Integrative Pericyclic Cascade: An Atom Economy, Multi C-C Bond Forming Strategy for the Construction of Molecular Complexity

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Abstract: An all-pericyclic manifold is developed for the construction of topologically diverse, structurally complex and natural product-like polycyclic chemotypes. The manifold uses readily accessible tertiary propargyl vinyl ethers as substrates and an imidazole as a catalyst to form up to 2 new rings, 3 new C-C bonds, 6 stereogenic centers and one transannular oxo-bridge. The manifold is efficient, scalable and instrumentally simple to perform and entails a Propargyl Claisen rearrangement-[1,3]H-shift, an oxa-6 π - electrocyclization and an intramolecular Diels-Alder reaction.

The scalable construction of architectural complexity from simple raw materials using atom-, step-, pot- and labor-economical processes remains as a great challenge in organic synthesis and drug discovery. Nature does it using an eon-perfected biosynthetic weaponry through perfectly orchestrated continuous processes (enzyme catalysis). This biosynthetic machinery delivers myriads of intricate molecular structures endowed with wide arrays of functionalities and biological annotations. Cascade (domino) processes^[1] have emerged as a practical approach to this Nature's molecular construction blueprint.^[2] Among the different and distinct cascade processes described to date, those integrating pericyclic reactions have proven to be unique in their capacity to generate complex structures with predictive stereochemical outcome.^[3] Within the numerous pericyclic-integrative cascade manifolds, those involving a tandem oxa-6 π -electrocyclization/[4+2] cycloaddition (DA) reaction have found

interesting applications in the biomimetic synthesis of natural products (Eq. (1)).^[3c] An important hindrance to overcome in these cascades is the reversible character of the electrocyclization and the predominance of the opened form (1-oxatriene). It has been shown that steric interactions between substituents (steric crowding)^[4] and/or specific electronic effects of the π -conjugated system allow to reverse this tendency,^[3c] allowing the cycloaddition to take place to generate the 2-oxabicyclo[2.2.2]oct-5-ene scaffold. We envisioned that this cascade process could be a convenient synthetic manifold for the construction of different molecular scaffolds hosting this structural motive.^[5] Key to this idea was the design of a simple, and direct access to highly substituted 2*H*-pyrans (or their 1-oxatriene precursors^[6]) accommodating maximal functional and topological diversity. We hypothesized that this issue could be conveniently satisfied incorporating in the pericyclic manifold a tandem propargyl Claisen / imidazol-catalyzed [1,3]H-shift rearrangement^[7a] of tertiary propargyl vinyl ethers (PVEs)^[8] (Scheme 1a). The use of readily accessible tertiary PVEs as starting materials offers important advantages in terms of: 1) diversity: they accommodate wide and diverse substitution patterns; 2) configurational control: the Claisen rearrangement determines the configuration of the 1-oxatriene intermediate and thus the structure (substituents' configuration) of the cycloadduct; and 3) scalability: they are accessible in gram amounts, which allows for performing the manifold under multigram scales.

The main concern with our design stemmed from the possible branching of the pericyclic manifold through the enol ester form of the 1-oxatriene intermediate (Scheme 1a). In the absence of additional elements of reactivity, this is a favored reaction pathway. When the PVE bears a methylene ($R^2 = \text{CH}_2R^4$) or a methine (CHR^4R^5) group at the homopropargylic position, it affords the corresponding 6π -electrocyclization products (i.e., salicylaldehydes^[7a] in the former case and 2,4-cyclohexadienones^[9] in the latter one). Mindful of these considerations, we decided to incorporate the alkene moiety into the starting ketone to transform the DA reaction in its intramolecular version (IMDA) and thus reduce its energy barrier.^[10] Additionally, the transformation of the latter DA into its IMDA version would introduce a higher degree of topological complexity into the final structures (Scheme 1b). We report herein the proof of concept of this cascade design and its preparative application to the generation of a series of architecturally complex scaffolds sharing a 2-oxabicyclo[2.2.2]oct-5-ene core. The

generated structures represent examples of complex natural product (NP)-like scaffolds incorporating defined topologies, three-dimensionality, sp^3 -richness and stereogenicity. Thus, they constitute uncharted chemotypes to populate the chemical space in search for new biological annotations.

We began this work studying the cascade reactivity of PVE **3aa** (Table 1, R = Ph) which was readily synthesized in two steps from commercially available 2-allylcyclohexanone (**1a**), phenylacetylene (**2a**) and methyl propiolate.^[11] Based on our previous studies on the rearrangement of PVEs to salicylaldehydes,^[7a] we knew that the [1,3]H-shift rearrangement needed heat and imidazole (basic catalyst) to proceed, thus we

Scheme 1. Integrated pericyclic cascade manifold.

performed the pericyclic cascade reaction using thermal conditions (toluene, reflux) and imidazole as a catalyst (10 mol%). Under these conditions, we were pleased to observe that the reaction manifold delivered the tetracyclic product **4aa** after 7h in excellent yield (91%) and as a mixture of two separable epimers **4aa-anti** and **4aa-syn** (6.3:1.0 dr),^[12] delivering only trace amounts of the undesired 6π -electrocyclization products (Table 1). (For additional early experiments, see SI). These tetracyclic structures represent the first example of two NP-like

scaffolds stemmed from a novel and unprecedented 1,2,4a,5,6,7,8,8a,9,9a-decahydro-2,4b-epoxyfluorene scaffold.^[13] The preparative power of this manifold was further demonstrated by performing the reaction on a 5 mmol scale to deliver 1.4 grams of the desired products (86% yield, 6.3:1.0 dr) under similar reaction conditions (Table 1, entry 1). We next studied the tolerance of the pericyclic manifold with regard to the alkyne component using 2-allylcyclohexanone (**1a**) as the ketone component. The reaction regularly delivered the tetracyclic products **4ab-4ae** in excellent yields (87-97%) and good diastereoselectivity (5.3-7.8:1 dr). Remarkably, the use of trimethylsilacetylene (**2b**) as the alkyne component (R = TMS; Table 1, entry 3) totally suppressed the formation of the 6 π -electrocyclization products. This fact together the versatile reactivity of the TMS-vinyl group^[14] (chemical handle incorporated into the final structure) prompted us to use it as a universal alkyne component for this manifold.

Once the alkyne tolerance was established, we next studied the scope with regarding to the ketone. Table 2 outlines a selection of examples showing the wide diversity and topological complexity that can be generated from simple cyclic or acyclic ketones using this integrative pericyclic manifold (additional examples are depicted in Table S1). These topological patterns include different bridged fused ring systems (named chemotypes **I-VIII**), all of which except chemotype **IV** represent novel structures with uncharted biological profiles.^[13]

Chemotype I could be constructed using different alkynes (Table 1, **4aa-ae**) and different substitution patterns on the olefin (which is the dienophile, Table 2, **4bb-db**). As expected for a Diels-Alder cycloaddition the stereochemistry of the substituents at the double bond is translated to the final polycyclic product. For instance, PVE **3cb**, which contains a double bond with *E* stereochemistry ($R^2=Ph$), delivers the desired product **4cb** as a separable mixture of epimers with a well-defined relative stereochemistry at the carbon atom bearing the phenyl group. It can also be highlighted that even the PVE **3db** bearing a doubly substituted terminal olefin ($R^2 = R^3 = Me$) reacted to give the expected decahydro-2,4b-epoxyfluorene scaffold **4db** in 54% yield albeit a longer reaction time was needed (96h). Chemotypes **I-III** illustrate the influence of the ketone ring size in the manifold outcome. Thus, whereas the PVEs generated from 2-allyl-cyclohexanone and cycloheptanone were well tolerated and delivered the corresponding tetracycles **4ab** and **4eb** in 97% and 92% yield respectively, the PVE derived from 2-allyl-cyclopentanone delivered product **4fb** in a significant lower yield (48%). In this case, olefin activation was required to obtain in order to obtain chemotypes III **4gb** in excellent yield (91%). The ring size influence was ascribed to the ease of enolization of the 1-oxatriene intermediate (see Scheme 1A), which leads

to the undesired 6π -electrocyclizations products. The formation of an endocyclic double bond within a five membered ring is

Table 1. Implementation of a cascade manifold to access 1,2,4a,5,6,7,8,8a,9,9a-decahydro-2,4b-epoxyfluorene structural motives.

Entrv	R	Exp. Cond.	Prod.	Yield	anti/syn
1	Ph	Toluene. 7h	4aa ^[a]	91 ^[b]	6.3/1
2	Me ₃ Si	Toluene.	4ab	97	7.8/1
3	Me ₃ Si	Xylenes. 8h	4ab	94	5.3/1
4	<i>t</i> Bu	Toluene.	4ac	93 ^[b]	7/1
5	<i>t</i> Bu	Xylenes. 16h	4ac	92 ^[b]	6.4/1
6	Me	Toluene.	4ad	87 ^[b]	7.3/1
7	H	Toluene.	4ae	87 ^[b]	6.4/1

[a] Scaled up to 1,4g: 86% yield, same diastereoselectivity. [b] Less than 5% of 6π -electrocyclization products.

energetically less demanding than within six and seven membered rings.^[15] It must also be highlighted that the size of the ketone ring has also an influence on the epimeric distribution. While the *anti* 6,5-fused cycloadduct is preferred (7.8/1 for **4ab**) when 2-allyl-cyclohexanone is used, the *syn* 5,5-fused cycloadduct is preferred when a cyclopentanone is used (1/3.8 for **4fb** or exclusive formation of the *syn* fused for **4gb**). On the other hand, when 2-allyl-cycloheptanone is used there is little preference for the *anti* or *syn* 7,5-fused cycloadduct (1.1/1 for **4eb**).

Chemotype **IV**, which is embedded in the backbone of biologically relevant molecules as the potent neurotoxin batrachotoxin^[16] and the angucyclinones gephyromycin^[17] and grisemycin,^[18] required the use of 2-

homoallylcyclohexanone. The 6,6,6-fused pattern of **4hb** is easily constructed by simply altering the length of the sidechain containing the alkene functionality. On the other hand, the use of 2-bishomoallylcyclohexanone did not lead to the 6,7,6-fused cycloadduct, and shows, that chemotypes with internal ring size over six cannot be accessible using this strategy. Chemotypes **V** and **VI** illustrate how the use of readily available heterocyclic ketones can easily deliver other interesting bridged fused ring systems. Finally, chemotypes **VII** and **VIII** are constructed

Table 2. Ketone (alkene) scope of the pericyclic cascade manifold.^[a]

^[a] Table 2 shows the results according to the type of the main scaffold (core) (**Chemotypes I-VIII**). The novelty of the scaffold is specified together with the type of main core. The major diastereoisomer is depicted. ^[b] dr refers to the *anti/syn* ratio. ^[c] Scaled-up to 2.0 gr. ^[d] 1 day under microwave heating at 180 °C (51% yield).

from simple acyclic ketones. The nature of the ketone and the substituents on the double bond determine the substitution patterns on the desired products, while the distance between the carbonyl group and the double bond determines the ring size of the bridged fused ring system (5,6-fused or 6,6-fused). Interestingly, chemotype **VII** mimics the oxabicyclic core of several abyssomicin polyketides,^[19] whereas the cis-dehydrodecalin core of chemotype **VIII** is present in several natural sesquiterpenes as the antibiotic nargenicin A₁ and related.^[20] Product **4lb** was synthesized in a 2.0 gram scale proving again the preparative power of this manifold.

With regard to the observed *anti*-preference of the peri-cyclic manifold, it can be rationalized according to the equilibrium outlined in Equation (2). The reversible 6 π -electrocyclization of the 1-oxatriene generates the two diastereomeric (eq, ax) and (eq eq)-2*H*-pyrans (considering the allyl chain and the C-O bond respectively) which provide the corresponding isomeric tetracyclic scaffolds. Molecular models show that the allyl chain in the (eq, ax)-diastereomer is better positioned for the IMDA reaction than in the (eq, eq) one, and accordingly, the energy barrier for this reaction should be lower such as it is experimentally observed. In the case of the cyclopentanone, the geometrical requirements for the IMDA reaction favour the formation of the *syn*-isomer. Last but not least, although we have performed the manifold using racemic materials, we have also demonstrated that the manifold provides chiral scaffolds if chiral ketones are used (See SI for details).

In summary, we have shown the synthetic utility of a de novo designed all-pericyclic-domino manifold based on the imidazole-catalyzed rearrangement of tertiary PVEs endowed with an alkene chain in their structures. The manifold has proved to be an excellent synthetic platform for the direct generation of structural complexity because it is general (functional diversity), scalable (preparative) and instrumentally simple to perform (bench-friendly). The manifold is able to deliver at least eight different polycyclic chemotypes with the formation of up to three fused cycles, one transannular oxo-bridge, six stereogenic centers and three new C-C bonds.

Experimental Section

Representative procedure for the synthesis of polycyclic compounds (4): PVE **3aa** 1.60g (4.93 mmol) and imidazole 34 mg (0.50 mmol) were heated in refluxing toluene (10 mL) for 8 hours. After removing the solvent at reduced pressure, the products were purified by flash column chromatography (silica gel, n-hexane/EtOAc 90/10) to yield 1.198 g **4aa-anti** (75%) and 177 mg **4aa-syn** (11%).

4aa-anti: White crystalline solid. M.p.: 119-120°C. ^1H NMR (400 MHz, $[\text{D}]\text{HCCl}_3$, 25°C): δ = 1.11-1.21 (m, 3H), 1.46-1.72 (m, 8H), 1.83 (dd, $^3J_{(\text{H,H})}$ = 12.4 and 5.3 Hz, 1H), 2.14-2.19 (m, 1H), 2.29-2.36 (m, 1H), 2.73 (d, $^3J_{(\text{H,H})}$ = 5.1, 1H), 3.59 (s, 3H), 4.91 (d, $^3J_{(\text{H,H})}$ = 5.3, 1H), 7.23-7.25 (m, 2H), 7.27-7.36 (m, 3H). ^{13}C NMR (100 MHz, $[\text{D}]\text{HCCl}_3$, 25°C): δ = 21.2, 26.0, 27.4, 29.7, 34.7, 38.7, 42.9, 45.0, 51.2, 54.6, 66.3, 82.5, 127.6 (2C), 127.79, 127.83 (2C), 131.6, 140.0, 151.5, 164.8. HRMS (ESI $^+$): m/z $[\text{M}^+\text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{24}\text{O}_3\text{Na}$: 347.1623. Found: 347.1631. Elemental analysis calcd (%) for $\text{C}_{21}\text{H}_{24}\text{O}_3$: C 77.75; H 7.46; found: C 77.76; H 7.44. **4aa-syn:** Light yellowish oil. ^1H NMR (400 MHz, $[\text{D}]\text{HCCl}_3$, 25°C): δ = 0.96-1.07 (m, 1H), 1.09-1.25 (m, 2H), 1.36 (td, $^3J_{(\text{H,H})}$ = 13.6 and 4.6 Hz, 1H), 1.54-1.75 (m, 6H), 1.84 (ddd, $^3J_{(\text{H,H})}$ = 12.9, 4.8 and 1.3 Hz, 1H), 1.88-1.99 (m, 2H), 2.20-2.25 (m, 1H), 3.12 (d, $^3J_{(\text{H,H})}$ = 4.8, 1H), 3.59 (s, 3H), 4.90 (d, $^3J_{(\text{H,H})}$ = 4.6, 1H), 7.24-7.26 (m, 2H), 7.29-7.38 (m, 3H). ^{13}C NMR (100 MHz, $[\text{D}]\text{HCCl}_3$, 25°C): δ = 23.4, 25.3, 30.7, 34.0, 34.8, 40.9, 41.0, 43.1, 48.6, 51.2, 66.4, 84.5, 127.5 (2C), 127.9, 128.0 (2C), 132.1, 140.0, 151.4, 164.9. HRMS (ESI $^+$): m/z $[\text{M}^+\text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{24}\text{O}_3\text{Na}$: 347.1623. Found: 347.1621. Elemental analysis calcd (%) for $\text{C}_{21}\text{H}_{24}\text{O}_3\text{Na}$: C 77.75; H 7.46; found: C 77.85; H 7.53.

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