene cyclization[15] quickly emerged as a particularly attractive and simple means to affect the stereochemical course of this tandem protodesilylation and Friedel–Crafts cyclization reaction. As illustrated in Figure 3B, chiral complexes of BINOL with $SnCl_4$ had a profound impact on the stereochemical course of this C9–C10 bond-forming process. Matched double asymmetric reactions led to a substantial increase in stereoselection, producing the *anti*-isomer (**22**) with 20:1 diastereoselection, while the mismatched double asymmetric process led to a significant erosion of stereoselection, delivering a nearly 1:1 mixture of tetracyclic products (**22:23**).

Intramolecular Heck Reaction—Stereoselective Access to the C9,C13-*syn*-Isomer.

The inability of the mismatched double asymmetric Brønsted acid-mediated cyclization to reverse the stereochemical course of the C9–C10 bond formation depicted in Figure 3B led to investigations aimed at understanding the means by which the chiral Brønsted acid promotes the cyclization reaction. In Yamamoto's pioneering study of BINOL·$SnCl_4$ complexes as chiral mediators of enantioselective polyene cyclization reactions,[15] it was proposed that the chiral Brønsted acid initiates polyene cyclization by face-selective protonation of a trisubstituted alkene with concomitant/concerted *anti*-addition (e.g., C–C bond formation occurs *anti*- to protonation). Given that the hydrindane substrates for the current transformations are chiral and that there should be a bias regarding which face of the C9–C11 alkene participates in the initial reaction with the Brønsted acid, experiments were conducted to clarify the facial selectivity of protonation in the unselective mismatched double asymmetric reaction (**17 → 22 + 23**; Figure 3B). The central question was whether the protonation and cyclization occur in an *anti*-fashion across the C9–C11 alkene during the course of producing the C9,C13-*anti* (**22**) and C9,C13-*syn* (**23**) products. If so, the mismatched double asymmetric reaction would be delivering isomeric products through a poorly stereoselective protonation at C11.

As depicted in Figure 4, hydrindane **17** was converted to the deuterated and protected substrate **24** via initial methylation (NaH and MeI), followed by deuterodesilylation with DCl. In considering the use of **24** as a substrate for Brønsted acid-mediated cyclization,

it was understood that the deuterium label at C11 provided a means to assess the facial selectivity of protonation at this carbon. As illustrated in Figure 4A, mismatched double asymmetric cyclization of **24** with (*S*)-BINOL·SnCl$_4$ led to a 3:1 mixture of C9-substituted estranes (**25** and **26**), slightly favoring the *anti*-isomer **25**. Interestingly, the stereochemistry at C11 of both products was identical, indicating that protonation at C11 occurs uniformly from the *α*-face. This finding indicates a mechanistic difference in the formation of products **25** and **26**. In one case, the protonation occurs *anti*- to C–C bond formation (**25**) and is consistent with the empirical model proposed for enantioselective polyene cyclization by Yamamoto. In the other case, protonation occurs *syn*- to C–C bond-formation (**26**). The fundamental reason for this difference in mechanism as a function of the pairing of absolute stereochemistry between BINOL and the hydrindane is currently not well understood, but it is suspected that the initial formation of the allylic carbocation may play a significant role, and ion pairing with the BINOL·SnCl$_4$ complex may influence the stereochemical course of these reactions.

With a stereoselective means for preparing tetracyclic products bearing a C9,C13-*anti* stereochemical relationship by way of a matched double asymmetric tandem protodesilylation/Friedel–Crafts cyclization, attention was directed toward establishing a complementary process to stereoselectively produce the C9,C13-*syn* isomer. After gaining an understanding that the polyunsaturated hydrindane substrates of interest (e.g., **24**; Figure 4A) have a strong inherent facial preference for how the C9–C11 alkene is engaged in reaction with a Brønsted acid, namely, selective protonation from the *α*-face, we imagined that an intramolecular carbometallation reaction may proceed with a similar sense of stereoselection. In such processes, it was anticipated that C–C bond formation at C9 may take place preferentially through a carbometallation process that engages the *α*-face. In particular, it was reasoned that an intramolecular Heck reaction would be an ideal means to stereoselectively generate the C9,C13-*syn* product.[17] As illustrated in Figure 4B, this expectation proved to be correct. Heating the aryl triflate **27** and catalytic Pd$_2$(dba)$_3$ in the presence of (±)-BINAP and 1,2,2,6,6-pentamethyl piperidine in toluene resulted in a highly stereoselective intramolecular Heck reaction and delivered the C9,C13-*syn*-substituted estrane **29** in 75% yield with ds 20:1.[12]

Establishment of an Oxidative Dearomatization and Wagner–Meerwein Rearrangement.

With complementary approaches to tetracycle formation in hand that generate either the C9,C13-*anti* or C9,C13-*syn* product with very high levels of stereoselectivity, attention was focused on the next critical step of the aforementioned synthetic strategy to access a range of terpenoid systems (Figure 2C). In short, it was imagined that an oxidative dearomatization and group-selective Wagner–Meerwein rearrangement might be capable of relocating the methyl group from C9 to C10, establishing a unique means of transposing a quaternary center in these steroidal systems. If successful, such a process would allow for the conversion of tetracyclic systems containing structural features of cucurbitanes or 9-substituted estranes to molecular skeletons having features of euphanes, limonoids, androstanes, pregnanes, or cardenolides.

As depicted in Figure 5A, it was imagined that treatment of tetracyclic phenol **30** with phenyliodine diacetate may promote the desired oxidative dearomatization and alkyl shift. Unfortunately, the precedent in this general area of reactivity offered little support for this expectation.[18] Related established processes are terminated by semipinacol rearrangement —a reaction that requires substrates bearing a benzylic tertiary alcohol, not a benzylic quaternary center (as is the case with **30**). Furthermore, the precedent indicates that methyl groups are least likely to migrate during the terminal semipinacol rearrangement.[18] As such, the planned oxidative dearomatization and Wagner–Meerwein rearrangement of interest aimed to achieve what established reactions do not and targeted establishing a transformation of great potential value for the construction of tetracyclic terpenoid-inspired systems.

In consideration of the mechanistic course of the desired oxidative rearrangement, after formation of the activated intermediate **31**, it was anticipated that the reaction would proceed by one of two major pathways, both of which would occur through alkyl shift with the generation of a tertiary allylic carbocation[19] (**31** → **32** or **33**). Considering the nature and expected stability of these two possible intermediates led to a clear expectation regarding selectivity. If C11 were to migrate during the Wagner–Meerwein rearrangement, the bridged bicyclic cation **32** would be produced. This intermediate contains both a bridgehead alkene[20] and a cation at the apical position of a bridged bicyclic nucleus. Due to stereoelectronic effects,[21] this proposed cation could not be resonance-stabilized by the neighboring alkene. Therefore, while this intermediate would be expected based on a preferred rearrangement that migrates a more substituted carbon (in comparison to the C19 methyl group), stereoelectronic considerations lead to the expectation that the rearrangement leading to **32** would not be preferred. Alternatively, if C19 (the methyl group of **31**) underwent the Wagner–Meerwein rearrangement, the tertiary allylic cation **33** would be generated. Here, while the selective rearrangement would engage an otherwise less favorable group for migration, the resulting penta-substituted allylic cation **33** would be far superior to **32**.

As illustrated in Figure 5B, a simple two-step sequence (demethylation and then oxidative rearrangement) converted the C9,C13-*syn* isomer **23** to the C10,C13-*syn*-substituted tetracycle **34** in 65% overall yield. Notably, this transformation converts molecules bearing structural features of cucurbitanes to molecules that bear structural features of relevance to androstanes, pregnanes, and cardenolides. Importantly, no evidence was found for the formation of a product derived from the migration of a different carbon from C9. This two-step demethylation and oxidative rearrangement proceeds similarly with the isomeric substrate **35** and delivers the stereodefined product **36** in 60% overall yield. This latter example of the oxidative rearrangement establishes a novel retrosynthetic link between 9*a*-*ent*-estranes and limonoid and euphane systems that typically have C10,C13-*anti* stereochemistry.

Establishing Generality for This Four-Stage Asymmetric Synthesis of Tetracyclic Terpenoid Systems.

State-of-the-art approaches to drive medicinal chemistry programs in this area of natural product-related science are heavily dependent on semisynthesis and, as a result, are generally limited with respect to stereochemical variation and substitution, particularly with respect to quaternary centers that reside at ring fusions.[23] In contrast, it was apparent that the sequence of chemical transformations discussed previously could be viewed as defining a general enantioselective *four-stage* means of stereoselectively accessing complex tetracyclic terpenoid systems not easily accessible from semisynthesis (e.g., providing access to unnatural enantiomeric systems, as well as generating products that have quaternary carbons boasting substituents larger than methyl).

As illustrated in Figure 6, stage 1 is simply the conversion of epichlorohydrin to functionalized enynes through well-established synthetic methods.[24] Stage 2 is the conversion of these enyne substrates to densely functionalized hydrindanes through the use of recently developed alkoxide-directed metallacycle-mediated annulative cross-coupling.[13] Stage 3 is the stereoselective formation of the C9–C10 bond through either matched double asymmetric Friedel–Crafts cyclization (to establish C9,C13-*anti* stereochemistry) or intramolecular Heck reaction (to establish C9,C13-*syn* stereochemistry). Finally, stage 4 is deprotection (e.g., demethylation) and oxidative rearrangement. While previous efforts have revealed the generality of stages 1 and 2 of this process,[13] little was known about the latter stages of this sequence and how the key transformations (C9–C10 bond formation and oxidative rearrangement) would be affected by the nature of the substituents R^1 and R^2.

As illustrated in Figure 7A, moving beyond a methyl substituent at C9 led to unanticipated variations in stereoselectivity during the matched double asymmetric reaction for C9–C10 bond formation (stage 3). For example, tandem protodesilylation and Friedel–Crafts cyclization of **37**, a substrate bearing an ethyl group at C9 rather than a methyl group, resulted in a significant drop in stereoselectivity (from 20:1 for Me to 11:1 for Et). While seemingly workable as a means to generate C9,C13-*anti*-substituted tetracycles bearing an ethyl group at C9, further variation in the nature of this substituent led to dramatically dampened diastereoselectivity. For example, matched double asymmetric reaction of **39**, a substrate that bears a benzyl group at C9, generated the tetracyclic product **40** with only 2:1 selectivity for the depicted *anti*-isomer.

In trying to identify a means to overcome this unforeseen drop in *anti*-selectivity, the mechanistic complexities of this tandem process were considered. First, deuterium labeling studies previously depicted in Figure 4A support the expectation that protonation at C11 should occur on the *α*-face and that subsequent cyclization may or may not proceed in an *anti*-fashion with respect to that protonation event. In the matched double asymmetric reaction previously discussed with C9 methyl substitution (Figure 3B), the protonation and C–C bond formation presumably occur *anti*- and with very high levels of stereocontrol. This matched double asymmetric reaction could proceed through a mechanism whereby protonation and C–C bond formation are concerted or through a mechanism where a carbocationic intermediate is first formed and stereoselective cyclization is influenced by

the nature of the chiral counterion (as previously considered in the mismatched double asymmetric reaction). The matched double asymmetric reactions depicted in Figure 7A now proceed with a substantial erosion in selectivity that reflects an unwanted shift in mechanism as a function of the nature of the C9 substituent (protonation and C–C bond formation are no longer occurring with high *anti*-selectivity, indicating the potential relevance of initial carbocation formation and cyclization by way of an ion pair).

While not having a clear understanding of the causative molecular details associated with the observed erosion in stereoselectivity for the matched double asymmetric reactions depicted in Figure 7A, effort was directed toward contemplating the potential complexities associated with this tandem Brønsted acid-mediated transformation. As illustrated in eq 1 of Figure 7B, it was understood that during these tandem reactions, BINOL is silylated as a result of the initial protodesilylation reaction. As the desired transformation proceeds, this results in the generation of a structurally distinct chiral Brønsted acid (TMS-BINOL·SnCl$_4$) that can compete with BINOL·SnCl$_4$ as the agent that induces the Friedel–Crafts cyclization (1.1 equiv of BINOL·SnCl$_4$ are typically employed in the tandem protodesilylation/Friedel–Crafts cyclization reaction). Also, it was appreciated that the C16 alcohol residing on the cyclization substrates could, itself, serve as a chiral Brønsted acid when complexed to SnCl$_4$ (eq 2, Figure 7B). If accurate, these competing sources of chiral Brønsted acid could greatly complicate attempts to control the stereoselective course of C9–C10 bond formation in the desired matched double asymmetric process. As such, we aimed to gain finer control over the cyclization reaction by removing these potential mechanistic complexities.

As illustrated in Figure 8A, a stepwise investigation of the substrates prepared to explore these potential sources of mechanistic complexity resulted in a significant discovery. First, initial removal of the C11 TMS group to avoid the potential of silylated BINOL to impact the stereoselective course of the cyclization led to a modest increase of stereoselection (**41 → 42**; 89% isolated yield, ds = 4.5:1). Next, removal of the C16 proton source by methylation of the alcohol delivered a substrate that underwent cyclization with much better levels of stereocontrol (**43 → 44**; *unoptimized* 46% isolated yield, ds = 10:1). Finally, a substrate that had neither a TMS group at C11 or a proton source at C16 underwent cyclization with exquisite levels of stereoselectivity (**45 → 44**; 91% isolated yield, ds > 20:1).

Now, with a better understanding of the molecular features of the substrates that undergo highly stereoselective double asymmetric Friedel–Crafts cyclization, attention was directed toward understanding the generality of this C9–C10 bond-forming process. As depicted in Figure 8B, the hydrindane products of stage 2 were desilylated by the action of TFA in CH$_2$Cl$_2$ and then methylated (NaH and MeI).[22] Treatment with (S)-BINOL·SnCl$_4$ was effective for conversion to a range of tetracycles (**46–53**) in 45–98% yield. Notably, no evidence was found for the production of stereoisomeric products in any of these transformations.[22] Also, the absolute stereochemistry and substitution of these products render them quite challenging to access from semisynthesis (i.e., all of these products are *ent*-estranes, and most of them contain substitution at C9 and/or C13 that would be difficult to access from any available natural product starting material).[23]

While not directly related to the double asymmetric Friedel–Crafts cyclization reactions depicted in Figure 8 that deliver products that lack substitution at C17, we note that acid-mediated cyclization of a related substrate derived from the Hajos–Parrish ketone proceeds with high levels of *anti*-selectivity (Figure 9; **54 → 55**). This bond construction may be useful as a means to access congeners that house C17 functionality.

With a highly stereoselective and general means to prepare C9,C13-*anti*-substituted tetracyclic terpenoid systems in hand, effort was directed toward investigating the generality of the complementary C9–C10 bond-forming process that delivers the C9,C13-*syn* isomers. While initial attempts at achieving double asymmetric Brønsted acid-mediated cyclization revealed compromised stereoselection with C9–Et and C9–Bn substitution (Figure 7A), the intramolecular Heck reaction proved to be highly selective with substrates bearing such substitution at C9. As depicted in Figure 10, substrates **56** and **58** were smoothly converted to products **57** and **59** with very high levels of selectivity (ds 20:1).

With stage 3 of the synthetic strategy firmly established as a means to achieve C9–C10 bond formation with high *anti*- or *syn*-selectivity, attention was directed to stage 4—oxidative dearomatization and Wagner–Meerwein shift. The substrates examined to explore this process were prepared in one or two steps, as depicted in Figure 11A. Gratifyingly, as illustrated in Figure 11B, the oxidative rearrangement proved effective with substrates of varying stereochemistry and substitution (C9,C13-*syn*- or C9,C13-*anti*; C9–Et, Bn, or Ph substitution). In each case, the anticipated rearranged product was generated with exquisite group selectivity (isolated yields from 56 to 86% yield; no evidence found for the production of isomeric products).

CONCLUDING REMARKS

Natural products have long played a central role in drug development, and tetracyclic terpenoid-derived examples represent the most successful class of natural product-inspired therapeutics.[1] While this fact speaks to the availability of synthetic approaches that are capable of driving medicinal chemistry programs, it is important to appreciate that semisynthesis is the predominant molecular means that enables such pursuits.[4] Dating back to more than half a century, this approach has had a transformational impact on medicine, essentially leading to the establishment of the 20th century steroid pharmaceutical industry. Despite this track record of success, semisynthesis comes with substantial limitations that are based, in part, on the structures of available natural product starting materials, as well as chemistry capable of selectively modifying their skeletons. The chemistry discussed here was conceived with the goal of establishing synthetic technology that can accomplish what semisynthesis cannot while also providing a unique general approach to the asymmetric construction of a wide range of tetracyclic terpenoid systems that are differentiated by the position and stereochemistry of ring fusion quaternary centers throughout their skeletons. What has emerged is a strategically simple four-stage asymmetric de novo synthesis pathway that is based on stepwise assembly of the relevant tetracyclic systems through bond-forming processes that provide inherent flexibility with respect to the position, nature, and stereochemistry of quaternary centers located at ring fusion carbons: stage 1—the absolute stereochemistry is established through the use of enantiodefined epichlorohydrin,

and C13 substitution is introduced with a substituted vinyl Grignard reagent; stage 2—the stereochemistry of the C13 quaternary center is established and variable substitution at C9 is realized by alkoxide-directed metallacycle-mediated annulative cross-coupling with differentially substituted TMS-alkynes; stage 3—the tetracyclic skeleton is forged through C9–C10 bond formation (at this point, a stereodefined estrane- or cucurbitane-like skeleton is established); and stage 4—oxidative dearomatization/Wagner–Meerwein rearrangement enables the transposition of a quaternary center from C9 to C10 and delivers systems that have C10/C13 stereochemistry common to scores of natural products (e.g., androstanes, pregnanes, cardenolides, limonoids, lanostanes, and euphanes, among others). Overall, this synthetic approach provides exceptional flexibility with respect to the relative and absolute stereochemistry of the resulting tetracyclic systems, does so while enabling differential substitution at each of the formed quaternary centers (C9, C10, and C13), and proceeds with high levels of step economy. These characteristics are viewed as being of great potential value in programs that are focused on the synthesis and exploration of tetracyclic terpenoid-inspired agents in biology and medicine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

REFERENCES

(1). (a)Fernández-Cabezón L; Galán B; García JL New Insights on Steroid Biotechnology. Front. Microbiol. 2018, 9, 958. [PubMed: 29867863] (b)The United States Pharmacopeia. The National Formulary; United States Pharmacopeial Convention, Inc: Rockville, Md, 1979.

(2). (a)Müller G Medicinal Chemistry of Target Family-Directed Masterkeys. Drug Discov. 2003, 8, 681–691.(b)El-Desoky E-SI; Reyad M; Afsah EM; Dawidar A-AM Synthesis and Chemical Reactions of the Steroidal Hormone 17α-Methyltestosterone. Steroids 2016, 105, 68–95. [PubMed: 26639430] (c)Zhao C; Ye Z; Ma Z.-x.; Wildman SA; Blaszczyk SA; Hu L; Guizei IA; Tang W A general strategy for diversifying complex natural products to polycyclic scaffolds with medium-sized rings. Nat. Commun. 2019, 10, 4015. [PubMed: 31488839]

(3). Lednicer D Steroid Chemistry at a Glance; Wiley: Hoboken, 2011.

(4). (a)Salvador JAR; Carvalho JFS; Neves MAC; Silvestre SM; Leitão AJ; Silva MMC; Sá e Melo ML Anticancer Steroids: Linking Natural and Semi-Synthetic Compounds. Nat. Prod. Rep. 2013, 30, 324–374. [PubMed: 23151898] (b)Wang Z; Hui C Contemporary Advancements in the Semi-Synthesis of Bioactive Terpenoids and Steroids. Org. Biomol. Chem. 2021, 19, 3791–3812. [PubMed: 33949606] (c)Ben Nejma A; Znati M; Daich A; Othman M; Lawson AM; Ben Jannet H Design and Semisynthesis of New Herbicide as 1,2,3-Triazole Derivatives of the Natural Maslinic Acid. Steroids 2018, 138, 102–107. [PubMed: 30016641] (d)Nising CF; Bräse S Highlights in Steroid Chemistry: Total Synthesis versus Semisynthesis. Angew. Chem., Int. Ed. 2008, 47, 9389–9391.(e)Dewick PM Pharmaceutical Steroids and Their Production for Hormone Replacement Therapy. Br. Menopause Soc. J. 1999, 5, 12–22.(f)Dembitsky V; Gloriozova T; Poroikov V Pharmacological Activities of Epithio Steroids. J. Pharm. Res. Int. 2017, 18, 1–19.(g)Tapiero H; Townsend DM; Tew KD Phytosterols in the Prevention of Human Pathologies. Biomed. Pharmacother. 2003, 57, 321–325. [PubMed: 14568225] (h)Tolmacheva IA; Nazarov AV; Eroshenko DV; Grishko VV Synthesis, Cytotoxic Evaluation, and Molecular Docking Studies of the Semi-Synthetic "Triterpenoid-Steroid" Hybrids. Steroids 2018, 140, 131–

143. [PubMed: 30315840] (i)Hanson JR Steroids: partial synthesis in medicinal chemistry. Nat. Prod. Rep. 2010, 27, 887–899. [PubMed: 20424788]

(5). (a)Hill RA; Connolly JD Triterpenoids. Nat. Prod. Rep. 2017, 34, 90–122. [PubMed: 27813539] (b)Shi Y-M; Xiao W-L; Pu J-X; Sun H-D Triterpenoids from the Schisandraceae Family: An Update. Nat. Prod. Rep. 2015, 32, 367–410. [PubMed: 25483912] (c)Isaka M; Sappan M; Choowong W; Boonpratuang T; Choeyklin R; Feng T; Liu J-K Antimalarial lanostane triterpenoids from cultivated fruiting bodies of the basidiomycete *Ganoderma* sp. J. Antibiot. 2020, 73, 702–710.(d)Yao J-N; Chen L; Tang Y; Chen H-P; Zhao Z-Z; Li Z-H; Feng T; Liu J-K Lanostane triterpenoids from fruiting bodies of basidiomycete *Stereum* sp., structures and biological activities. J. Antibiot. 2017, 70, 1104–1111.(e)Su H-G; Peng X-R; Shi Q-Q; Huang Y-J; Zhou L; Qiu M-H Lanostane triterpenoids with anti-inflammatory activities from Ganoderma lucidum. Phytochem 2020, 173, 112256.(f)Su H-G; Zhou Q-M; Guo L; Huang Y-J; Peng C; Xiong L Lanostane triterpenoids from *Ganoderma luteomarginatum* and their cytotoxicity against four human cancer cell lines. Phytochem 2018, 156, 89–95.(g)Hill RA; Connolly JD Triterpenoids. Nat. Prod. Rep. 2020, 37, 962–998. [PubMed: 32055816]

(6). (a)Li Y-N; He J; Zhang J; Shi Y-X; Guo L-B; Peng Z-C; Yang T; Ding K; Zhang W-K; Xu J-K Existing Knowledge on Euphorbia Fischeriana Steud. (Euphorbiaceae): Traditional Uses, Clinical Applications, Phytochemistry, Pharmacology and Toxicology. J. Ethnopharmacol. 2021, 275, 114095. [PubMed: 33819505] (b)Wang L-Y; Wang N-L; Yao X-S; Miyata S; Kitanaka S Kitanaka Euphane and Tirucallane Triterpenes from the Roots of *Euphorbia kansui* and Their in Vitro Effects on the Cell Division of Xenopus. J. Nat. Prod. 2003, 66, 630–633. [PubMed: 12762796] (c)Qi Y; Liu W; Chen Y; Guan M; Yuan T Euphatexols A and B, two unusual euphane triterpenoids from the latex of *Euphorbia resinifera*. Tetrahedron Lett. 2019, 60, 151303. (d)Lee S; Choi E; Jeon S; Zhi X; Yu J; Kim S-H; Lee J; Park K-M; Kim K Tirucallane Triterpenoids from the Stems and Stem Bark of Cornus walteri that Control Adipocyte and Osteoblast Differentiations. Molecules 2018, 23, 2732.(e)Pettit GR; Numata A; Iwamoto C; Morito H; Yamada T; Goswami A; Clewlow PJ; Cragg GM; Schmidt JM Antineoplastic Agents. 489. Isolation and Structures of Meliastatins 1–5 and Related Euphane Triterpenes from the Tree *Melia dubia*. J. Nat. Prod. 2002, 65, 1886–1891. [PubMed: 12502333]

(7). (a)Zhang Y; Xu H Recent Progress in the Chemistry and Biology of Limonoids. RSC Adv. 2017, 7, 35191–35220.(b)Fu S; Liu B Recent Progress in the Synthesis of Limonoids and Limonoid-like Natural Products. Org. Chem. Front. 2020, 7, 1903–1947.(c)Gualdani R; Cavalluzzi M; Lentini G; Habtemariam S The Chemistry and Pharmacology of Citrus Limonoids. Molecules 2016, 21, 1530.(d)Roy A; Saraf S Limonoids: Overview of Significant Bioactive Triterprens Distributed in Plants Kingdom. Biol. Pharm. Bull. 2006, 29, 191–201. [PubMed: 16462017] (e)Zhang Y; Xu H Recent progress in the chemistry and biology of limonoids. RSC Adv. 2017, 7, 35191–35220.(f)Gupta SC; Prasad S; Sethumadhavan DR; Nair MS; Mo Y-Y; Aggarwal BB Nimbolide, a Limonoid Triterpene, Inhibits Growth of Human Colorectal Cancer Xenografts by Suppressing the Proinflammatory Microenvironment. Clin. Cancer Res. 2013, 19, 4465–4476. [PubMed: 23766363] (g)Shi Y-S; Zhang Y; Li H-T; Wu C-H; El-Seedi HR; Ye W-K; Wang Z-W; Li C-B; Zhang X-F; Kai G-Y Limonoids from Citrus: Chemistry, anti-tumor potential, and other bioactivities. J. Funct. Foods 2020, 75, 104213.

(8). (a)Liu D-Z A Review of Ergostane and Cucurbitane Triterpenoids of Mushroom Origin. Nat. Prod. Res. 2014, 28, 1099–1105. [PubMed: 24673284] (b)Liu J-Q; Chen J-C; Wang C-F; Qiu M-H New Cucurbitane Triterpenoids and Steroidal Glycoside from Momordica charantia. Molecules 2009, 14, 4804–4813. [PubMed: 20032860] (c)Chen D-L; Xu X-D; Li R-T; Wang B-W; Yu M; Liu Y-Y; Ma G-X Five New Cucurbitane-Type Triterpenoid Glycosides from the Rhizomes of Hemsleya penxianensis with Cytotoxic Activities. Molecules 2019, 24, 2937.(d)Nakamura S; Murakami T; Nakamura J; Kobayashi H; Matsuda H; Yoshikawa M Structures of New Cucurbitane-Type Triterpenes and Glycosides, Karavilagenins and Karavilosides, from the Dried Fruit of *Momordica charantia* L. in Sri Lanka. Chem. Pharm. Bull. 2006, 54, 1545–1550.

(9). (a)Corey EJ; Guzman-Perez A The Catalytic Enantioselective Construction of Molecules with Quaternary Carbon Stereocenters. Angew. Chem., Int. Ed. 1998, 37, 388–401.(b)Christoffers J; Mann A Enantioselective Construction of Quaternary Stereocenters. Angew. Chem., Int. Ed. 2001, 40, 4591–4597.(c)Christoffers J; Baro A Stereoselective Construction of Quaternary Stereocenters. Adv. Synth. Catal. 2005, 347, 1473–1482.(d)Cherney EC; Baran PS Terpenoid-
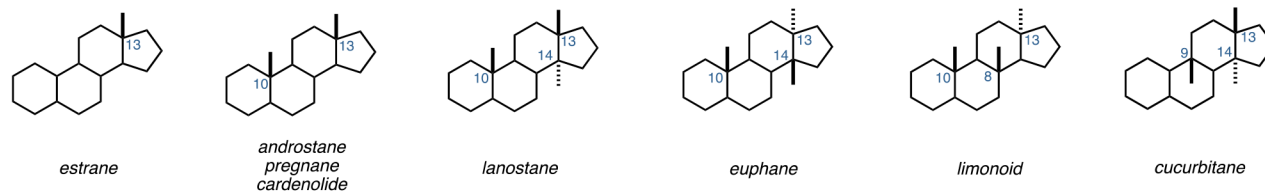
Alkaloids: Their Biosynthetic Twist of Fate and Total Synthesis. Isr. J. Chem. 2011, 51, 391–405. [PubMed: 26207071] (e)Khatri HR; Carney N; Rutkoski R; Bhattarai B; Nagorny P Recent Progress in Steroid Synthesis Triggered by the Emergence of New Catalytic Methods: Recent Progress in Steroid Synthesis Triggered by the Emergence of New Catalytic Methods. Eur. J. Org. Chem. 2020, 755–776.

(10). (a)Kim WS; Shalit ZA; Nguyen SM; Schoepke E; Eastman A; Burris TP; Gaur AB; Micalizio GC A Synthesis Strategy for Tetracyclic Terpenoids Leads to Agonists of ERβ. Nat. Commun. 2019, 10, 2448. [PubMed: 31164645] (b)Millham AB; Bhatt CP; Micalizio GC From Metallacycle-Mediated Annulative Cross-Coupling to Steroidal Tetracycles through Intramolecular C9–C10 Bond Formation. Org. Lett. 2020, 22, 6595–6599. [PubMed: 32806140]

(11). Crispin DJ; Whitehurst JS A Total Synthesis of 0Estrone. Proc. Chem. Soc. 1962, 356.

(12). Du K; Guo P; Chen Y; Cao Z; Wang Z; Tang W Enantioselective Palladium-Catalyzed Dearomative Cyclization for the Efficient Synthesis of Terpenes and Steroids. Angew. Chem., Int. Ed. 2015, 54, 3033–3037.

(13). (a)Greszler SN; Reichard HA; Micalizio GC Asymmetric Synthesis of Dihydroindanes by Convergent Alkoxide-Directed Metallacycle-Mediated Bond Formation. J. Am. Chem. Soc. 2012, 134, 2766–2774. [PubMed: 22235773] (b)Micalizio GC; Mizoguchi H The Development of Alkoxide-Directed Metallacycle-Mediated Annulative Cross-Coupling Chemistry. Isr. J. Chem. 2017, 57, 228–238. [PubMed: 28652644] (c)Shalit ZA; Valdes LC; Kim WS; Micalizio GC From an *Ent* -Estrane, through a *Nat* -Androstane, to the Total Synthesis of the Marine-Derived 8,9 -Pregnene (+)-03219A. Org. Lett. 2021, 23, 2248–2252. [PubMed: 33635666] (d)Markham LE; Tolbert JD; Kull FJ; Midgett CR; Micalizio GC An Enantiodefined Conformationally Constrained Fatty Acid Mimetic and Potent Inhibitor of ToxT. ACS Med. Chem. Lett. 2021, 12, 1493–1497. [PubMed: 34531958]

(14). (a)Aquino C; Greszler SN; Micalizio GC Synthesis of the Cortistatin Pentacyclic Core by Alkoxide-Directed Metallacycle-Mediated Annulative Cross-Coupling. Org. Lett. 2016, 18, 2624–2627. [PubMed: 27193994] (b)Leon RM; Ravi D; An JS; del Genio CL; Gaur AB; Micalizio GC; Micalizio GC Synthesis of C14-Desmethylene Corialactone D and Discovery of Inhibitors of Nerve Growth Factor Mediated Neurite Outgrowth. Org. Lett. 2019, 21, 3193–3197. [PubMed: 30995050] (c)O'Rourke NF; Kier MJ; Micalizio GC Metallacycle-Mediated Cross-Coupling in Natural Product Synthesis. Tetrahedron 2016, 72, 7093–7123. [PubMed: 27765997]

(15). Ishihara K; Ishibashi H; Yamamoto H Enantio- and Diastereoselective Stepwise Cyclization of Polyprenoids Induced by Chiral and Achiral LBAs. A New Entry to (−)-Ambrox, (+)-Podocarpa-8,11,13-Triene Diterpenoids, and (−)-Tetracyclic Polyprenoid of Sedimentary Origin. J. Am. Chem. Soc. 2002, 124, 3647–3655. [PubMed: 11929254]

(16). Masamune S; Choy W; Petersen JS; Sita LR Double Asymmetric Synthesis and a New Strategy for Stereochemical Control in Organic Synthesis. Angew. Chem., Int. Ed. Engl. 1985, 24, 1–30.

(17). <j/>(a). Dounay AB; Overman LE The Asymmetric Intramolecular Heck Reaction in Natural Product Total Synthesis. Chem. Rev. 2003, 103, 2945–2964. [PubMed: 12914487] (b)Büschleb M; Dorich S; Hanessian S; Tao D; Schenthal KB; Overman LE Synthetic Strategies toward Natural Products Containing Contiguous Stereogenic Carbon Atoms. Angew. Chem., Int. Ed. 2016, 55, 4156–4186. For examples, see also:(c)Kong K; Enquist JA Jr.; McCallum ME; Smith GM; Matsumaru T; Menhaji-Klotz E; Wood JL An Enantioselective Total Synthesis and Stereochemical Revision of (+)-Citrinadin B. J. Am. Chem. Soc. 2013, 135, 10890–10893. [PubMed: 23837485] (d)Chogii I; Njardarson JT Asymmetric [3+2] Annulation Approach to 3-Pyrrolines: Concise Total Syntheses of (−)-Supinidine, (−)-Isoretronecanol, and (+)-Elacomine. Angew. Chem., Int. Ed. 2015, 54, 13706–13710.(e)Nugent J; Banwell MG An Eleven-Step Synthesis of Galanthamine from Commercially Available Materials. Eur. J. Org. Chem. 2016, 5862–5867.(f)Makarova M; Endoma-Arias MAA; Dela Paz HE; Simionescu R; Hudlicky T Chemoenzymatic Total Synthesis of *ent*-Oxycodone: Second, Third, and Fourth-Generation Strategies. J. Am. Chem. Soc. 2019, 141, 10883–10904. [PubMed: 31184866] (g)Zheng C; Dubovyk I; Lazarski KE; Thomson RJ Enantioselective Total Synthesis of (−)-Maoecrystal V. J. Am. Chem. Soc. 2014, 136, 17750–17756. [PubMed: 25495370]

(18). (a)Guérard KC; Guérinot A; Bouchard-Aubin C; Ménard M-A; Lepage M; Beaulieu MA; Canesi S Oxidative 1,2- and 1,3-Alkyl Shift Processes: Developments and Applications in Synthesis.

J. Org. Chem. 2012, 77, 2121–2133. [PubMed: 22332792] For interesting applications of a semipinacol rearrangement to generate bridged bicyclic moieties within a polycyclic natural product skeleton, see: (b) Epstein OL; Cha JK Rapid Access to the "in,out"-Tetracyclic Core of Ingenol. Angew. Chem., Int. Ed. 2005, 117, 123–125.(c)Jørgensen L; McKerrall SJ; Kuttruff CA; Ungeheuer F; Felding J; Baran PS 14-Step Synthesis of (+)-Ingenol from (+)-Carene. Science 2013, 341, 878–882. [PubMed: 23907534] (d)McKerrall SJ; Jørgensen L; Kuttruff CA; Ungeheuer F; Baran PS Development of a Concise Synthesis of (+)-Ingenol. J. Am. Chem. Soc. 2014, 136, 5799–5810. [PubMed: 24712341]

(19). Naredla RR; Klumpp DA Contemporary Carbocation Chemistry: Applications in Organic Synthesis. Chem. Rev. 2013, 113, 6905–6948. [PubMed: 23819438]

(20). For a review on strained bridgehead alkenes, see: Warner PM Strained Bridgehead Double Bonds. Chem. Rev. 1989, 89, 1067–1093.

(21). Deslongchamps P Stereoelectronic Effects in Organic Chemistry, 1st ed.; Organic chemistry series; Pergamon Press: Oxford [Oxfordshire], New York, 1983.

(22). See the Supporting Information for details.

(23). (a)Concepción JI; Francisco CG; Hernández R; Salazar JA; Suárez E Intramolecular Hydrogen Abstraction. Iodosobenzene Diacetate, an Efficient and Convenient Reagent for Alkoxy Radical Generation. Tetrahedron Lett. 1984, 25, 1953–1956.(b)Corey EJ; Stoltz BM Novel Annulation Products Derived by Selective Attack on the C(18) Angular Methyl Group of the Cardenolide Ouabain. Tetrahedron Lett. 1999, 40, 2061–2064.(c)Hernando E; Villalva J; Martínez ÁM; Alonso I; Rodríguez N; Gómez Arrayás R; Carretero JC Palladium-Catalyzed Carbonylative Cyclization of Amines via γ-C(Sp 3)–H Activation: Late-Stage Diversification of Amino Acids and Peptides. ACS Catal. 2016, 6, 6868–6882.

(24). Dai M; Krauss IJ; Danishefsky SJ Total Synthesis of Spirotenuipesines A and B. J. Org. Chem. 2008, 73, 9576–9583. [PubMed: 18973385]

A. Distinct structural features of tetracyclic terpenoids include stereochemistry and position of quaternary centers.*

estrane   androstane   lanostane   euphane   limonoid   cucurbitane
                 pregnane
                 cardenolide

* = simplified structures are shown to emphasize the stereochemistry of quaternary centers at ring junctions

B. C9–C10 bond formation followed by rearrangement delivers diverse tetracyclic terpenoid systems.
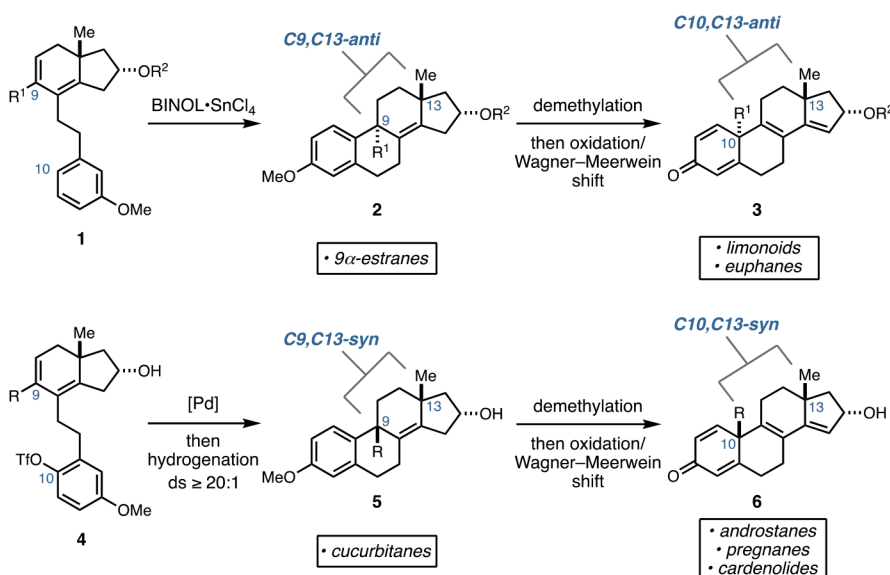
C. Established methods for tetracycle formation based on C9–C10 bond formation.
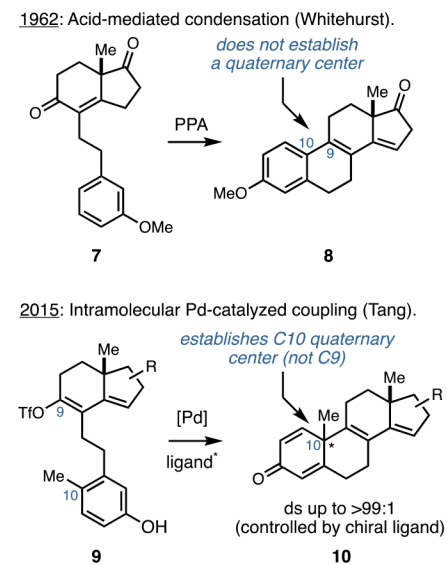
Figure 1.
Introduction to a synthetic pathway of broad relevance for the construction of fused tetracyclic terpenoid systems.

A. From epichlorohydrin to angularly substituted hydrindanes.

epichlorohydrin
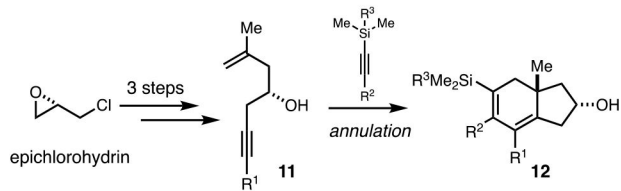
B. Applications in the context of natural product synthesis.

13
tetracyclic core
of cortistatin A

14
C14-desmethylene
corialactone D

15
(2S)-hydroxy-3,4-dehydro-
neomajucin
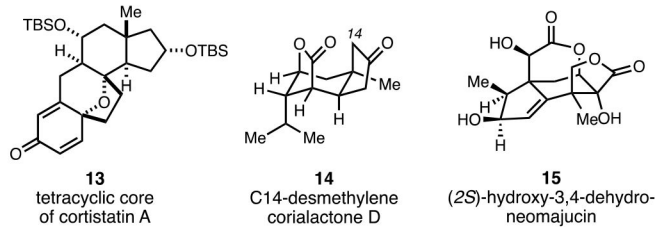
C. A synthetic strategy for the construction of tetracyclic terpenoid natural products with C9/C13 or C10/C13 substitution

*stereocontrol
at C9?*

*group-selective akyl shift
from C9 to C10?*

18

C9/C13 substitution:
• cucurbitanes
• C9α-substituted estranes

19

C10/C13 substitution:
• androstanes   • limonoids
• pregnanes   • lanostanes
• cardenolides   • euphanes
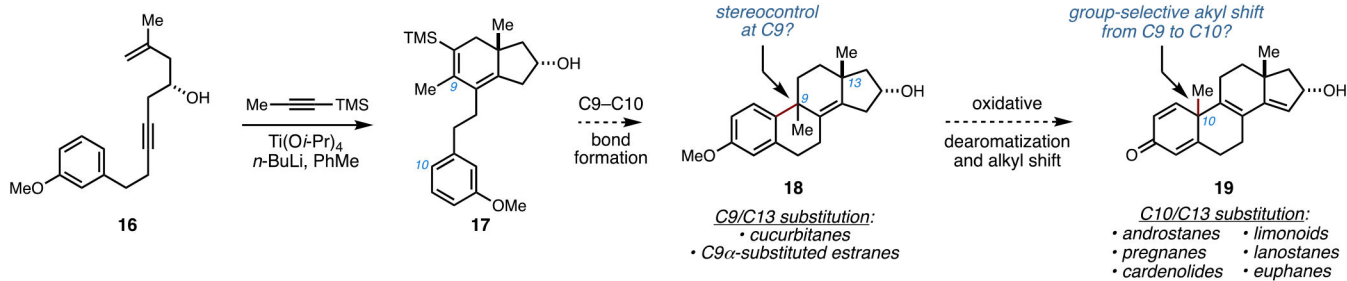
Figure 2.
Introduction to a synthetic pathway of broad relevance for the construction of fused
tetracyclic terpenoid systems.

A. Relative diastereoselectivity in the acid-mediated cyclization.
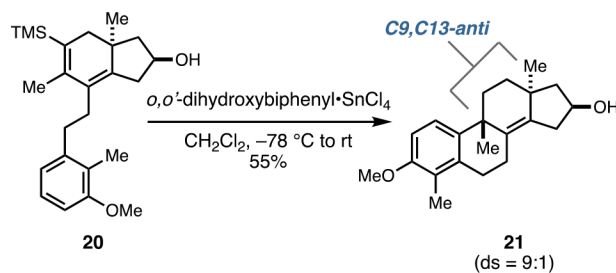
B. Double asymmetric acid-mediated cyclization reactions.
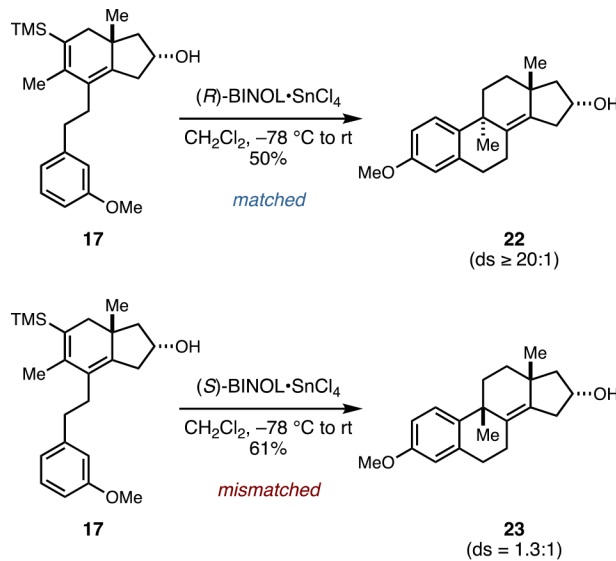
Figure 3.
Stereoselectivity in the Brønsted acid-mediated sequential protodesilylation and Friedel–Crafts cyclization.

A. Deuterium labeled substrate to explore facial selectivity of protonation in the mismatched reaction.

protonation at C11 is from α-face
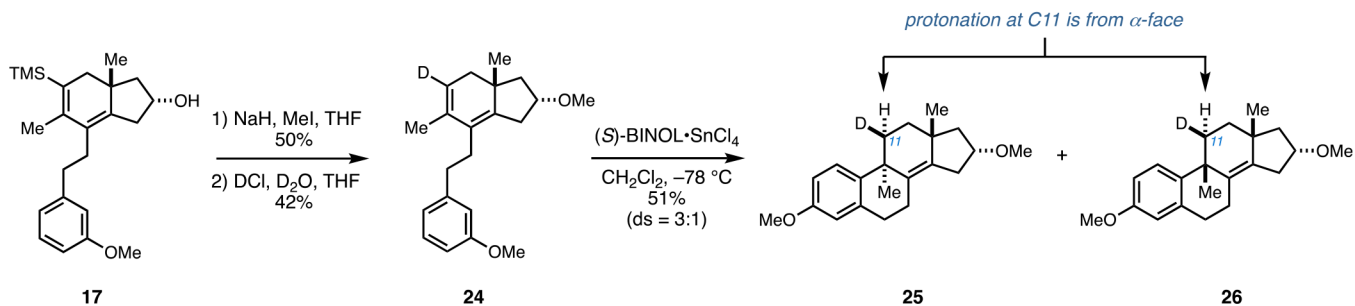
B. Intramolecular Heck reaction proceeds via carbometallation on the α-face of the C9–C11 alkene.

carbometalation on α-face of C9–C11
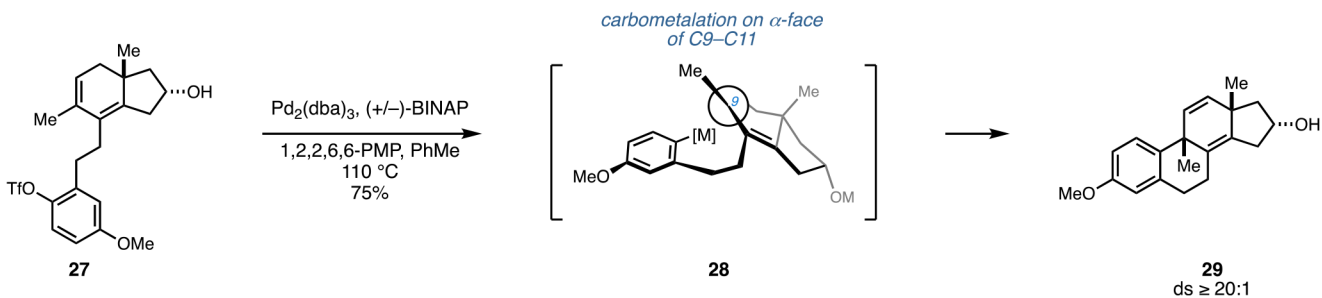
Figure 4.
Exploration of the mechanistic course of the mismatched cyclization promoted by BINOL·SnCl₄ and establishment of a highly selective cyclization to access the C9,C13-*syn* isomer.

A. Oxidative dearomatization followed by Wagner–Meerwein shift: *Concerning group selectivity in the migration event.*
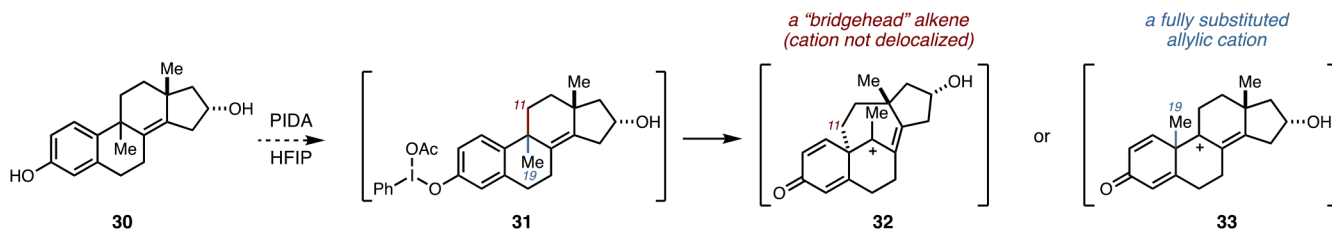
B. Oxidative rearrangement proceeds with selective shift of the C19-Me group and is effective with both diastereomers (C9,C13).
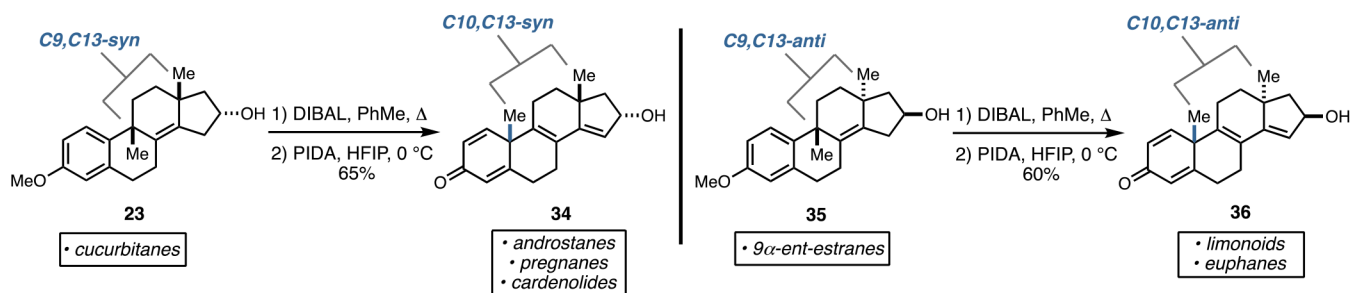
Figure 5.

Oxidative rearrangement/Wagner–Meerwein rearrangement to access tetracyclic skeletons possessing quaternary centers at C10 and C13.
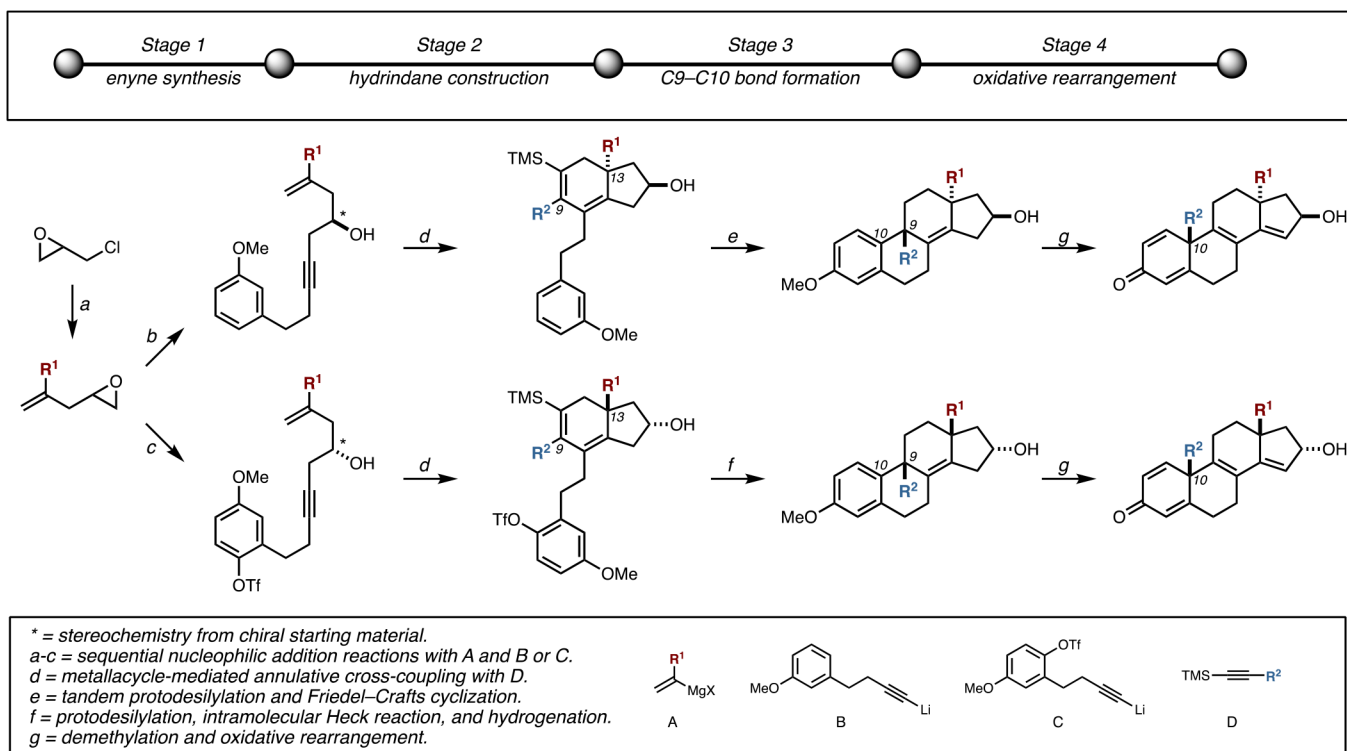
Figure 6.
Four-stage approach to the asymmetric and stereoselective synthesis of differentially substituted tetracyclic terpenoid-like motifs.

A. C9 substitution plays a significant role in stereoselective tandem protodesilylation/Brønsted acid-mediated ring closure.
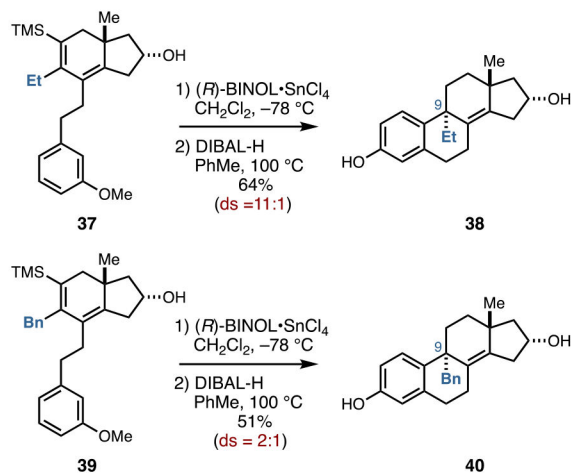
B. Complicating features of the tandem double asymmetric reaction.

(1) Silylation of the chiral Brønsted acid occurs in the first step:
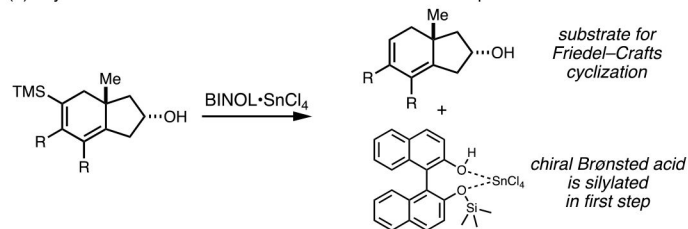
(2) The hydrindane substrate for tandem reaction is protic:
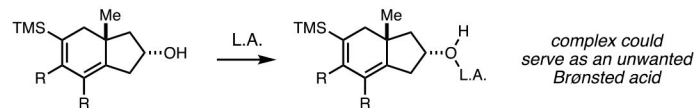
Figure 7.
C9-substitution plays a significant role in stereoselection during the tandem protodesilylation/Friedel–Crafts cyclization
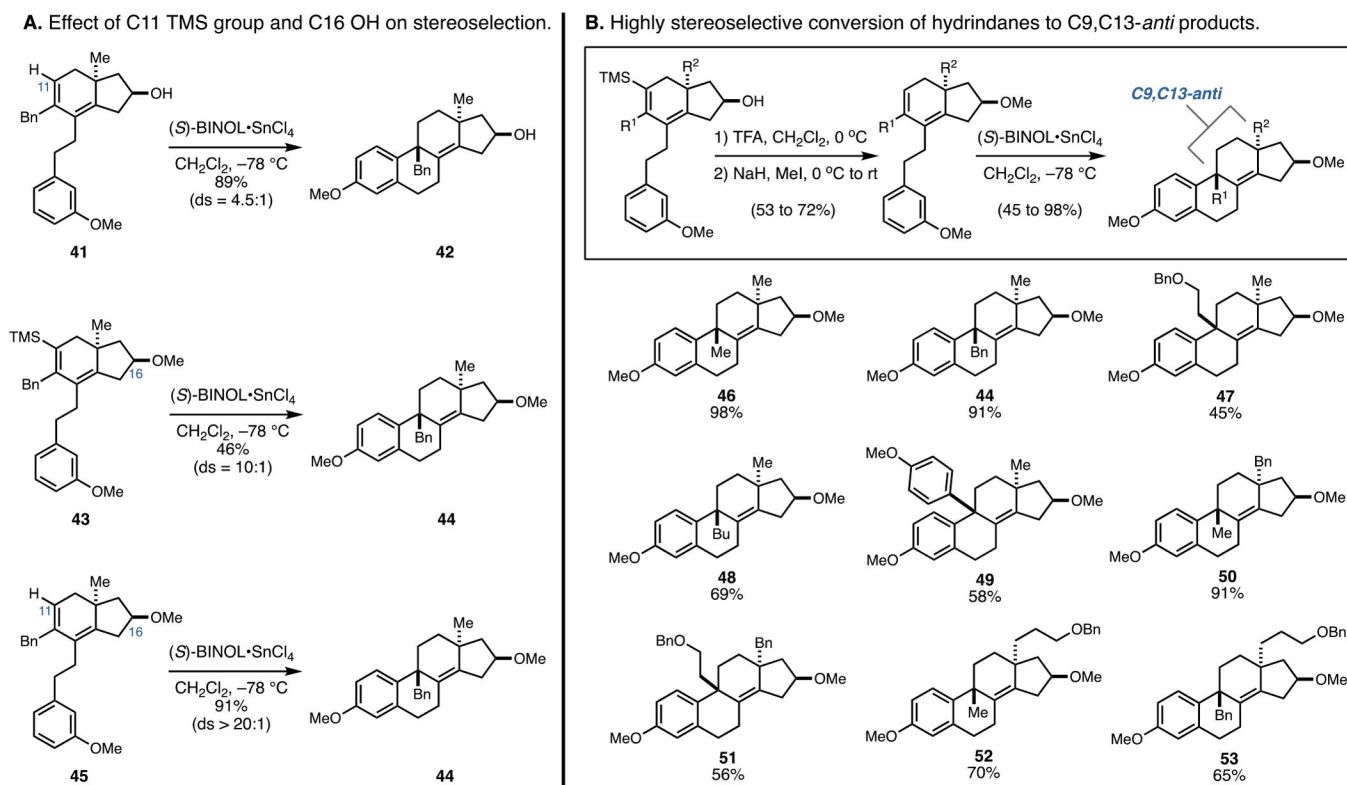
Figure 8.
Establishing a highly *anti*-selective Friedel–Crafts cyclization for C9–C10 bond formation.
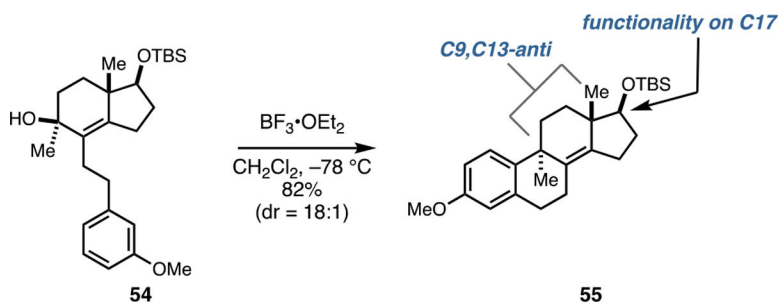
Figure 9.
Related Friedel–Crafts cyclization to access C9,C13-*anti* product possessing C17 oxygenation.
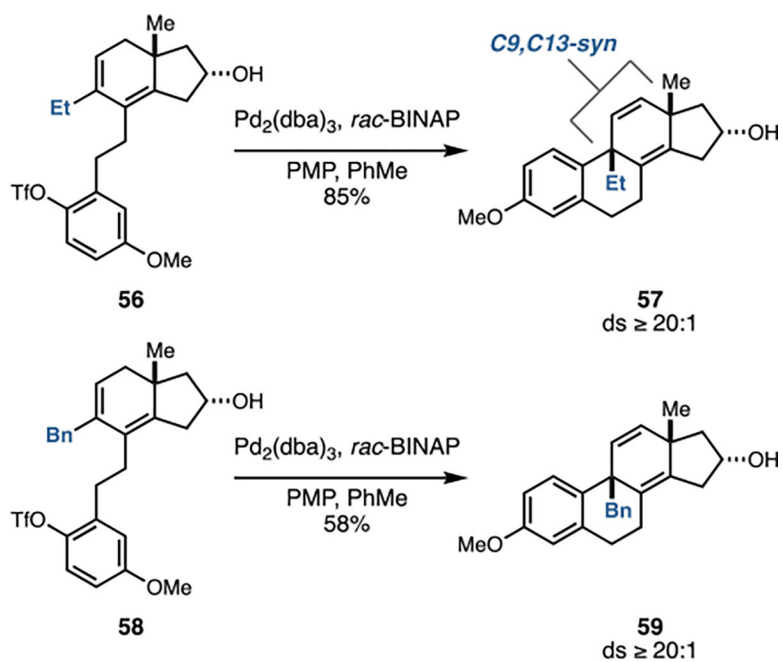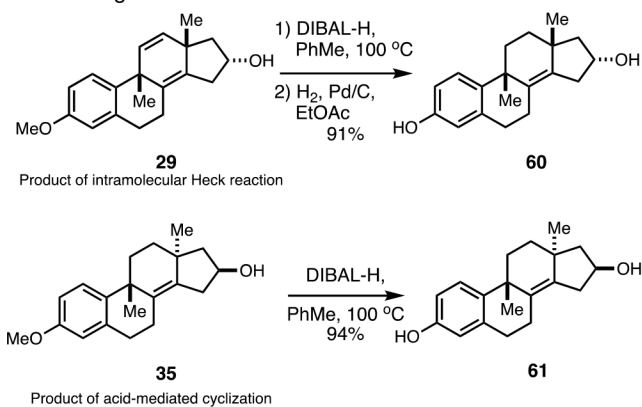
Figure 10.
Intramolecular Heck reaction is uniformly successful with substrates bearing Et- and Bn-substitution at C9.
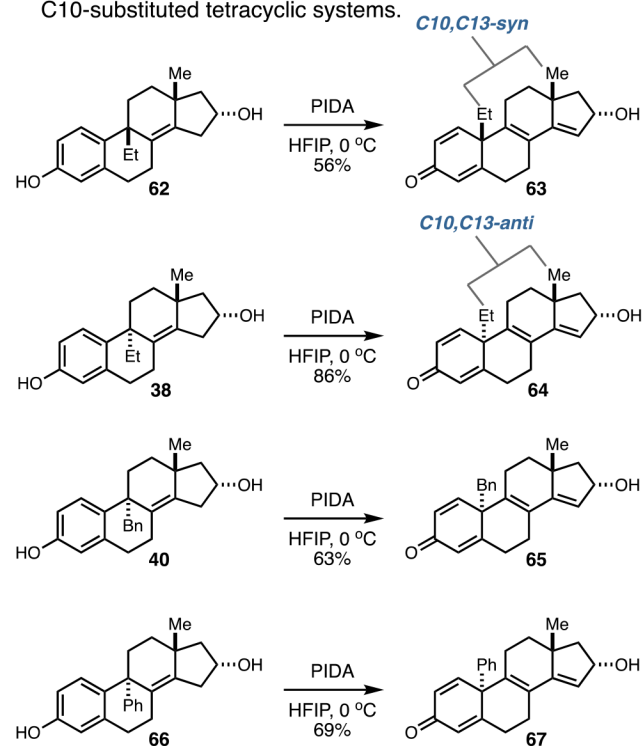
Figure 11.
Oxidative rearrangement occurs selectively with C9,C13-*syn*- and *anti*-isomers bearing varied substituents at C9.