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Bispericyclic Diels–Alder Dimerization of *ortho*-Quinols in Natural Product (Bio)Synthesis – Bioinspired Chemical 6-Step Synthesis of (+)-Maytenone

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Abstract: Many natural products of plant or microbial origins are derived from enzymatic dearomative oxygenation of 2-alkylphenolic precursors into 6-alkyl-6-hydroxycyclohexa-2,4-dienones. These so-called *ortho*-quinols cyclodimerize *via* a remarkably selective bispericyclic Diels–Alder reaction. Whether or not the intervention of catalytic or dirigent proteins is involved during this final step of the biosynthesis of these natural products, this cyclodimerization of *ortho*-quinols can be chemically reproduced in the laboratory with the same strict level of site-specific regioselectivity and stereoselectivity. This unique yet unified process, which finds its rationale in the inherent chemical reactivity of those *ortho*-quinols, is illustrated herein by an efficient and bioinspired first chemical synthesis of one of the most structurally complex and synthetically challenging examples of such natural cyclodimers, the bisditerpenoid (+)-maytenone.

Introduction

The Diels–Alder [4+2] cycloaddition belongs to the category of those venerable chemical transformations that continue to provide organic chemists with key tactical solutions for the synthesis of complex molecules. Since its discovery in 1928,[1] the Diels–Alder reaction has been the subject of countless applications, variations and investigations on its mechanism, modes of activation and levels of selectivity.[2] This two-bond-forming pericyclic combination of a planar conjugated diene (4π component) with a dienophile (2π component), which is not restricted to olefins as it can also involve heteroatomic reacting centers (*e.g.*, N, O, S),[2d,3] is strongly influenced by the stereoelectronic nature of substituents directly or even remotely connected to the reacting π systems. The facility with which the reaction takes place, the manner through which both π components approach each other, the selection of transition states, and hence the regio- and stereochemical outcomes all critically depend on the substitution patterns of the starting π systems. It is commonly accepted that these systems usually react with each other according to the principles of the frontier molecular orbital theory in line with the Woodward–Hoffmann rules of orbital symmetry conservation[4] in a thermally-allowed and concerted cyclizing process through orbital interactions between the same faces (*i.e.*, suprafacial) of both 4π and 2π components. The four connecting sp^2-centers are converted into sp^3-centers, all possibly stereogenic, and the remaining 2π unit of the cyclohexenic adducts can be exploited for further transformations. It is therefore not surprising that such reactivity characteristics, bond-forming events and selectivity performances have promoted the Diels–Alder reaction among organic chemists' all-time favorite chemical transformations.

The chemical synthesis of numerous natural products, analogues thereof, as well as pharmaceutical drugs and diverse agrochemicals has been rendered possible thanks to the utilization of one or another variant of the Diels–Alder reaction.[5] The biosynthesis of many natural products also relies on [4+2] cycloaddition processes. The intervention of specialized enzymes, referred to as Diels-Alderases, has often been invoked,[6] although there exist several cases for which the cycloaddition step can be reproduced in the laboratory under mild conditions without any enzyme or any other type of catalysts or controlling additives.[7] In this regard, the [4+2] cyclodimerization of 6-alkyl-6-hydroxycyclohexa-2,4-dienones (commonly referred to as *ortho*-quinols) into bicyclo[2.2.2]octenone derivatives constitutes a fascinating example of such processes that relates to the biosynthesis of numerous plant and microbial metabolites. The bismonoterpenoid (+)-biscarvacrol (**1**),[8a] bissesquiterpenoids (+)-aquaticol (**2**)[8b] and (–)-bacchopetiolone (**3**),[8c] bisditerpenoids (+)-maytenone (**4**)[8d,e] and (–)-hugonone A (**5**),[8f] the plant cyclohexene oxide anabolite (–)-grandifloracin (**6**),[8g,h] the phytoquinonoid (+)-illihendione A (**7**),[8i] the fungal polyketide (+)-bisorbicillinol (**8**),[8j] and the bacterial phenol degradation metabolite (–)-bis-2,6-xylenol (**9**)[8k] are representative examples of such natural Diels–Alder cyclodimers (Figure 1).

The requisite *ortho*-quinol intermediates would be biosynthetically generated by enzymatic dearomative oxygenation of 2-alkylphenolic precursors. Thorough investigations into this hypothesis were conducted for the biosynthesis of sorbicillinoids and led to the identification of the *ortho*-quinol sorbicillinol (**10**) (Scheme 1).[9a] The dearomatization origin of this fungal quinol was initially questioned,[9b] but was recently and firmly established by the Cox group with the cloning of a polyketide synthase gene encoding a flavin adenine dinucleotide-dependent monooxygenase (SorbC) capable of dearomatizing enantioselectively the 2,6-dimethylphenolic precursor sorbicillin (**11**) into (*S*)-**10**,[10a] which can thereafter spontaneously cyclodimerize into **12** to furnish (+)-bisorbicillinol (**8**) *via* a keto-enol tautomerism (Scheme 1).[10b,c]

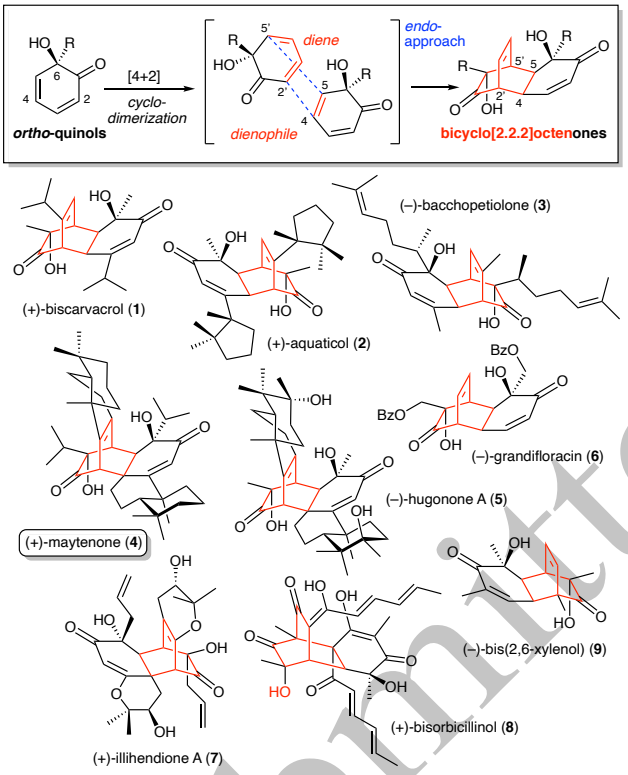
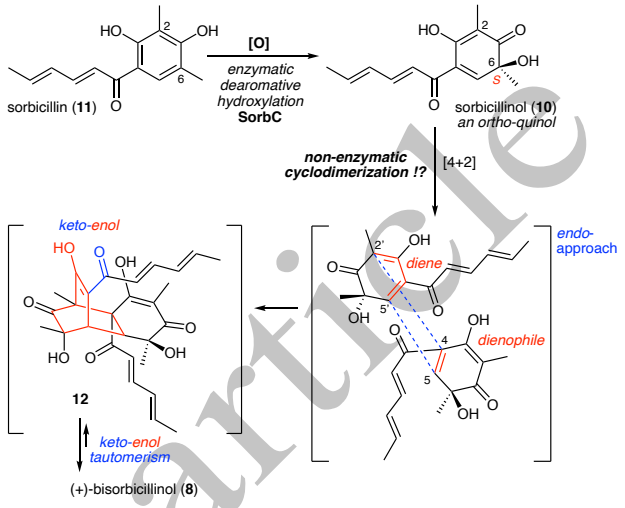


Figure 1. Examples of natural Diels–Alder cyclodimers of *ortho*-quinols. All of these natural products of plant or microbial origins are elaborated by a [4+2] cyclodimerization of *ortho*-quinols that strictly follows the same rules of site-specific regioselectivity and stereoselectivity. R = alkyl groups.

If biocatalysis is compulsory for mediating the biosynthetic dearomative hydroxylation of natural 2-alkylphenols and for controlling its stereoselectivity, the subsequent cyclodimerization of the resulting chiral *ortho*-quinols does not require any enzyme intervention for stereoselective control. Most *ortho*-quinols are highly prone to participation in [4+2] cycloaddition events, and the duality of reactivity of their cyclohexa-2,4-dienone core as both diene and dienophile means that their self-cyclodimerization often occurs spontaneously, unless their substitution pattern sterically retards or prevents it. In fact, many *ortho*-quinols self-cyclodimerize so rapidly even at ambient temperature that their isolation is hardly possible.[10b,11]

What is enthralling is that their cyclodimerization follows the exact same strict rules of regio- and stereocontrol, whose underlying rationale had therefore to be searched only in the inherent chemical reactivity preferences and structural particularities of those *ortho*-quinols. This enigmatic search has kept organic chemists busy for decades since Wessely's pioneering work on *ortho*-quinol acetates sixty years ago.[12]



Scheme 1. Final steps of the biosynthesis of (+)-bisorbicillinol (**8**). This polyketide metabolite derives from the [4+2] cyclodimerization of the (*S*)-enantiomer of sorbicillinol (**10**), the access to which being stereocontrolled by the enzyme SorbC that mediates the enantioselective dearomative hydroxylation of sorbicillin (**11**).

Over the years, several chemical methods relying on the use of, *inter alia*, lead(IV)-, Se(IV)-, iodine(III)-, iodine(V)-, iodine(VII)-, and copper(I)-based reagents have been developed to prepare *ortho*-quinols in either racemic or stereocontrolled formats,[13] and their self-cyclodimerizing variants were successfully utilized in the chemical synthesis of a number of natural products, including biscarvacrol (**1**),[11a,14] aquaticol (**2**),[14b,15] bacchopetiolone (**3**),[16] grandifloracin (**6**),[8h,11a,17] illihendione A (**7**)[18] and bisorbicillinol (**8**)[19] (Figure 1). Our own work on (chiral) iodine(V)-mediated hydroxylative phenol dearomatization (HPD) reactions drove us to accomplish several of these "biomimetic" syntheses,[11a,14c,15,16] and hence to investigate what makes the behavior of those *ortho*-quinols so special in their [4+2] cyclodimerization.

An *ortho*-quinol with a single stereogenic center at its C6-alcoholic position gives rise to only one diastereomer, even if the *ortho*-quinol is racemic, as exemplified in Scheme 2 by the conversion of 6-hydroxy-3-*iso*-propyl-6-methylcyclohexa-2,4-dienone (**13**) into biscarvacrol (**1**).[11a,14] There is no cross-reaction between the two enantiomers, each cyclodimerizing only with itself. Only upon heating at high temperatures (*i.e.*, 165 °C), which enables retro-Diels–Alder events, have cyclodimers resulting from such cross-reactions been observed.[20] This exclusive and stereospecific formation of cyclodimers is initially set by the dienophilic behavior of the *ortho*-quinol, which solely engages its Δ–4,5 bond in an *endo*-selective back-to-back approach with its dienic counterpart. This regio- and facioselective combination of two *ortho*-quinols is

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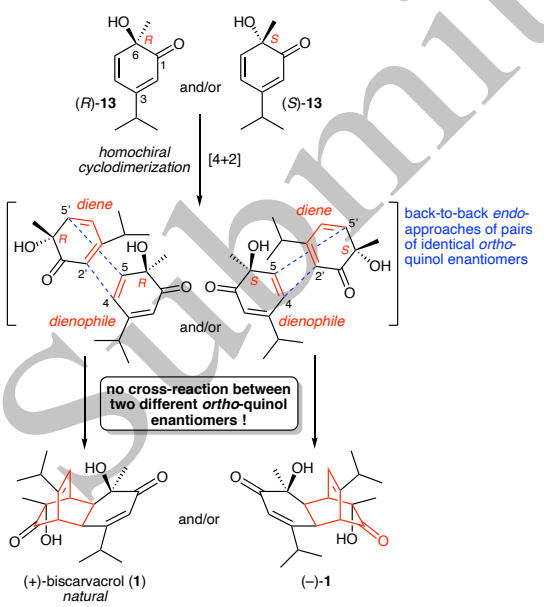
further fine-tuned to restrict connections specifically between their C5 atoms (and hence between the dienophilic C4 atom and the dienic C2 atom) according to a double diastereofacial control through which the two faces bearing the C6-hydroxy groups approach each other. Thus, out of 16 isomeric dimers that could conceivably result from a racemic *ortho*-quinol, a single pair of enantiomeric dimers is formed (Scheme 2). No other cyclodimer that could result from an *exo*-process, from alternative connections between reacting carbon sites, from another mutual approach of the two *ortho*-quinol faces, or from a dienophilic participation of the Δ-2,3 bond has yet been either isolated or chemically observed under standard conditions.

The ensemble of our experimental observations and computational inquiries, combined with the examination of numerous literature precedents reported since the end of the 1950s[12,20,21] led us to propose a first comprehensive rationale of the factors controlling this extraordinary level of site-specific regioselectivity and diastereofacial discrimination.[15,21d] Independently of their substitution pattern, *ortho*-quinols thus approach each other in a back-to-back manner to reach energetically favored *endo*-transition states leading to the observed products (see Figure 1, and Schemes 1 and 2). These transition states are (*i*) C_2-symmetric, and hence (*ii*) bispericyclic, both [4+2] and [2+4] cycloaddition pathways being fully equivalent,[22] (*iii*) sealed by a combination of classical Woodward–Hoffmann (C3↔C3' *p*-orbitals) and additional Salem–Houk (C2↔C4' *p*-orbitals) secondary orbital interactions (SOIs).[21d,22] The privileged connection between the C5 and C5' atoms would be due to stabilizing Cieplak–Fallis hyperconjugative effects[23] between both electron-donating C6–C_{alkyl} σ-bonds and the vacant σ*-orbital of the incipient C5–C5' bond with which they are both mutually antiperiplanar[21d] (*vide infra*).



Scheme 2. Homochiral Diels–Alder cyclodimerization of *ortho*-quinols. An *ortho*-quinol enantiomer, such as (*R*)-**13** or (*S*)-**13**, gives rise to the formation of a single diastereomer, such as (+)-biscarvacrol (**1**) from (*R*)-**13**. The same diastereomer and its enantiomer are the only cyclodimers formed in equal amounts from a racemic mixture of the *ortho*-quinol.

Results and Discussion

Here, we have put these theoretical elements to the test to further underpin basic knowledge on these bispericyclic dimerizations of *ortho*-quinols. To this aim, we took up the challenge of synthesizing one of the most structurally complex natural cyclodimers known as of today, (+)-maytenone (**4**) (Figure 1). This bisditerpenoid was first isolated in 1961 from the outer root bark of the tree *Maytenus dispermus* (Celastraceae) by Johnson and co-workers,[8d] who had already suspected that the biogenesis of **4** could involve the [4+2] self-cyclodimerization of an *ortho*-quinol derived from the diterpene ferruginol (**17**) (Figure 2a). They had even attempted to generate **4** by treating **17** with $Pb(OAc)_4$ in glacial acetic acid, which gave rise to the *ortho*-quinol acetate **18a** in about 3% yield (115 mg from 3.2 g of **17**).[24] The failure of attempts to cyclodimerize this substance or its deacetylated version **18b** (Figure 2b) was blamed on the high steric demand of the tricyclic ferruginol system.[24] The structure of **4** was unambiguously established only 20 years later by Falshaw and King on the basis of the X-ray crystal structure of its mono-reduction product.[8e] In 2000, Jankowski and co-workers reported the isolation of a bisditerpenoid cyclodimer, which they named celastroidine B, from the roots of *Hippocratea celastroides*.[25a] Later on, a comparison of the available atomic coordinates led Jaroszewski and co-workers to conclude that Jankowski's celastroidine B was in fact identical to Johnson's maytenone (**4**).[25b]

Thus, our contribution to yet another, perhaps ultimate, episode to this several decade-long serial on (+)-maytenone (**4**) commenced with the synthesis of (+)-ferruginol (**17**) (Figure 2a). This short and efficient synthesis is inspired from the work previously reported by González and Pérez-Guaita, who obtained (+)-**17** in 24% yield over 6 steps.[26a] Our synthesis also starts from commercially available (+)-dehydroabietylamine (**14**), and the Rapoport's oxygenative deamination[26b] was carried out first. Thus, **14** was treated with 4-formyl-1-methylpyridinium benzenesulfonate (**15**) in a CH_2Cl_2/DMF mixture, in the presence of 4Å molecular sieves, at ambient temperature for 12 hours, after which time DBU was added dropwise and the reaction mixture was further stirred for 2 hours. A hydrolytic workup procedure using 1 M aqueous HCl converted the resulting Schiff base into the aldehyde **16** in 59% yield (Figure 2a). This aldehyde was then subjected to a Wolff–Kishner reductive deoxygenation,[26a] and the resulting dehydroabietane was transformed through a regioselective Friedel–Crafts acetylation and a Baeyer–Villiger oxygenation, according to a slightly modified version of Gademann's procedure.[26c] A methanolysis of the resulting *O*-acetyl-ferruginol furnished the desired (+)-ferruginol (**17**), which was thus advantageously obtained in 32% yield over only 4 steps from (+)-**14** (Figure 2a, see the Supporting Information, Figure S1).

With several hundreds of milligrams of (+)-**17** in hand, we initiated our attempts to convert it into maytenone (**4**) by relying on the use of hypervalent iodine(V) reagents such as 2-iodylbenzoic acid (IBX, **19a**) or its stabilized variant SIBX, since these oxygenating λ^5-iodanes had amply proven their worth in analogous HPD/[4+2] cascade reactions.[11a,15,16] Unfortunately, these attempts were fruitless, as well as those performed using our chiral C_2-symmetrical *Salen*-type bisiodyl reagents **19b** and **19c** (Figure 2c).[16,27] The desired *ortho*-quinol **18b** was not generated, and the known *ortho*-quinonoid 8,12-abietadiene-

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11,12-dione **18c**[28] was instead produced (Figure 2c, see the Supporting Information, Figure S2). Notwithstanding this deviation of regioselectivity toward oxygenation at the unsubstituted instead of the *iso*-propylated *ortho*-position of the starting phenol **17**, we searched for more appropriate oxygen-atom transfer λ^5-iodanes and opted for the axially chiral biphenylic

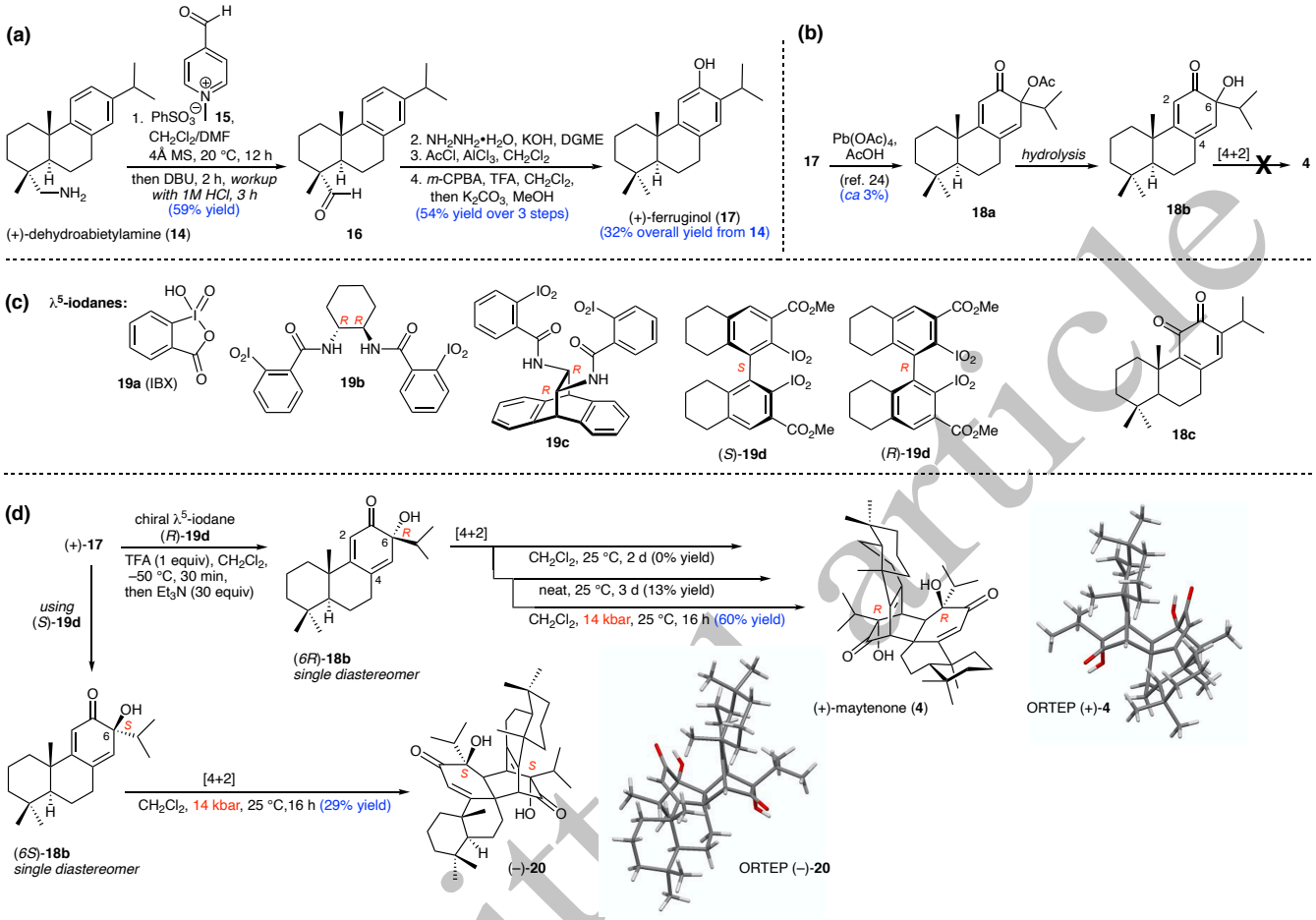

Figure 2. Chemical synthesis of (+)-maytenone (**4**) and its diastereomer (–)-**20**: **(a)** Preparation of (+)-ferruginol (**17**) from (+)-dehydroabietylamine (**14**).[26] **(b)** Johnson's early attempts to generate **4** from **17** through a dearomative oxygenation/[4+2] cycloaddition sequence.[24] **(c)** Structures of λ^5-iodanes **19a-d** used as oxygen-atom transfer reagents for the dearomative oxygenation of **17**, and structure of 8,12-abietadiene-11,12-dione (**18c**), the undesired *ortho*-quinone resulting from the use of the λ^5-iodanes **19a-c**. **(d)** The completion of our 6-step asymmetric synthesis of (+)-**4** and its diastereomer (–)-**20** through the regio- and diastereoselective dearomative oxygenation of (+)-**17** by using the biphenylic λ^5-iodanes (*R*)-**19d** or (*S*)-**19d**, respectively, followed by the site-specific regio- and diastereoselective [4+2] cyclodimerization of the *ortho*-quinols (*6R*)-**18b** or (*6R*)-**18b** under high pressure conditions.

bisiodyl reagent **19d**[14c] available in atropopure forms in our laboratory iodanes toolbox (Figure 2c). Gratifyingly, a full conversion of (+)-**17** into a single dearomatized species different from the *ortho*-quinone **18c** was observed when using (*R*)-**19d** (1 equiv.) in the presence of TFA (1 equiv.) in CH_2Cl_2 at –50 °C. The ^{1}H NMR analysis of the crude reaction product indicated that the desired *ortho*-quinol **18b** had been generated as a single diastereomer. Therefore, a solution of this crude reaction product in CH_2Cl_2 was stirred at ambient temperature for enabling **18b** to cyclodimerize into **4**. After 2 days, no [4+2] cycloadduct was formed and only degradation of **18b** was observed. To our surprise, a neat sample of **18b** left standing at ambient temperature for 3 days gave rise to the formation of a single cyclodimer, which was isolated in 13% yield as a white solid. This solid was crystallized from a solution in ethyl acetate and its analysis by X-ray crystallography unambiguously confirmed that its structure was that of (+)-**4**. This glimpse of success reminded us of Johnson and co-workers who, 56 years ago, had judiciously imputed their failure to generate **4** to the bulkiness of the tricyclic diterpenoid system,[24] which could nevertheless be overcome herein, at least in part, under solventless conditions.

To better thwart the steric barrier in the mutual approach of two molecules of **18b**, we decided to rely on high pressure to force them into closer proximity for accelerating the [4+2] cyclodimerization event, while preventing retro-cyclodimerization.[2b,29] Fully aware of the risk of perturbing the fine stereoelectronic factors of the required double diastereofacial control under such conditions, we were delighted to isolate (+)-**4** in 60% yield as the sole cyclodimer [m.p. = 189 °C, lit.[25a] m.p. = 189-190 °C; $[\alpha]_D^{25}$ = + 116 (*c* = 0.16, $CHCl_3$), lit.[8d] $[\alpha]_D^{18}$ = + 115 ($CHCl_3$)] after performing the reaction on a solution of **18b** in CH_2Cl_2 under 14 kbar for 16 h (Figure 2d, see the Supporting Information). This successful outcome

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permitted us to conclude that the use of the bisiodyl oxygen-atom transfer reagent (*R*)-**19d** exclusively gives rise to the *R* configuration at the C6-alcoholic center of the *ortho*-quinol **18b**. The same HPD/high-pressure [4+2] reaction sequence carried out using instead the bisiodyl reagent (*S*)-**19d** furnished the expected diastereomeric *endo*-cyclodimer derived from the *ortho*-quinol **18b** with the *S* configuration at its C6 center (Figure 2d). The NMR analysis of this cyclodimer **20** [m.p. = 196 °C; $[\alpha]_D^{25}$ = – 15 (*c* = 1.05, $CHCl_3$)], which could also be analyzed by X-ray crystallography (Figure 2d), indicated that it was similar to a compound isolated from the roots of *Harpagophytum procumbens* (Devil's claw) by Jaroszewski and co-workers.[25b] We then accordingly performed the extraction of a sample of Devil's claw roots from which we could also purify a compound eluting in a major peak at a very similar retention time. Its structure was confirmed by NMR analysis to be that of the *endo*-cyclodimer **20** (see the Supporting Information, Figures S6-S8), which was herein chemically produced in 29% yield from (*6S*)-**18b** (Figure 2d). This lower yield relative to that obtained for **4** might be attributed to a stereochemical mismatched pairing between (+)-**17** and the bisiodyl reagent (*S*)-**19d**. This possibility was conclusively assessed by running a test reaction on (+)-**17** using the racemate **19d**, which gave rise to a *ca* 2:1 mixture of **4** (matched case) and **20** (mismatched case). In both cases, each atropoisomer of the racemic biphenylic reagent **19d** manages to transfer its oxygen atom with full stereocontrol at C6, and no cross-reaction between the resulting two *ortho*-quinols (6*R*)- and (6*S*)-**18b** was observed (see the Supporting Information, Table S1 and Figure S3).

To further enlighten the rules of control in these [4+2] cyclodimerizations, the different available options open to the diterpenoid *ortho*-quinols **18b** for dimerizing were passed under the yoke of theoretical calculations. We were of course particularly eager to verify if the Cieplak–Fallis hyperconjugation that was put forward to explain the dimerization of a sesquiterpenoid *ortho*-quinol into aquaticol (**2**)[15] could again be relied upon to rationalize the (bio)synthesis of maytenone (**4**) and its diastereomer **20**. A search of the transition states (**TS**) of the different possible *endo*-combinations of *ortho*-quinols (6*R*)- and (6*S*)-**18b** was first performed and optimized at the B3LYP/6-31G(d) level (Figure 3, see the Supporting Information, Tables S2-S4).

The lowest-energy transition state thus calculated (**TS-A**) was identified to be the one leading to (+)-maytenone (**4**) from two molecules of (6*R*)-**18b** with the faces bearing the C6-hydroxyl groups in *pseudo*-equatorial orientations (possibly fostered by intramolecular H-bonding with the adjacent C1-carbonyl functions) approaching each other. The two electron-richer C6–C*iso*-propyl bonds are both *quasi* antiperiplanar to the first forming C5–C5' bond (both dihedral angles = 162°, Table S4). As expected, this transition state is C_2-symmetric and hence bispericyclic.[22] The [4+2] and [2+4] cyclodimerization modes are fully equivalent with the C4–C2' and C2–C4' distances being identical (see **TS-A'**, and Table S3). Imposing two molecules of (6*R*)-**18b** to approach each other with their faces flipped, while maintaining the same site connectivities, gives rise to a transition state higher in energy by 27.7 kcal/mol (**TS-B**)

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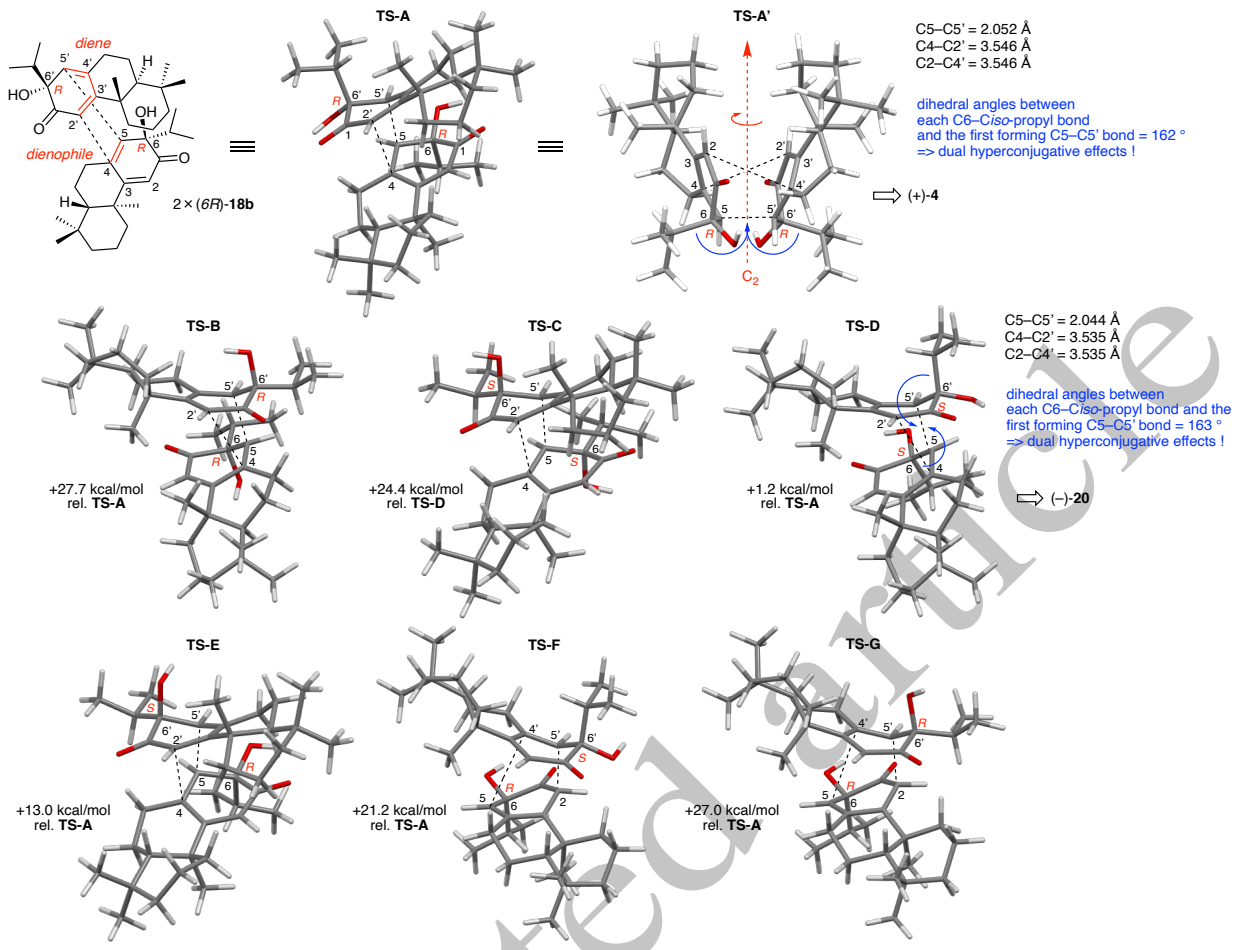

Figure 3. Calculated *endo*-transition states (**TS**) of the Diels–Alder cyclodimerization of the ferruginol-derived *ortho*-quinol **18b**. **TS-A**: Transition state derived from 2 × (*6R*)-**18b** with the faces bearing the C6-hydroxyl groups approaching each other to furnish (+)-maytenone (**4**); **TS-A'**: C_2-symmetric view of the same transition state; **TS-B**: Transition state derived from 2 × (*6R*)-**18b** with the faces bearing the C6-*iso*-propyl groups approaching each other; **TS-C**: Transition state derived from 2 × (*6S*)-**18b** with the faces bearing the C6-*iso*-propyl groups approaching each other; **TS-D**: Transition state derived from 2 × (*6S*)-**18b** with the faces bearing the C6-hydroxyl groups approaching each other to furnish the cyclodimer (–)-**20**; **TS-E**: Transition state derived from (*6R*)-**18b** + (*6S*)-**18b** with the same site connectivities as **TS-A**; **TS-F**: Transition state derived from (*6R*)-**18b** + (*6S*)-**18b** connecting C5 to C4' and C5' to C2; **TS-G**: Transition state derived from 2 × (*6R*)-**18b** connecting C5 to C4' and C5' to C2.

Similarly, the transition state calculated from two molecules of (6*S*)-**18b** with the faces bearing the *pseudo*-equatorial C6-*iso*-propyl groups approaching each other (**TS-C**) is also a higher-energy state with a difference of + 24.4 kcal/mol relatively to the energy of the transition state for which the faces bearing the C6-hydroxyl groups are approaching each other (**TS-D**) and for which the C6-*iso*-propyl groups are again mutually oriented in a *quasi* antiperiplanar fashion with the first forming C5–C5' bond (Figure 3, and Tables S2-S4). In fact, **TS-D** is the appropriate C_2-symmetric transition state leading to the diastereomeric cyclodimer (–)-**20**, and its calculated energy differs from that of **TS-A** by only 1.2 kcal/mol. According to Maxwell–Boltzmann statistics, this difference of energy would correspond to a ratio of 88:12 between **TS-A** and **TS-D**, which is also, at least qualitatively, in agreement with the higher chemical yield observed for the formation of (+)-**4** relatively to that observed for (–)-**20** under the same reaction conditions (see Figure 2d and Figure S3). Moreover, switching the configuration at C6 of just one molecule, while maintaining the same *endo*-approach and site connectivities, prevents the adequate orientation of the corresponding C6–C*iso*-propyl bond antiperiplanar to the forming C5–C5' bond. The resulting non-C_2-symmetric transition state **TS-E** is 13.0 kcal/mol higher in energy than the most stable C_2-symmetric **TS-A**. Attempting to reorient the C6–C*iso*-propyl bond in order to have both *iso*-propyl groups pointing away from the connecting faces, like in the case of **TS-A** or **TS-D**, implies a facial reversal of the corresponding reacting partner. However, this operation imposes a switch of site connectivities (*i.e.*, C5 to C4' and C5' to C2) in order to maintain an approach of the two molecules in an *endo*-mode. Each C6–C*iso*-propyl bond ends up being antiperiplanar to either the forming C5–C4' or the C5'–C2 bond instead of being both antiperiplanar to the C5–C5' bond. The corresponding transition state **TS-F** is higher in energy than **TS-A** by 21.2 kcal/mol, which is in agreement with the lack of observation of any cross-reaction between the two enantiomers of the *ortho*-quinol **18b**. A similar situation is found when two identical enantiomers are forced to connect *via* C5 to C4' and C5' to C2, hence imposing a facial reversal of one enantiomer with an in-plane reorientation of the molecule to enable its *endo*-approach toward its reacting partner. The corresponding

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transition state **TS-G** has also an energy that is much higher than that of **TS-A** by 27.0 kcal/mol.

The two most stable calculated transition states **TS-A** and **TS-D** are thus those experimentally leading to (+)-maytenone (**4**) and its diastereomer (–)-**20**, respectively. These C_2-symmetric transition states fulfill all the criteria for bispericyclic Diels–Alder cyclodimerization, as illustrated in Figure 4 for **TS-A**. Secondary orbital interactions (SOI) between the *p*-orbitals at C3 and C3' (*i.e.*, Woodward–Hoffmann SOI, C3↔C3' = *ca* 3.8 Å, Table S3) can stabilize the *endo*-approach of the two reacting partners, which is further stabilized by Salem–Houk SOI between *p*-orbitals at C2 and C4' or at C4 and C2', since the [4+2] and the [2+4] cycloaddition modes are equivalent. The alignment of the two C6–C*iso*-propyl bonds antiperiplanar to the C5–C5' connection could then also enable the privileged initial formation of this bond through dual Cieplak–Fallis effects.

To further inform us on those possible hyperconjugative effects and others, we performed natural bond orbital (NBO) analyses of the four C2-symmetric transition states (*i.e.*, **TS-A**, **-B**, **-C** and **-D**). These calculations first reveal that the two lower-energy **TS-A** and **TS-D** would be in part stabilized by a delocalization from the bonding orbital ($\sigma^{\#}$) of the incipient C5–C5' bond into the antiperiplanar antibonding orbitals (σ^{*}) of the two C6–C*iso*-propyl bonds, which amounts to *ca* 3.6 kcal/mol per orbital interaction (Table S5). Felkin–Ahn interactions between this same $\sigma^{\#}$ orbital and the vacant $\sigma*$ orbital of the two electron-poorer C6–OH bonds are also present, although they are of much smaller magnitudes (*ca* 1.0 kcal/mol, Table S5), since the C6–OH bonds are not properly oriented for hyperconjugation (Table S4). NBO analyses further indicate that Cieplak–Fallis effects, which are reversely associated to electron density transfers from the σ orbitals of the electron-rich C6–C*iso*-propyl bonds into the $\sigma^{\#*}$ orbital of the incipient C5–C5' bond, might also contribute to the stabilization of these two TSs with energies of *ca* 4.0 kcal/mol (Table S5). As a result of these hyperconjugative effects, the length of the C6–C*iso*-propyl bonds is systematically and expectedly longer (*e.g.*, 1.593 Å in **TS-A** versus 1.554 Å in **TS-B**, see Table S3).[30] In **TS-B** and **TS-C**, Cieplak–Fallis effects cancel out due to the unfavorable orientation of the C6–C*iso*-propyl bonds with respect to the incipient C5–C5' bond, while the antiperiplanar alignment of the C6-OH bonds reinforces Felkin–Ahn $\sigma^{\#}_{C5-C5'} \rightarrow \sigma^{*}_{C6-OH}$ interactions up to *ca* 5.5 kcal/mol (Tables S4 and S5). However, the much higher energies of **TS-B** and **TS-C** compared to those of **TS-A** and **TS-D** indicate that Cieplak–Fallis interactions constitute a better descriptor than Felkin–Ahn interactions for rationalizing the relative stabilities of these late transition states (Figure S9).

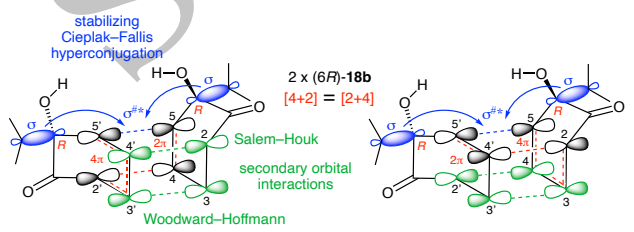

Figure 4. Cyclodimerization of the ferruginol-derived *ortho*-quinol into (+)-maytenone (**4**). This simplified drawing of the C_2-symmetric Diels–Alder **TS-A** (the terpenoid decalin motif connected at C3 and C4 of the *ortho*-quinol monomer (6*R*)-**18b** is omitted for clarity) shows the positioning of the Woodward–Hoffmann and Salem–Houk secondary orbital interactions, and the dual Cieplak–Fallis hyperconjugation that sealed this bispericyclic ([4+2] = [2+4]) transition state leading to (+)-**4**. NB: the same stabilizing effects are at play in the making of its diastereomer (–)-**20** from the *ortho*-quinol (6*S*)-**18b** *via* **TS-D** (Figure 3).

Conclusion

The first chemical synthesis of the bisditerpenoid (+)-maytenone (**4**) described here required only 6 steps (19% overall yield) from commercially available (+)-dehydroabietylamine (**14**). This synthesis of such a complex natural product follows the manner by which this Diels–Alder cyclodimer of an *ortho*-quinol derived from the diterpenoid (+)-ferruginol (**17**) is plausibly biosynthesized and showcases (*i*) the performance of chiral iodyl reagents in regioselective asymmetric dearomative oxygenation reactions and (*ii*) the utility of high pressure conditions to force Diels–Alder processes with recalcitrant materials without any loss of expected selectivities. The computational calculations underlined the significant role played by Cieplak–Fallis hyperconjugative effects in controlling the connecting site-specific regioselectivity and the stereoselectivity in such a natural case of bispericylic Diels–Alder reactions.

To the best of our knowledge, all other reported cases of cyclodimerization of natural[31] or unnatural chiral *ortho*-quinols strictly follow the exact same selectivities, as well as those of related *ortho*-quinone (spirolactonic) monoketals[13,20,21,32] and even those of dimerizing cyclohexa-2,4-dienones bearing non-oxygenated substituents at C6.[21a,33] The question as to whether or not natural cases of such bispericyclic [4+2] cycloadditions benefit from the intervention of particular enzymes (*i.e.*, Diels-Alderases) remains open, but the spontaneity with which most of these cyclizations experimentally occurred casts doubt on this possibility. Other biosynthetically relevant examples of Diels-Alderase-free [4+2] dimerizations have been demonstrated, notably with alkenylbutenolides for which the process is also bispericyclic.[7] Nevertheless, the fact that we had to rely on high pressure conditions to drive the construction of (+)-maytenone and its diastereomer *ex vivo* might indicate that some kind of a [4+2] cyclase accelerates the process *in vivo*.[5c] However, the role of such a protein would be essentially to chaperone two *ortho*-quinol monomers toward operational proximity, as all the elements of controls and transition state stabilization are inherently embedded in the structure of those monomers

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Crystallographic parameters for compounds **4** and **20** are available free of charge from the Cambridge Crystallographic Data Centre under CCDC-1148173[25a] and CCDC-1967527. The coordinate files of the calculated transition states are available from the authors on request as .pdb files (**TS-A** to **TS-G**) for 3D molecular viewing.

Keywords: total synthesis • cycloaddition • asymmetric synthesis • hypervalent compounds • transition states

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