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Strategic elements in computer-assisted retrosynthesis: A case study of the pupukeanane natural products

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Abstract

Computer-assisted synthesis planning represents a growing area of research, especially for complex molecule synthesis. Here, we present a case study involving the pupukeanane natural products, which are complex, marine-derived, natural products with unique tricyclic scaffolds. Proposed routes to members of each skeletal class informed by pathways generated using the program Synthia™ are compared to previous syntheses of these molecules. In addition, novel synthesis routes are proposed to pupukeanane congeners that have not been prepared previously.

Keywords

Automated retrosynthesis; Natural products; Terpenes; Pupukeananes

1. Introduction

1.1. Computer-assisted synthesis in the 2020s

Nearly half a century after several influential publications outlined an approach for computer-assisted synthesis [1], recent advances in machine learning (ML), accessibility of data, and fast calculations have led to renewed interest in computer-assisted synthesis [2]. In the last decade, increasingly sophisticated algorithms to navigate synthetic pathways [3], predict reaction products [4], and determine optimal reaction conditions [5] have been developed. Computer-assisted retrosynthesis encompasses programs designed to assist users in developing a human-generated route by identifying key elements of strategy [6], as well as programs that provide detailed routes to the target compound 3c,7.

A well-known challenge in the synthesis of complex molecules is predicting how faithfully methods for the preparation of relatively flat, sp^2-rich molecules would apply to more topologically complex, sp^3-rich, caged structures [8]. It is these structurally complex sp^3-

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Declaration of competing interest

The authors declare no competing interests in any commercial products including the program Synthia™ that was used in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132584.

rich scaffolds that often imbues natural products with important biological function and therefore generate interest in strategies, tactics, and methods for their synthesis. In addition to recent advances that enable retrosynthetic planning programs to accurately predict routes and conditions for the synthesis of drug-like molecules 7f,g, the program Synthia™ has recently been deployed to plan the synthesis of sp^3-rich, complex targets by using enhanced searching strategies. Notably, Synthia™-planned syntheses of multiple natural products have now been validated in the laboratory [9].

In this Article, we will examine synthetic strategies that Synthia™ applies toward the pupukeanane natural products. In particular, we will consider these Synthia™-proposed routes in comparison with previously established strategies for the synthesis of these natural products, focusing on the formation of the key C–C bonds that forge their tricyclic skeletons. The goal of this analysis is to elucidate the capabilities of Synthia™ as well as identify areas for development of the program in tackling the total synthesis of moderately complex natural products. While several metrics exist to compare syntheses (e.g., step count, yield, cost of materials, etc.) we sought to qualitatively evaluate how Synthia™ proposed routes advance the science of synthesis by introducing new perspectives on the possible strategies to access the complex, tricyclic core of the pupukeanane family of natural products. An important criterion for evaluating each route, *a priori*, would be to determine whether key steps in the route are feasible in order to justify an investment in time and resources to pursue them in the laboratory. Such decisions can be largely subjective and based on a chemists' intuition. To probe this in a more quantitative way, here, we explore the use of physics-based principles and computational analysis to support or refute the probability of success of these proposed routes.

1.2. The inner workings of Synthia™

Synthia™, formerly known as Chematica, has been developed over the past decade and has recently been commercialized by MilliporeSigma [10]. The program includes a detailed set of more than 100,000 expert-coded reaction rules. Each rule details the outcome of a particular transform (i.e., data needed to map any affected functional group(s) back to the requisite precursor compound(s)) as well as provides illustrative references, sample conditions, and additional reaction metadata that indicates functional group compatibility and expected selectivity outcomes for the forward transformation [11]. Synthia™ applies these by a workflow that is analogous to how a chemist may analyze a synthetic target (Fig. 1).

From a given synthetic target, a chemist would likely consider many possible disconnections, explicitly or subconsciously, that may simplify a given target using their learned knowledge (Step 1); the chemist would then select a promising transform on the basis of how simplifying it would be as well as its compatibility with the target in question (Step 2). Synthia™ mimics this by applying coded reaction rules to generate potential substrates that would enable the synthesis of the desired target. The program then evaluates the effectiveness of any given rule based on the structural complexity of the precursor compounds using a Chemical Scoring Function (CSF). This scoring function is user editable but typically prioritizes the reduction of structural complexity at each step as measured

by metrics such as the number of rings, stereocenters, and atoms present in the precursor compounds.

At this stage, either a chemist or the software would identify whether the substrates are readily available (Step 3) by searching a chemical database. If the precursor compounds are not readily available, the process is repeated (Step 4) until suitable starting materials have been identified. At this stage, a synthetic chemist may write down the route to consider and iterate the process until several possible routes have been identified (Step 5). With several possible routes to consider, a chemist would need to choose the "best" synthetic strategy, which may rely on metrics such as step count, expected yield, the use of hazardous reagents, cost of starting materials or less quantifiable elements such as elegance, creativity, or the perceived ability to access other analogues of the target compound. Synthia™ will select the best scoring route through a Reaction Scoring Function (RSF) which typically takes into account factors such as the use of protecting groups, the number of steps, and the presence of possible reactivity conflicts.

This simplistic picture does not detail all the functions of Synthia™, but is meant to provide an overview of important components for the program and how a user can modify them. Another key consideration is that natural products synthesis often requires farsighted, multi-step strategies that may not be favored by an algorithm which prioritizes the reduction of structural complexity of the target compound. One approach to incorporate more factors congruent with a synthetic chemist's analysis into Synthia™ included the development of a database of tactical combinations that consisted of more than 100,000 two-step sequences that could be applied [12]. More recently, identification of causal relationships that led to improved treatment of certain classes of reactions (i.e., allowing multiple functional group interconversions without deprioritizing the route) have been implemented to assist in multi-step strategizing. These advances were key to enhancing Synthia™'s capabilities to enable proposals for the syntheses of multiple natural products that have been validated in the laboratory [9].

1.3. Unique scaffolds in the pupukeanane family

The pupukeananes are a family of structurally diverse marine sesquiterpenes that contain isonitrile groups or derivatives thereof. 9-Isocyanopupukeanane (**1**) was the first of the pupukeananes to be isolated [13]. For this reason, the caged tricyclo[4.3.1.$0^{3,7}$]-decane core (also known as an isotwistane) of this molecule has become known as the pupukeanane skeleton — named after Pupukea in Hawaii where the organism was collected [13]. 9-Isocyanopupukeanae (**1**) was also one of the first naturally occurring isocyanoterpenes to be isolated and sparked an interest in these natural products and congeners bearing isonitriles [14] or related functional groups [15] because of their potential antimalarial properties. Subsequent studies on the same organism, a sponge of the *Ciocalypta* species, led to the isolation of a natural product bearing a rearranged skeleton with a similar isotwistane core which has been labelled the neopupukeanane skeleton (see **2**). In 1979 another rearranged natural product bearing the related [5.2.1.$0^{4,8}$]decane scaffold, which became known as the allopupukeanane skeleton (**3**), was co-isolated with a sample of 9-isocyanopupukeanane (**2**) [16,17]. In the past decade, two additional unique pupukeanane natural products, 2-

formamidoabeopupukeanane (**5**) [15e] and 9-isocyanoneoallopupukeanane (**4**) [18], have been isolated from related organisms. Both of these natural products were co-isolated with known congeners suggesting that members of this family share a common biosynthetic origin.

In our computer-assisted synthesis survey, we subjected members of each pupukeanane scaffold type (Fig. 2) to Synthia™ in order to generate synthesis pathways. Often within only a few minutes of searching, Synthia™ was able to propose numerous routes. In each case, at completion of the search, we analyzed the best scoring pathway and present them herein. One potential roadblock in the integration of computer-assisted synthesis with traditional approaches to laboratory syntheses by organic chemists is the learning curve associated with understanding and using the software. For this reason, here, we have opted to show routes that are produced with near default parameters, selecting the recommended setting for natural products by the Synthia™ program. Using the program at this level is extremely straightforward by following intuitive on-screen prompts and does not require explicit training. Additional training and orientation are available from MilliporeSigma with the software.

2. Results and discussion

2.1. The pupukeanane skeleton

We began our survey by using the Synthia™ software to plan routes to the isotwistane containing pupukeananes. We first analyzed 9-pupukeanone (**6**, Scheme 1), a known degradation product of **1** which has previously been elaborated to **1** in a four-step sequence, given its popularity as a synthetic target [19].

2.1.1. Synthia™'s proposed route to 9-pupukeanone—Synthia™'s proposed route to 9-pupukeanone (**6**) proceeds through a key Diels–Alder [4 + 2] cycloaddition (see **16** to **6**, Scheme 2) to build the pupukeanane tricyclic core. In the forward direction, the proposed synthesis begins with an organocatalytic desymmetrization of prochiral cyclohexanone **7**. This type of selective deprotonation with a chiral phase-transfer catalyst has been previously used to access enantiomerically enriched silyl enol ethers which can be oxidized under Pd(II) conditions to the corresponding enone (**8**). At this stage, the software proposed a sequential α-methylation and O-methylation of the enone to arrive at diene **11**. Interestingly, Synthia™'s raw output explicitly proceeds through the enol tautomer (**10**), which, if implemented, would likely be only generated *in situ*. Subsequent reduction of the ester and Appel-type substitution would lead to alkyl halide **13**. To append the isopropyl group, an Ender's RAMP/SAMP alkylation of 3-methyl butanal (**14**) is proposed to give aldehyde **15**. Tebbe olefination of **15** would give cycloaddition precursor **16**. The [4 + 2] cycloaddition of this precursor was proposed to give the desired 9-pupukeanone (**6**) after an acidic workup.

Notably, disconnection across tricyclic cores such as **17** has been previously proposed and synthetically validated by the Yamamoto [19a], White [20], and Piers [21] groups in their syntheses of 9-pupukeanone (**6**, Scheme 3a). Each of these previous syntheses that employ a Diels–Alder cycloaddition proceed to give a single isomer of the desired tricycle (i.e., **19**). However, a primary difference in the route proposed by Synthia™ when compared to these

previous syntheses is that in Synthia™'s route, the isopropyl group is installed prior to the cycloaddition.

In Frater's synthesis of 2-pupukeanone (Scheme 3b) which employed an analogous Diels-Alder cycloaddition to build the isotwistane core (**24**) from a monocyclic precursor (**22**), the carbons of the isopropyl group were pre-installed. In the Frater cycloaddition, two isomers were observed following the Diels-Alder cycloaddition step that were a mixture of the desired isotwistane (**24**) and undesired twistane **23** in a 3:1 ratio. In a subsequent step, twistane **23** was converted to the more thermodynamically stable isomer (**24**) by heating at 250 °C for 5 min to presumably effect a retro-Diels–Alder/Diels–Alder sequence. These previous studies by Frater support the proposal by Synthia™ that using a mono-cyclic precursor bearing all the carbons of the skeleton (i.e., **16**), the Dielse–Alder reaction should be feasible.

However, given that the only example to build the isotwistane core with all carbons of the natural product intact led to a nonselective mixture (**23** and **24**), we sought to obtain a better understanding of the factors that determine formation of the desired isotwistane skeleton (**17**, Scheme 4) over the undesired twistane skeleton (**26**) in Synthia™'s proposed transformation (**16** to **17**). The cycloaddition reaction was studied using wB97XD/6–311+G** single point calculations. The SMD implicit solvent model using parameters for toluene on geometries optimized at the wB97XD/6–31G* in the gas phase using Gaussian16 [22] as has been demonstrated for Diels–Alder cycloadditions [22]. We computed the desired isotwistane skeleton to be both kinetically and thermodynamically favored (Scheme 4). Additionally, in this case, an extremely high selectivity was anticipated for the desired product ($\Delta\Delta G$(react) = +9.0 kcal/mol: $\Delta\Delta G^{\ddagger}$ = +7.4 kcal/mol).

Ultimately, without being explicitly trained using the existing syntheses of 9-pupukeanone, Synthia™ was able to identify strategic disconnections that led to proposed routes that were comparable, but distinct from previously published routes. In the case of 9-pupukeanone (**6**), the route proposed by Synthia™ would be the shortest synthetic sequence to access **6** were it to be successfully implemented in the laboratory. Furthermore, the Synthia™ route would provide access to enantioenriched material. This outcome speaks to the effectiveness of Synthia™ to propose routes that rival the best human-generated routes. The program is designed to prioritize selective reactions with ample precedent in its default search parameters.

2.2. The neopupukeanane natural products

The related neopupukeanane skeleton also contains an isotwistane scaffold that is proposed to arise through a series of carbocation rearrangements in the biosynthesis of these natural products [23]. This results in unique alkyl substitution patterns relative to the pupukeananes. To date, three unique neopupukeananes have been isolated including two rare thiocyanatecontaining natural products: 2-thiocyanatoneopupukeanane (**2**, Fig. 3) and 4-thiocyanatoneopupukeanane (**28**) [24]. In applying Synthia™ searches to identifying routes for the synthesis of the neopupukeananes, we first observed that searches that targeted the natural products bearing the thiocyanate group (**2** and **28**) were not productive. Instead, a

search for the precursor ketones (i.e., **27** and **29**), which have been previously synthesized and carried forward to the thiocyanate natural products [25], were more promising in identifying routes to the neopupukeanyl isotwistane scaffold. This modification of the search to exclude the thiocyanate group was critical and highlights the limited examples of this functional group in the Synthia™ rule library — thus, requiring an adjustment by the synthetic chemist to accommodate this limitation.

2.2.1. Synthia™'s proposed route to 2-neopupukeanone—Synthia™ proposed building 2-neopupukeanone (**27**, Scheme 5a and b) using a radical cyclization similar to tactics employed by Subba Rao [26] and by Srikrishna [27] in their syntheses of the 2-pupukeananes. The proposed synthesis begins from known dehydrocarvone (**30**) to access α-phellandrene (**31**). Introduction of a ketene equivalent would lead to the corresponding [2.2.2]-bicycle. Notably, Synthia™ correctly marks this step as "not selective" as it would likely give a mixture of epimers. However, this is expected to be inconsequential as these epimers would ultimately converge to a single product after subsequent manipulation. This dithiane (**32**) could be cleaved to give norbornenone **33**, which sets the stage to install the southern bridge of the tricycle.

In this proposal, the α-alkylation could occur through treatment of **33** with LDA followed by introduction of an electrophile such as bromo ethanol **34**. Notably, Synthia™ correctly flags the need for protection of bromo-ethanol (**34**) to prevent deprotonation of the alcohol group under the reaction conditions. One simple (human-proposed) solution would be to use THP-protected alcohol **37** as in previous syntheses of these molecules [21]. This decision would allow seamless integration of the THP acetal compound into the existing route, which could then be cleaved in an acidic workup without increasing the longest linear step count. The outcome, bicycle **35**, would be primed for the key radical cyclization following an Appel-type substitution of the hydroxy group for bromine to give **36**. Alternatively, dibromoethane could be a suitable alterntive and obviate the need to substitute the alcohol group for a bromine (Scheme 5c).

From bicycle **36**, a 5-exo-trig radical cyclization is proposed to give 2-neopupukeanone (**27**), which would complete a formal synthesis of (−)-**2** as it intercepts Uyehara's route [25b]. Synthia™ suggests that a protection of the ketone group may be necessary. However, previous syntheses of the pupukeananes have accomplished similar transformations with unmasked ketones in similar enviroments 26a,27b.

Given the importance of this key radical cyclization at a late-stage in the synthesis, we sought to more quantitatively evaluate the proposed transformation to provide an analysis that would engender confidence in the planned route and reduce the risk associated with undertaking this synthesis in the laboratory (Scheme 6). While isotwistane skeletons (i.e., **27** and **I3**) are typically less strained than the corresponding twistane skeletons (i.e., **I2**), because the twistane skeleton could be favored through an allowed *6-endo-trig* pathway and a tertiary radical, we aimed to quantify the expected selectivity of this transformation. Comparing **I1**→**I2** and **I1**→**I3** at the same level of theory as previously described which has been shown to be effective in similar radical cyclizations [28], we observed that the formation of the isotwistane radical (**I3**) was both thermodynamically and kinetically

favored when compared to the formation of the undesired twistane radical (**I2**, ΔΔG(react) = +5.5 kcal/mol, $\Delta\Delta G^{\ddagger}$ = +6.6 kcal/mol). Ultimately, this analysis is consistent with Synthia™'s rule-based proposal — selectivity conflicts were not flagged by the program.

Overall, the Synthia™-proposed synthesis of **27** uses relatively robust chemistry that bears similarity to tactics previously applied to the syntheses of related molecules to arrive at a relatively short synthesis. Additionally, this case study highlights the ability of human design to provide improvements in these modular computer-proposed routes. We posit that tools such as Synthia™ are most powerful when used in tandem with user (human) knowledge.

2.2.2. Synthia™'s proposed route to 4-neopupukeanone—Interestingly, in the case of the related 4-neopupukeanone (**29**), which bears the same skeleton as 2-neopupukeanone (**27**), the Synthia™-generated route is a very distinct strategy involving building the isotwistane core through a ring expansion of cyclobutanone **49** (Scheme 7a and b). This strained intermediate (**49**) is proposed to arise from a [2 + 2] photocycloaddition from masked ketene **47**. Notably, two steps of this pathway are flagged by Synthia™ as "not selective" because they are likely to furnish isomeric mixtures.

In considering this route, an experienced organic chemist would likely realize that intermediates such as **45** bear a lot of structural similarity to (*R*)-carvone (**50**) whereas Synthia™ identified a route from vinyl iodide **40**. Given the advantages inherent in starting from cheap, commercially available enantioenriched materials such as carvone, this situation represents an opportunity for a hybrid human-designed/Synthia™-inspired approach in which a route could be independently designed to access **45** to allow enantiospecific entry into a proposed route.

While the Synthia™ proposed synthesis of **29** has some selectivity challenges, it inspired us to consider the development of selective methods to address these challenges. One can envision that from compound **51** (Scheme 7c), inspired by Synthia™'s use of **49**, there would be opportunities to desymmetrize this prochiral compound at a late-stage, which would lead to an elegant approach to these molecules. For example, using a desymmetrizing Tiffeneau-Demjanov reaction [29] could lead to a compound such as **52**, following which the isopropyl group could be installed diastereoselectively at a late-stage. If realized, these creative designs would undoubtedly be of interest to the synthesis community. In this way, Synthia™'s proposals can be aspirational and, in the cases where certain proposed steps may seem improbable, push chemists to look beyond precedent in order to effect a desired transformation.

Ultimately these examples showcase that Synthia™'s routes can engender meaningful strategic elements that serve as a starting point in identifying synthesis routes an organic synthetic chemist may want to pursue.

2.3. Pupukeananes bearing the [5.2.1.0^{4,8}]Decane core

While several syntheses of the isotwistane core, the most well-studied of the pupukeanane family, have been reported, there are relatively fewer studies toward the synthesis of the rearranged [5.2.1.0^{4,8}]decane core found in 2-isocyanoallopupukeanane (**3**, Scheme

8) and 9-isocyanoneoallopupukeanane (**4**). Syntheses of natural products with these scaffolds are relatively underexplored. A single route has beenpublished to access 2-isocyanoallopupukeanane [30] while no synthetic studies toward the recently isolated neo-allopupukeananes have been reported thus far.

2.3.1. Synthia™'s proposed route to 2-isocyanoallopupukeanane—

Synthia™ proposes a direct disconnection of the allopupukeanyl core back to a fused bicycle. Interestingly, in all of our analyses of synthesis routes to the pupukeananes using Synthia™, this was the first time that the top scoring route proposed a disconnection of these highly bridged tricycles (i.e., **63**) to an all-fused system, specifically [4.3.0]-bicycle **62**. As first described by Corey [31] and in subsequent work from Wender [32], Hoffmann [33], and others, disconnections of the maximally-bridged ring can lead to a rapid simplification in the retrosynthetic direction. In the forward sense, Synthia™ proposed a radical cyclization to forge this bridged tricycle. However, the syntheses of this precursor compound (**62**) as proposed by Synthia™ are extremely lengthy and fraught with selectivity issues (e.g., as illustrated in Scheme 8) due to the complexity of installing multiple contiguous stereocenters to build these densely functionalized cores as well as intermediates that may be challenging to access in the laboratory (i.e., **56**). Nonetheless, the identification of this key disconnection could serve as a platform to inspire new strategies to arrive at **62**.

Notably, this general strategy of constructing a bridged bicyclic core has been applied in the synthesis of a related compound, 2-pupukeanone by Srikrishna and Subba Rao 26a,27a. However, in the existing syntheses of 2-isocyanoallopupukeanane (**3**) [30b], this disconnection has not been employed.

2.3.2. Synthia™'s proposed route to 9-isocyanoneoallopupukeanane—

Unsurprisingly, for the related neoallopupukeanane skeleton (**4**, Scheme 9), Synthia™ proposes the same key disconnection (see **65** to **66**) as was identified for 2-isocyanoallopupukeanane.

Ultimately, Synthia™'s proposals to build natural products bearing the allopupukeanane scaffold highlight the ability of the program to recognize the value of topologically simplifying disconnections. While the route proposed to 2-isocyanoallopupukeanane (**3**) is lengthy, it is comparable in overall step count to the first published synthesis of this molecule [30b]. The ability to rapidly generate these routes, which capture important elements of strategy, could enhance the route planning process for organic chemists by providing a unique starting place.

2.4. Proposed routes to 2-formamidobeopupukeanane

Only a single natural product, 2-formamidoabeopupukeanane (**5**, Scheme 10), has been isolated bearing the abeopupukeanane skeleton. To date, no synthetic studies toward this natural product have been reported. For this reason, we were particularly interested in the strategies Synthia™ would propose for its synthesis.

A Synthia™ analysis of 2-formamidoabeopupukeanane led to a proposed route that proceeds through a key Diels–Alder cycloaddition to close the tricyclic core from a

monocyclic precursor (**72**). In the forward sense, the proposed synthesis commences with the diastereoselective [4 + 2] cycloaddition of commercially available dienophile **67** and diene **68** to yield cyclohexene **69**. Wittig-Schlosser type homologation using a protected 4-bromobutan-2-one (**70**) could then lead to homologated cyclohexene **71**. Trapping this compound in the enamine form (**72**) would set the stage for the key cycloaddition to build the abeopupukeanane skeleton (**73**). Following this, heterogenous hydrogenation of the bridging olefin would give **74**. A subsequent formylation of the amine would furnish 2-formamidoabeopupukeanane (**5**).

One key challenge in the Synthia™-proposed cycloaddition to form **73** is the potential for a competing *E/Z* isomerization of the enamine in **72** prior to the cycloaddition, which may lead to a mixture of diastereomers at the amino-group-bearing C_2 position of **74**. To the best of our knowledge, cycloadditions to build [2.2.1]-bicycles in this manner are not known and may prove challenging. Specifically, the cycloaddition of **72** would have to proceed through a highly strained transition state in order to achieve the necessary overlap between the HOMO of the diene and the LUMO of the dienophile. While further studies are necessary to understand the feasibility of this transformation, this strategy, if realized, would be an effective way to access this natural product scaffold. Given these potential challenges, we analyzed this transformation in more detail through computational modeling in order to determine the feasibility of this late-stage step [34].

Initial modeling of the intramolecular cycloaddition of **72** to give **73** was conducted at the same level of theory as previously discussed(Scheme 11). The calculations showed that the proposed transformation is thermodynamically favorable ($\Delta G° = -6.3$ kcal/mol), but proceeds through a transition state with an extremely high activation barrier (67.8 kcal/mol). Given that intermediates such as **72** are relatively electroneutral, we envisioned that strategic introduction of an electron-withdrawing group, for example a nitrile group (see **75**), might improve the prospects for this key cycloaddition. Indeed, modeling this variant of the proposed cycloaddition led to a calculated activation barrier that was lower (61.3 kcal/mol) and the overall process was also computed to be more thermodynamically favorable ($\Delta G° = -11.8$ kcal/mol). However, given that this barrier was still extremely high, we also considered introducing a bulky group at the ring junction position (see **77**) in order to render the starting material in a conformation such that the diene would adopt a presumably more reactive axial placement. We envisioned that the introduction of a phenyl sulfone for this purpose might be synthetically attractive as the product (**78**) could be reduced to the corresponding alkane. Indeed, in modeling this system, we observed that the product was both thermodynamically more favorable ($\Delta G° = -18.2$ kcal/mol) and proceeded through the lowest activation energy that was calculated (50.4 kcal/mol). Given both the steric and electronic influences in lowering the transition state barrier associated with reaction of **77**, we sought to gain more insight into the steric versus electronic influences by modeling an analogous compound bearing a *t*Bu group (**79**). Although it would be difficult to envision the synthetic utility of **79**, the low activation energy we observed in this case (55.3 kcal/mol) supports our hypothesis that the effect of introducing the sulfone group were due largely to its steric properties.

While the associated activation barrier of >50 kcal/mol for the transformation of **77** to **78** is still very high, the overall computational exercise serves as an example of how synthetic chemists may work in concert with Synthia ™ to manipulate novel disconnections identified by the program to arrive at effective syntheses.

Additionally, this latter computational exercise serves as a prime example of how retrosynthesis software can benefit from a rapid physics-based analysis. Expert-coded rules cannot account for the steric, electronic, and stereoelectronic effects in the contorted transition states of topologically complex structures such as these that need to be considered on a case-by-case basis. Indeed, such tools for strain calculations have been already incorporated into the Synthia™ suite using manual post-processing, but the ability to rapidly model transition states of key steps (and human-proposed alternatives) would further boost confidence in the routes proposed or eliminate them if they were shown to be highly unlikely. Overall, this would accelerate the process of transitioning from the planning stages of synthesis to execution in the laboratory.

3. Summary and outlook

In this Article, we have detailed syntheses proposed by the retrosynthesis software Synthia™ to access members of the pupukeanane family. Complete routes to several compounds were proposed by Synthia™, including routes to three unique carbon skeletons that comprise the frameworks of five natural products with novel scaffolds. Overall, we observed that several of the routes to the topologically complex structures of the pupukeananes proposed by Synthia™ possess a high level of creativity by recognizing unusual disconnections that appear attractive and feasible. In addition, we have demonstrated how human-design can enhance the computer-generated proposals. Specifically, this can occur through strategic searches for routes to earlier stage intermediates, through the development of new synthetic proposals based on a key step identified by Synthia™, or through modifications to steps that are proposed to shorten a synthesis or enhance selectivity. Key advantages of the hybrid approach are the addition of subconscious intuition and creativity that can be incorporated based on the priorities of the user.

As advances continue, computational tools such as Synthia™ are likely to become integrated into the synthetic chemist's "toolbox". In our estimation, Synthia™'s interface is extremely user friendly, with default settings and searches that can be conducted without any background in coding. Additionally, the software integrates with an easy-to-use structure editor, or targets can be readily inputted by copying the associated SMILES string from ChemDraw, a quintessential program that most organic chemists use frequently.

Relative to the effort inherent in synthesizing a molecule, the time it takes for Synthia™ to identify routes is extremely short. Importantly, Synthia™ effectively identifies a wealth of reactions with literature precedent that may be immediately tested and possesses an integrated Reaxys search function that assists in finding the most closely related literature examples. Even if the exact route proposed by Synthia™ is not carried out in the laboratory, this information can greatly accelerate synthesis planning. Additionally, Synthia™ has already integrated several easy-to-use methods for chemists to accomplish these goals

including integrated molecular mechanics level calculations to estimate the strain energy of various intermediates.

Cases where target structures bear certain rare functional groups, for example thiocyanates in the case of the pupukeananes, present challenges for the program. In these instances, we propose that a combination of human-generated disconnections and strategic Synthia™ searches can allow for the design of hybrid routes. Additionally, the reaction rules and searching algorithms are continually being updated. In cases such as these where one can identify a likely cause as to why the program fails, the program offers a direct communication button with engineers at MilliporeSigma who immediately begin to work to address the problem — for example by adding additional reaction rules to address these cases. This feedback loop between the creators and the users of the program is key to staying current with the ever-expanding breadth of chemical space and literature.

Although education is not the express purpose of a retrosynthesis tool such as Synthia™, it's worth noting that the vast database of reactions that are readily applied to these targets make the use of these tools extremely valuable, especially for early-stage career scientists as well as those focused on identifying synthesis routes backed by precedent (e.g., in industry). Importantly, parsing through the synthesis of several different targets usually provides a wealth of different reactions, although some do appear quite frequently in cases where they build multiple bonds or stereocenters and may be prioritized for that reason. For example, in the case of the pupukeanane natural products, the Diels–Alder reaction was often invoked to build the bridged core of these molecules as the Diels–Alder transform is powerfully simplifying.

Ultimately, Synthia™ represents a powerful new computational tool that can augment the process of retrosynthetic planning. With recent modifications, it is well equipped to propose syntheses to complex natural products such as the pupukeananes. Depending on the target in question, the routes that are suggested by computer may serve as an aspirational goal that inspire creativity—serving as a starting point for synthetic chemists tackling complex targets, or even as a blueprint for the synthesis of the target compound.

4. Experimental section

4.1. Detailed Synthia™ search parameters

Each natural product or derivative was input as a SMILES string as a single enantiomer (as drawn in the manuscript). The search details are included in the order they are selected in the commercial Synthia™ application. These effects of these settings have been previously described 7g,9,11. For each search, the best scoring pathway using the following parameters was analyzed and presented in the manuscript.

Analysis type: Automatic Retrosynthesis.

Rules: none selected.

Filters: Multicut, Power Search, Legacy Strategies.

Max. paths returned: 50.

Max. iterations: 10,000.

Commercial: Max. molecular weight:1000 g/mol.

Max. price: 1000 $/g.

Published:

Max. molecular weight: 200 g/mol, Popularity: 5.

Shorter paths: yes.

Pathway linearity: CONVERGENT.

Protecting groups: MORE.

Reaction scoring formula: 100*(TUNNEL_COEF*FGI_COEF*20 + 1000000*(FILTERS + CONFLICT)+500*NON_SELECTIVITY+10*PROTECT).

Chemical scoring formula: 100*(SMALLER^3).

Min. search width: 500.

Max. reactions per product: 60.

4.2. Computational method

All density functional theory (DFT) calculations were performed using Gaussian 16 [35]. Geometries were fully optimized at the wB97XD/6–31G* level of theory in the gas phase. Solvent effect were taken into account using wB97XD/6–311+G** single point calculations with the implicit SMD model and the parameters for toluene. All optimized geometries were subjected to frequency calculations at the wB97XD/6–31G* level to verify their character (local minima or saddle points) and to calculate the Gibbs free energy correction at 298 K and 1 atm. All energies are wB97XD/6–311+G** (SMD) + Gibbs free energy corrections and are reported in kcal/mol.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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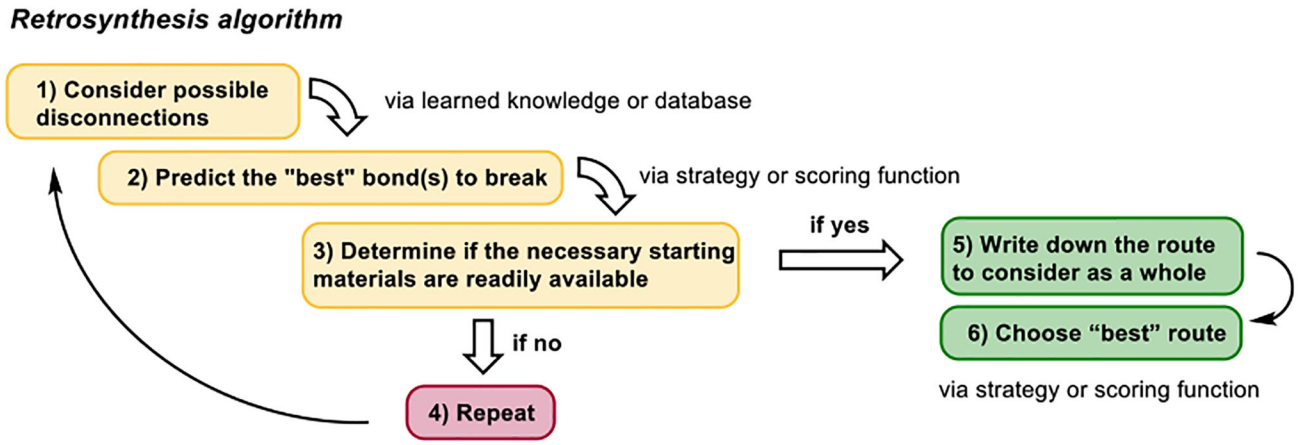


Fig. 1.

A general scheme for understanding computer-assisted retrosynthesis decision making. Portions of this figure were adapted from a similar workflow presented by the Jensen group [2f].

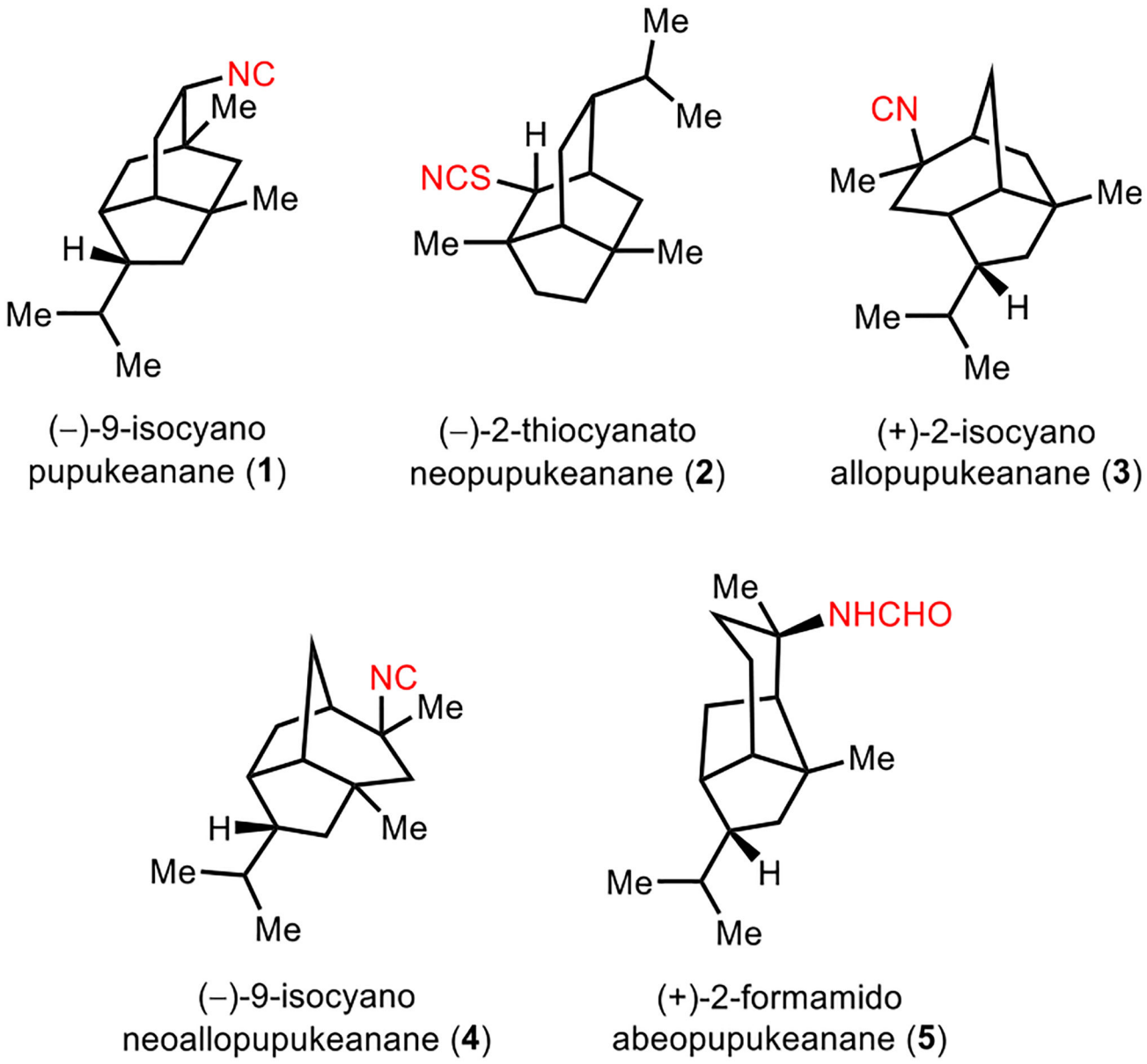
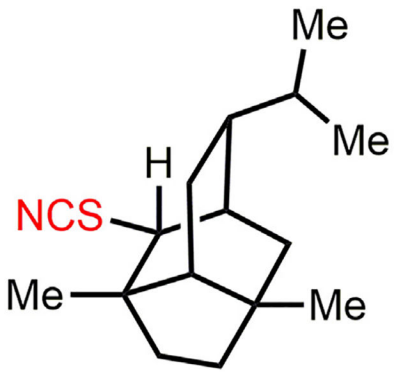
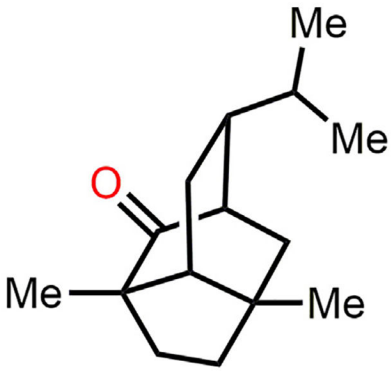


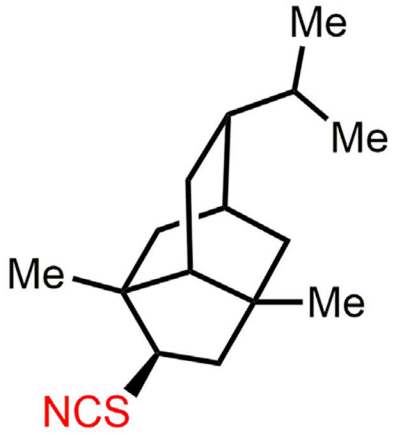
Fig. 2.
Selected natural products for each unique skeleton of the pupukeanane family.



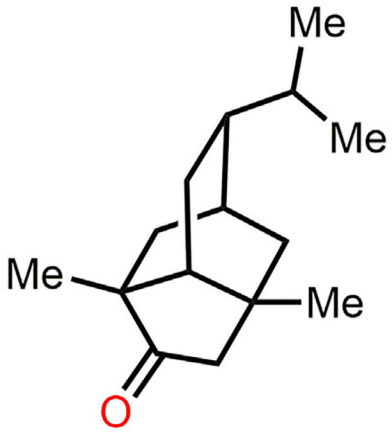
(–)-2-thiocyanato neopupukeanane (**2**)



2-neopupukeanone (**27**)

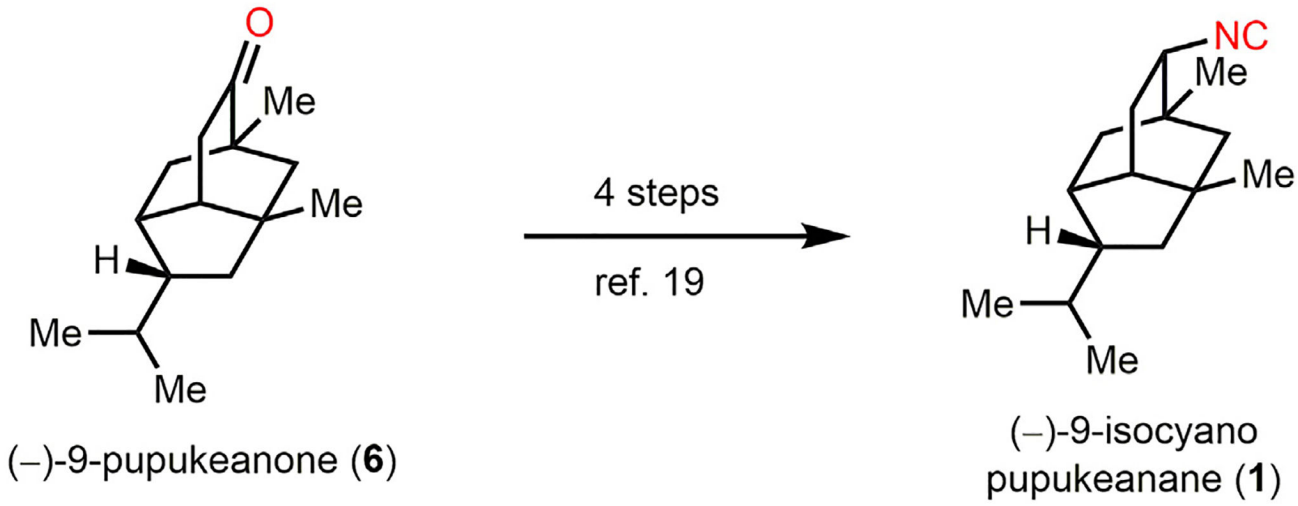


(–)-4-thiocyanato neopupukeanane (**28**)

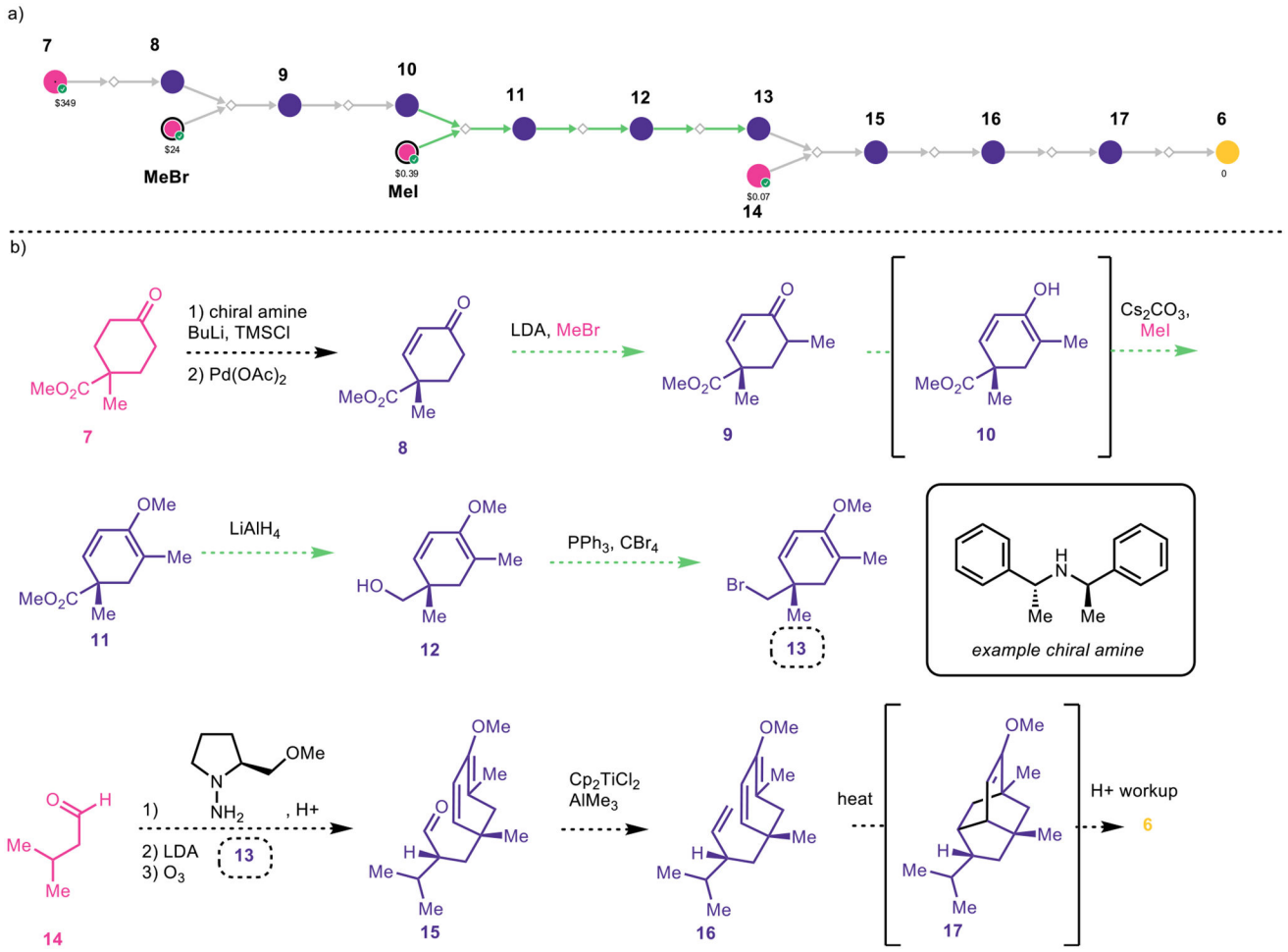


4-neopupukeanone (**29**)

Fig. 3.
Selected neopupukeanane targets.

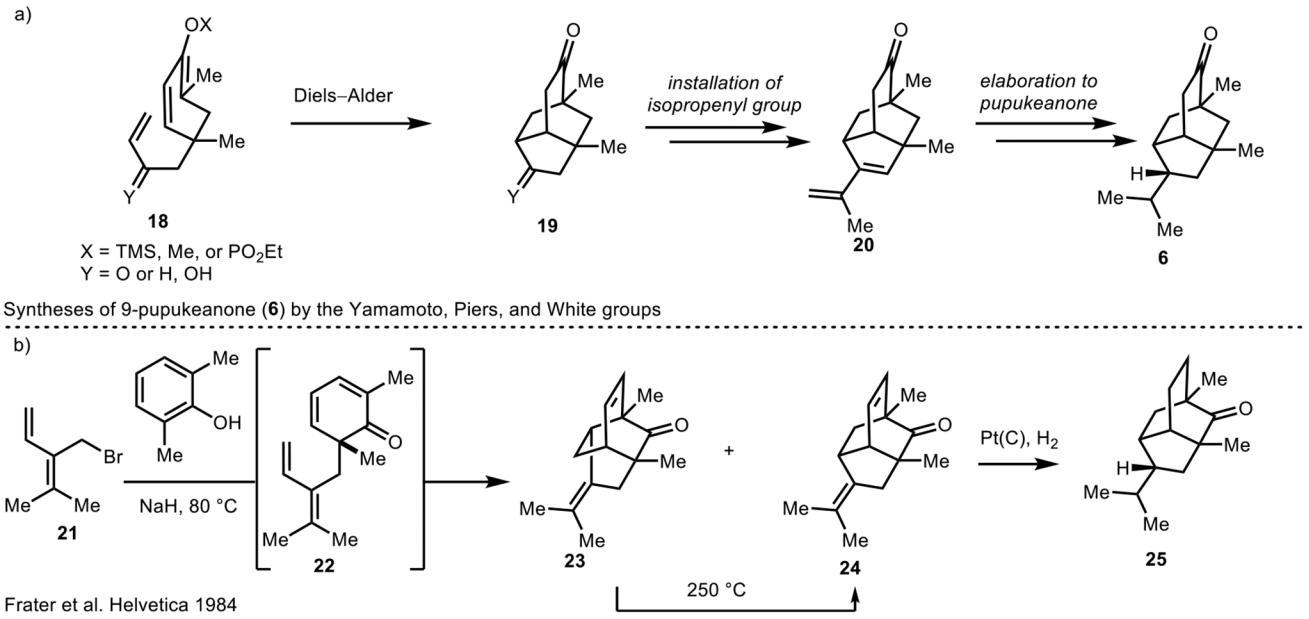


Scheme 1.
Elaboration of 9-pupukeanone (**6**) to 9-isocyanopupukeanane (**1**).



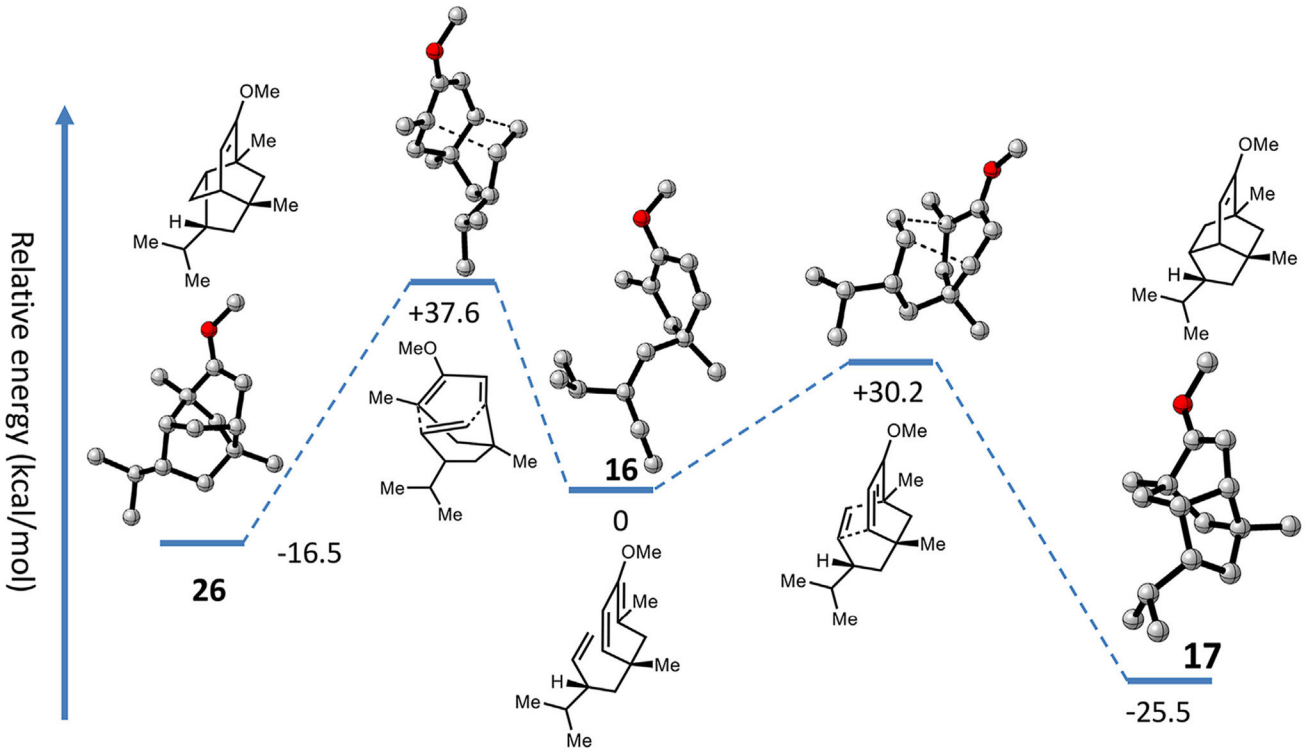
Scheme 2.

Synthia™'s proposed forward synthesis for 9-pupukeanone (**6**) as a) a summary graphic and b) detailed scheme. Each diamond represents a reaction step, showing the map of known starting materials (teal) and commercial starting materials (pink) through intermediates (purple) to the product (yellow). Green reaction arrows indicate that the transform was identified through a multi-step strategy. Red reaction arrows indicate that the transformation is either not selective or only diastereoselective.



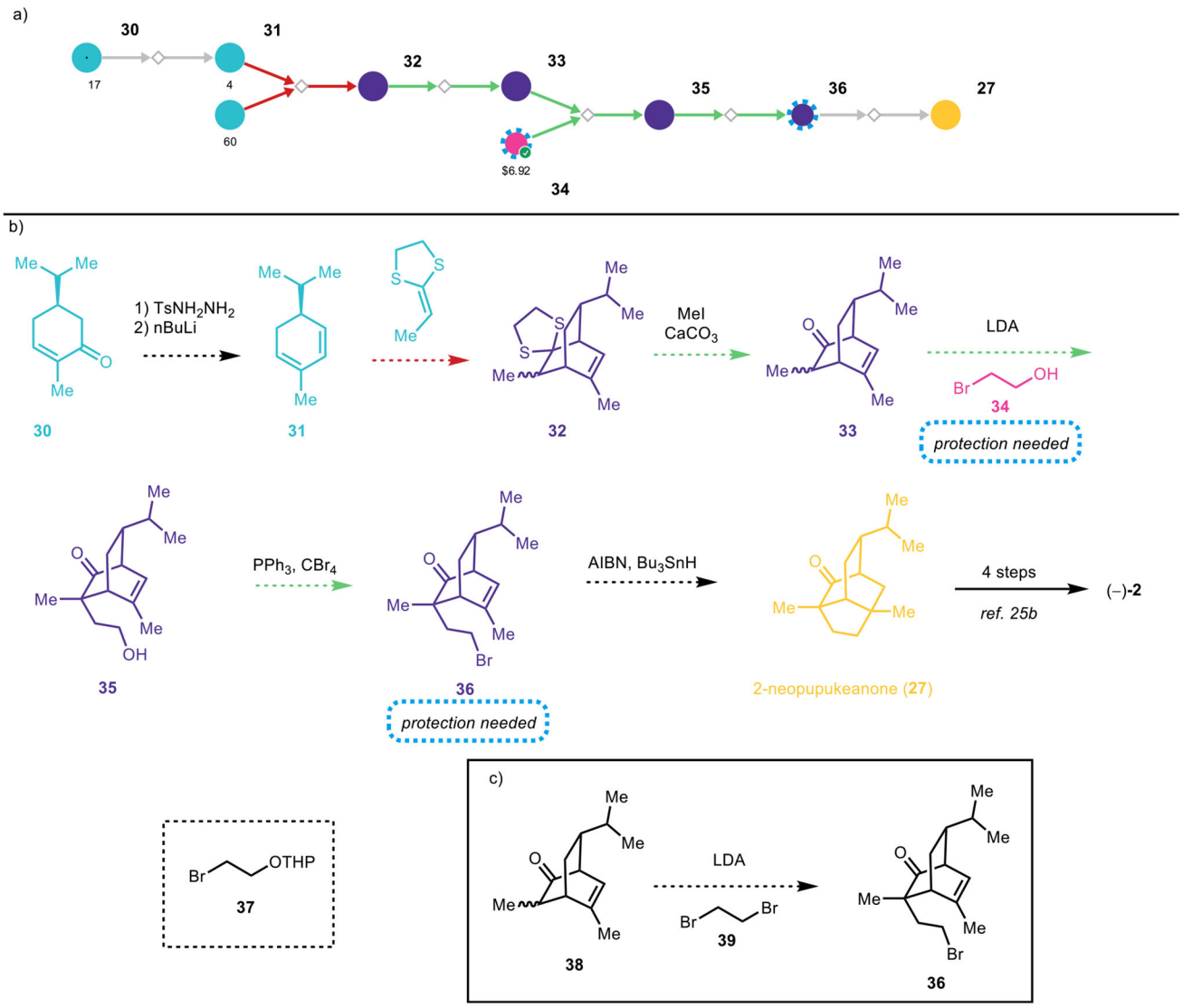
Scheme 3.

a) General strategy applied by the Yamamoto, White, and Piers groups in their synthesis of 9-pupukeanaone (**6**) and b) synthesis of 2-pupukeanone (**26**) by Frater's Diels–Alder approach.



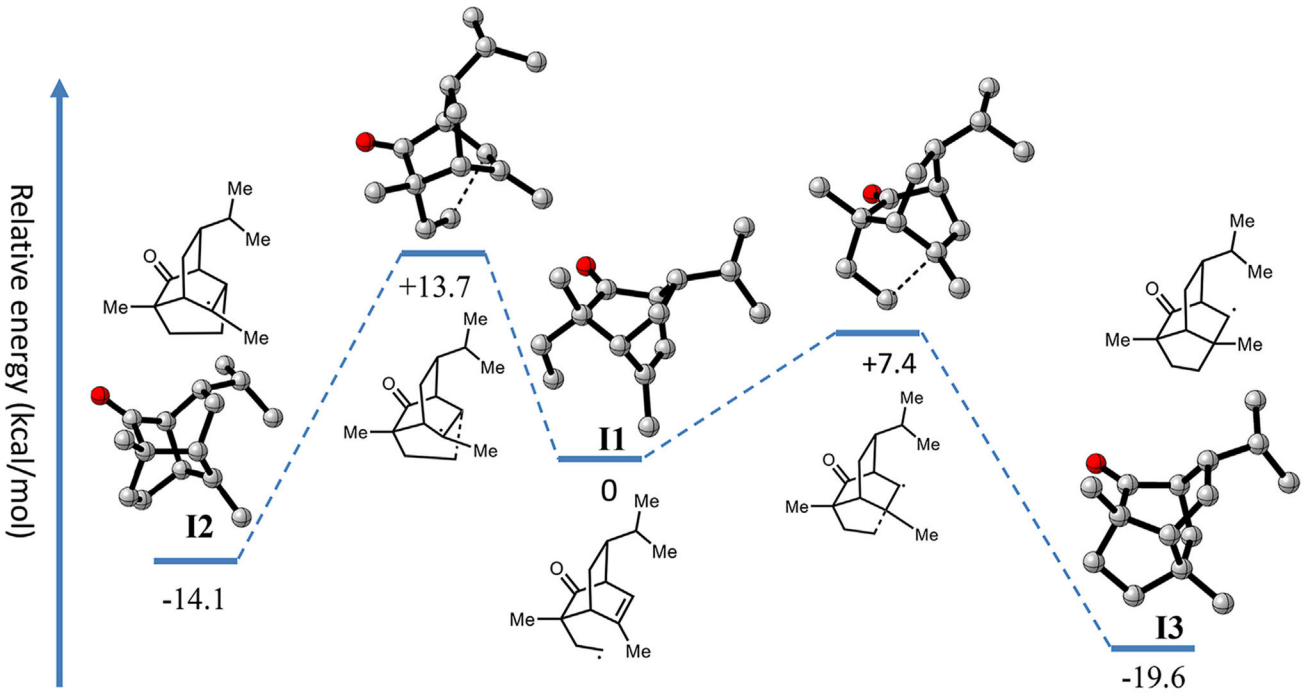
Scheme 4.

Computational studies on the Synthia™'s proposed Diels–Alder cycloaddition to forge the isotwistane core of 9-pupukeanone (**6**).



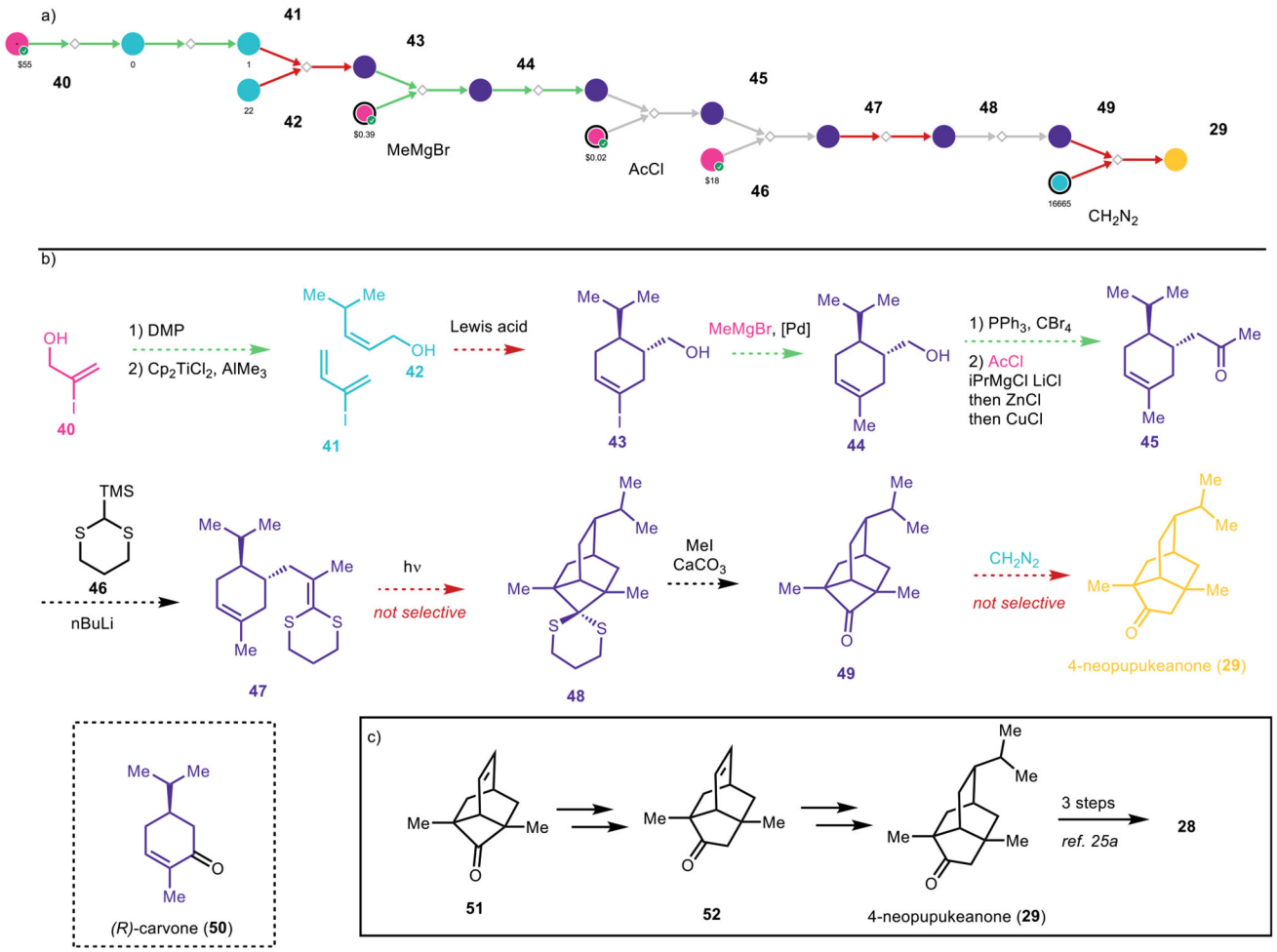
Scheme 5.

Synthia™'s proposed forward synthesis for 2-neopupukeanone (**6**) as a a) summary graphic and b) detailed scheme. c) Human-proposed modifications to Synthia™'s route. Each diamond represents a reaction step, showing the map of known starting materials (teal) and commercial starting materials (pink) through intermediates (purple) to the product (yellow). Green reaction arrows indicate that the transform was identified through a multi-step strategy. Red reaction arrows indicate that the transformation is either not selective or only diastereoselective.



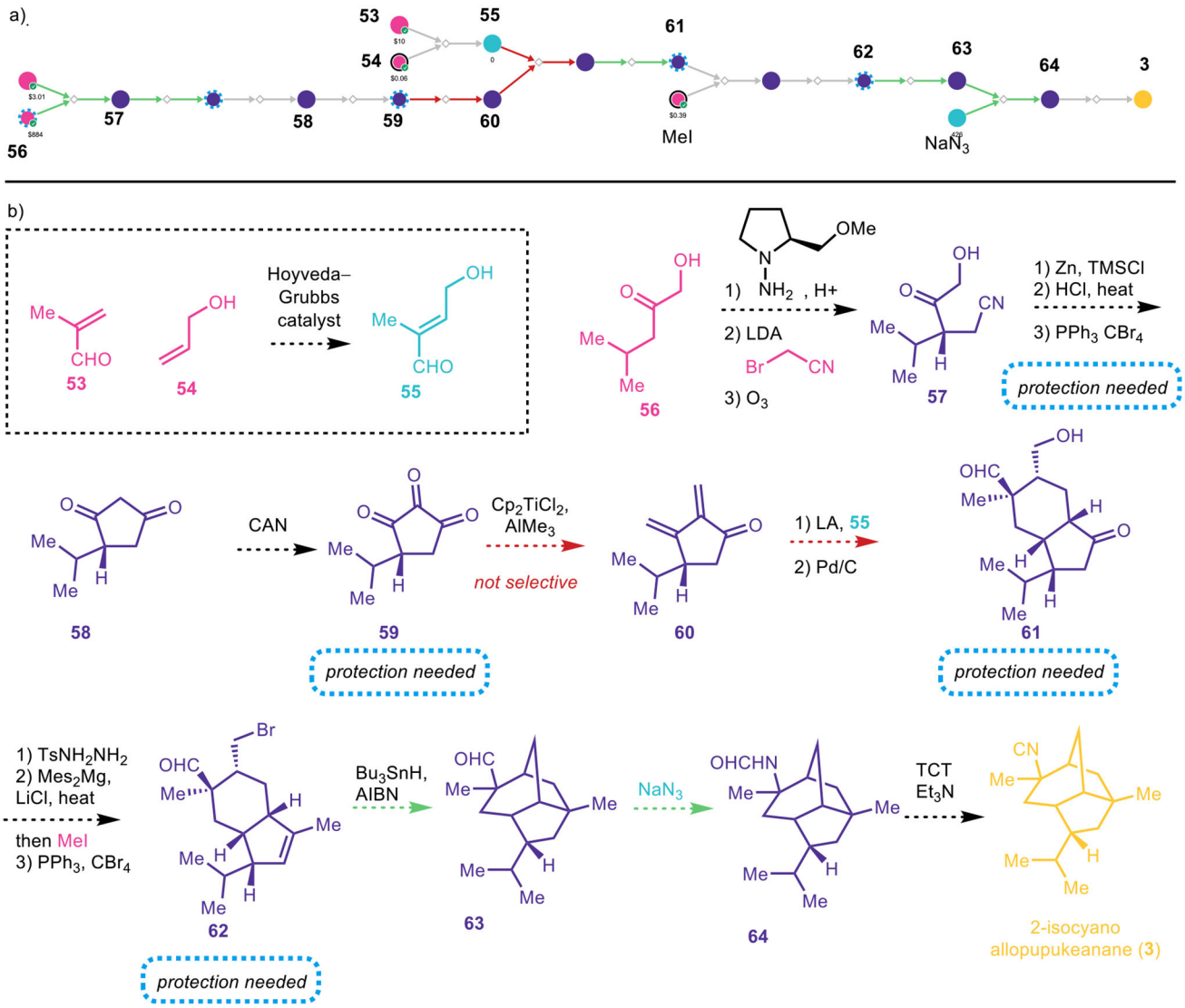
Scheme 6.

Computational studies on the Synthia™'s proposed 5-exo trig radical cyclization to forge the isotwistane core of 2-neopupukeanone (**27**).



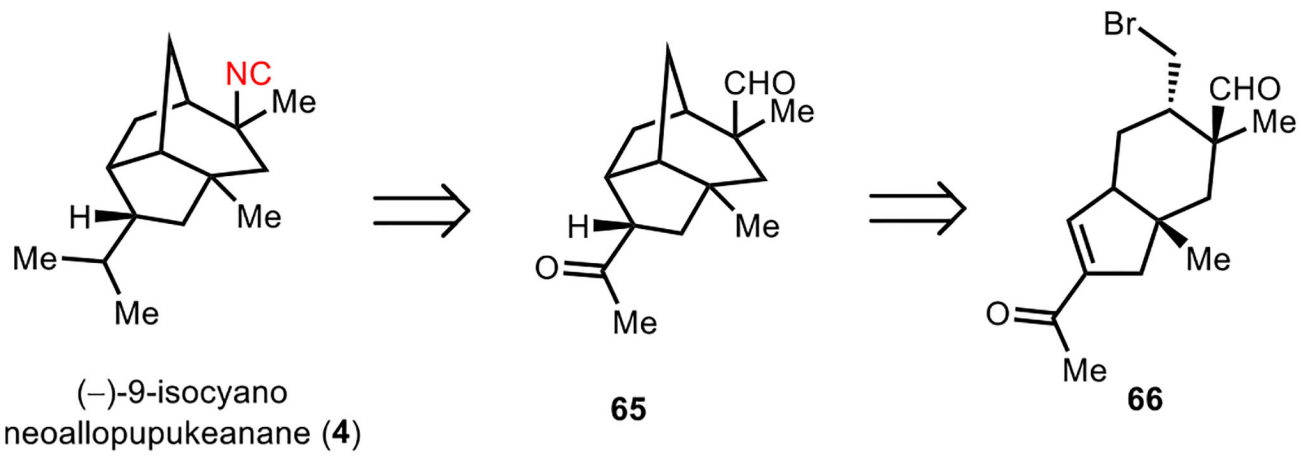
Scheme 7.

Synthia™'s proposed forward synthesis for 4-neopupukeanone (**28**) as a a) summary graphic and b) detailed scheme. c) Human-proposed modifications to Synthia™'s route. Each diamond represents a reaction step, showing the map of known starting materials (teal) and commercial starting materials (pink) through intermediates (purple) to the product (yellow). Green reaction arrows indicate that the transform was identified through a multi-step strategy. Red reaction arrows indicate that the transformation is either not selective or only diastereoselective.

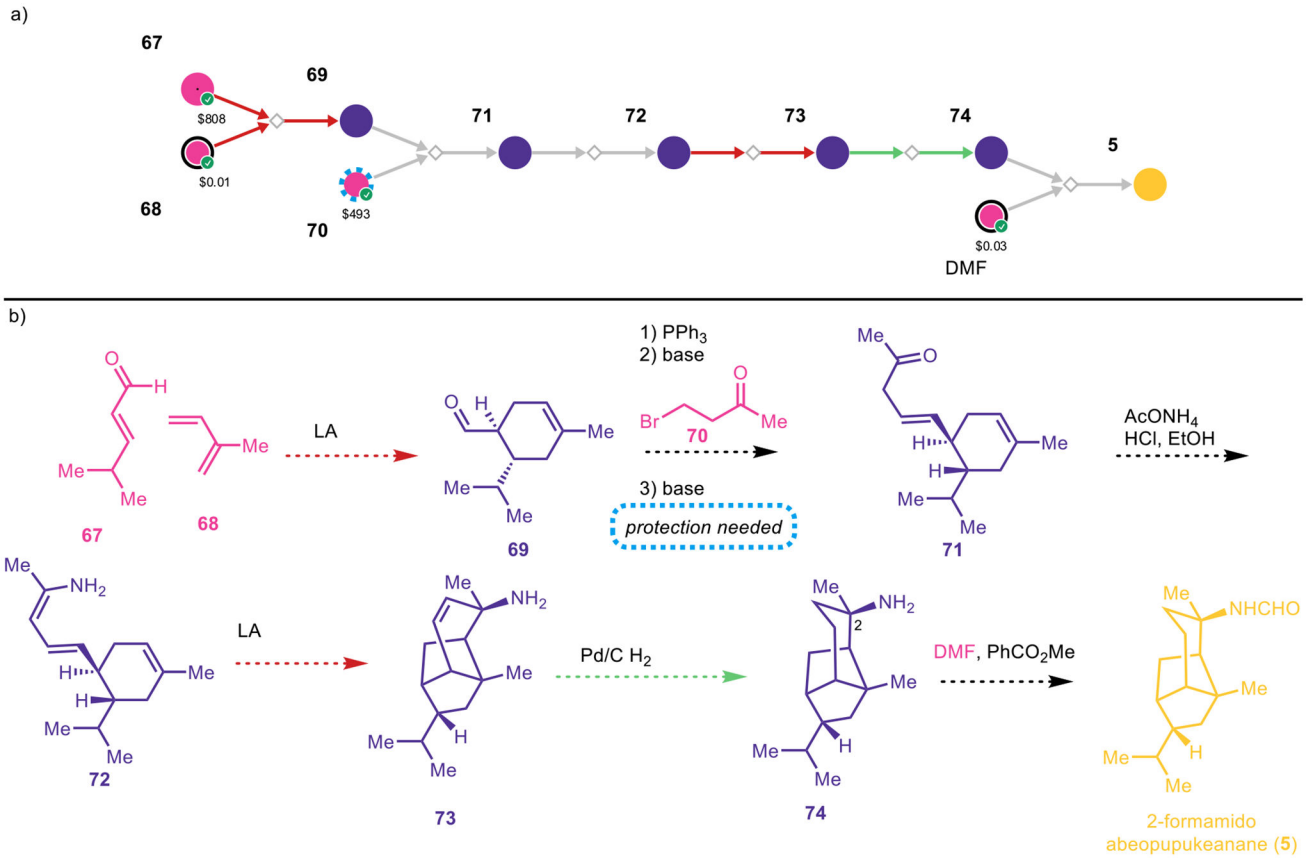


Scheme 8.

Synthia™'s proposed forward synthesis for 2-isocyanoallopupukeanane (**3**) as a a) summary graphic and b) detailed scheme. Each diamond represents a reaction step, showing the map of known starting materials (teal) and commercial starting materials (pink) through intermediates (purple) to the product (yellow). Green reaction arrows indicate that the transform was identified through a multi-step strategy. Red reaction arrows indicate that the transformation is either not selective or only diastereoselective.

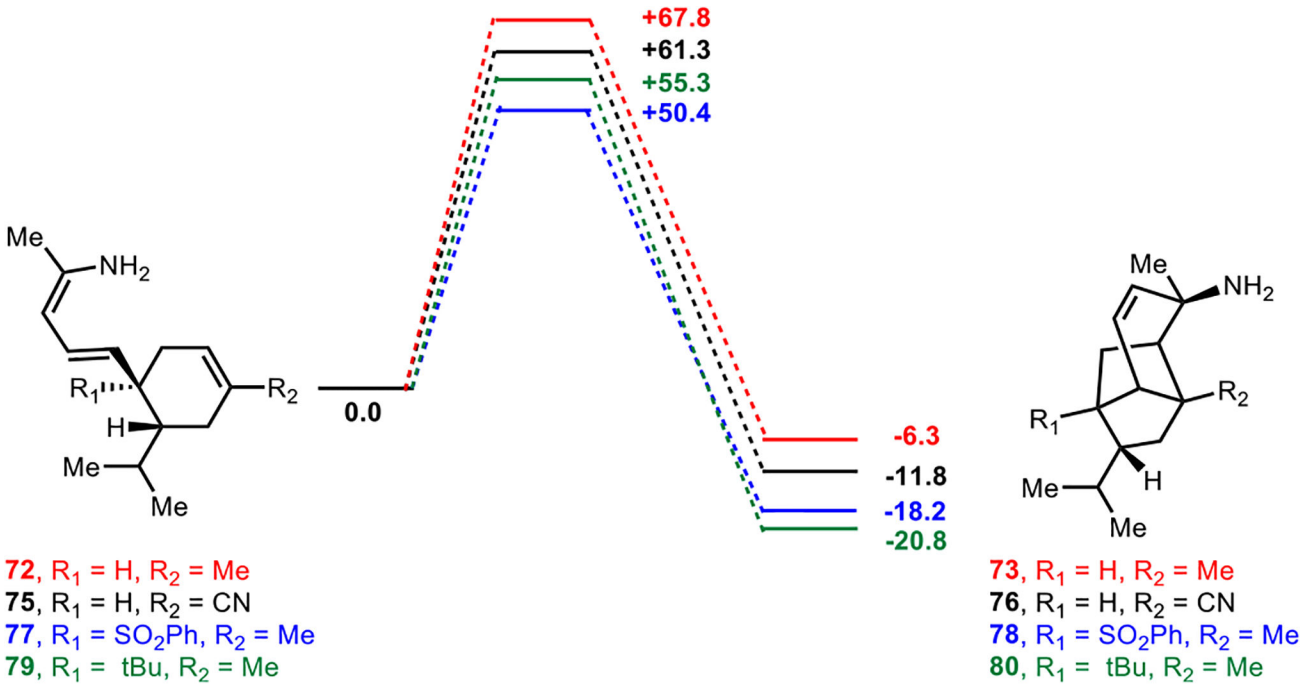


Scheme 9.
Synthia™'s proposed retrosynthesis of 9-isocyanoneoallopupukeanane.



Scheme 10.

Synthia™'s proposed forward synthesis for 2-formamidoabeopupukeanane (**5**) as a a) summary graphic and b) detailed scheme. Each diamond represents a reaction step, showing the map of known starting materials (teal) and commercial starting materials (pink) through intermediates (purple) to the product (yellow). Green reaction arrows indicate that the transform was identified through a multi-step strategy. Red reaction arrows indicate that the transformation is either not selective or only diastereoselective.



Scheme 11.

Computational studies on Synthia™'s proposed Diels–Alder cycloaddition as well as human-derived variations to forge the isotwistane core of 2-formamidoabeopupukeanane (**5**).