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Communication

Total Synthesis of the Hexacyclic Sesterterpenoid Niduterpenoid B via Structural Reorganization Strategy

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ABSTRACT: To date, it remains challenging to precisely and efficiently construct structurally intriguing polycarbocycles with densely packed stereocenters in organic synthesis. Niduterpenoid B, a naturally occurring ERα inhibitor, exemplifies this complexity with its intricate polycyclic network comprising 5 cyclopentane and 1 cyclopropane rings, featuring 13 contiguous stereocenters, including 4 all-carbon quaternary centers. In this work, we describe the first total synthesis of niduterpenoid B using a structural reorganization strategy. Key features include the following: (1) an efficient methoxy-controlled cascade reaction that precisely forges a highly functionalized tetraquinane (A−D rings) bearing sterically hindered contiguous quaternary stereocenters; (2) a rhodium-catalyzed [1 + 2] cycloaddition that facilitates the construction of a strained 3/5 bicycle (E−F rings) angularly fused with ring D.

The synthesis of complex polycyclic natural bioactive molecules remains a critical yet challenging area in organic chemistry.[1] Over the past few decades, numerous carbon annulation methodologies, such as Pauson−Khand reaction,[2] Nazarov cyclization[3] and cyclopropanation,[4] have been developed to construct a wide array of cyclic bioactive and drug molecules. However, these methods primarily facilitate the creation of relatively simple systems, such as bi- or tricyclic structures. Strategies for synthesizing highly strained fused or angular tetracyclic systems are scarce. Few one-step methods exist for constructing tetraquinane or more complex carbocyclic systems with densely packed stereocenters from simpler, readily accessible starting materials.[5] This challenge persists due to the inherent difficulty in constructing rigid five-membered carbocycle,[6] posing a significant and longstanding problem in organic synthesis and impacting related fields such as material science, where polyquinane structures are in high demand.[5c]

Adopting a structural reorganization strategy, which can produce the 'hardly accessible' structures from 'easily accessible' ones by reorganizing (breaking and forming) C−C single bond, offers a unique opportunity to construct the bibridged, fused or spirocyclic ring systems, thereby addressing the synthetic challenges unattainable by other methods (Figure 1a).[7−9] However, it is even more challenging and highly desirable for developing sophisticated structural reorganization strategies, by achieving selective and precise regulation of multiple C−C single bond reorganizations for synthesis of the complex polyquinane scaffolds with contiguous quaternary carbons (Figure 1b).[3b,5] In 2022, we pioneered a tandem Nazarov cyclization and double ring expansions of 1,3-dicyclobutylidene acetone, successfully achieving the one-step construction of a 5/5/5-angular tricycle (Figure 1b).[9] We now expanded this strategy to build tetraquinane architectures in a predicable manner. This refined approach aims to synthesize complex sesterterpenoid niduterpenoid B (**2**) (Figure 1c) more efficiently, as described below.

Sesterterpenoids represent a distinct subclass of polycyclic terpenoids characterized by intricate molecular architectures and a diverse range of biological activities, including cytotoxicity, enzymatic inhibition, antimicrobial effects, and defensive properties.[10] Among them, niduterpenoids A and B (**1**−**2**), isolated from *Aspergillus nidulans*, are unique sesterterpenoids featuring a compact carbocyclic framework consisting of 5 cyclopentane and 1 cyclopropane rings (Figure 1c).[11] Biological investigations revealed that compounds **1** and **2** are potential antagonists of estrogen receptor alpha (ERα), while compound **1** abolished 17-estradiol-induced proliferation of human breast tumor cell line MCF-7 (IC_{50} = 11.42 ± 0.85 μM) without exhibiting cytotoxic effects.[11] From a synthetic perspective, the sterically compact 5/5/5/5/3/5 hexacyclic framework of niduterpenoids presents several formidable synthetic challenges: (a) the fused/angular tetraquinane (A−D rings) and highly strained 3/5 bicyclic (E−F rings) skeletons; and (b) thirteen contiguous stereocenters, including four congested all-carbon quaternary centers and two *oxa*-quaternary centers.[12] To date, no chemical synthesis of niduterpenoids A and B (**1**−**2**) has been reported. Herein, we reported our achievement in the rapid and precise construction of a highly functionalized tetraquinane (B) scaffold using a methoxy-controlled cascade reaction (Figure 1d), enabling the first concise total synthesis of niduterpenoid B (**2**).

A critical aspect of our synthetic design was the strategic introduction of the basic skeleton of niduterpenoid B (**2**), in which the fused 3/5 bicyclic skeleton (E−F rings) would be

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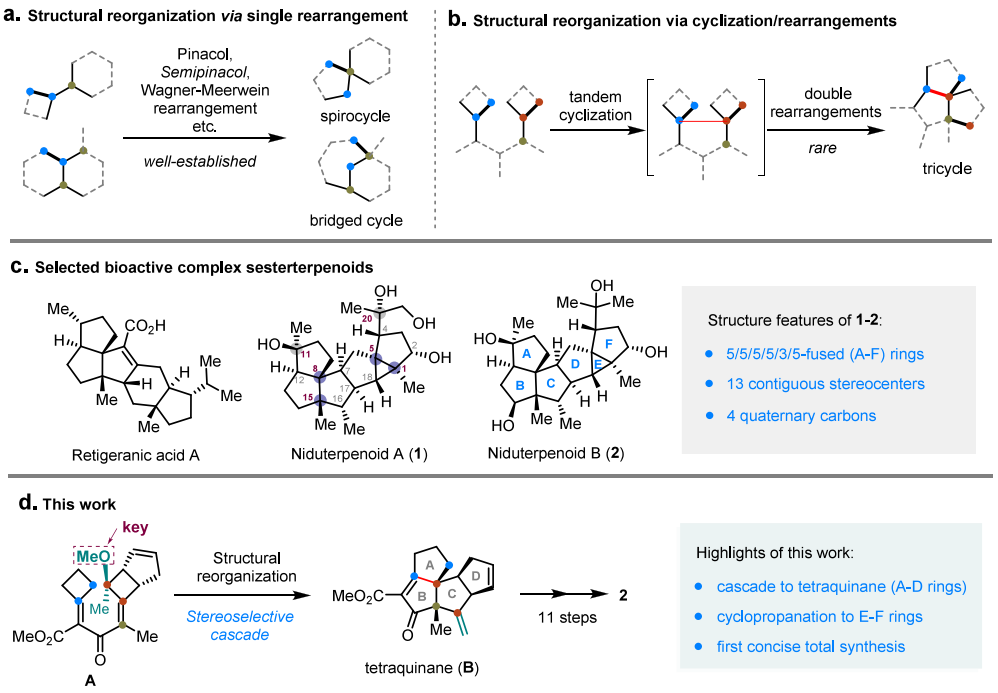

Figure 1. Structural reorganization in polycyclic scaffolds synthesis.

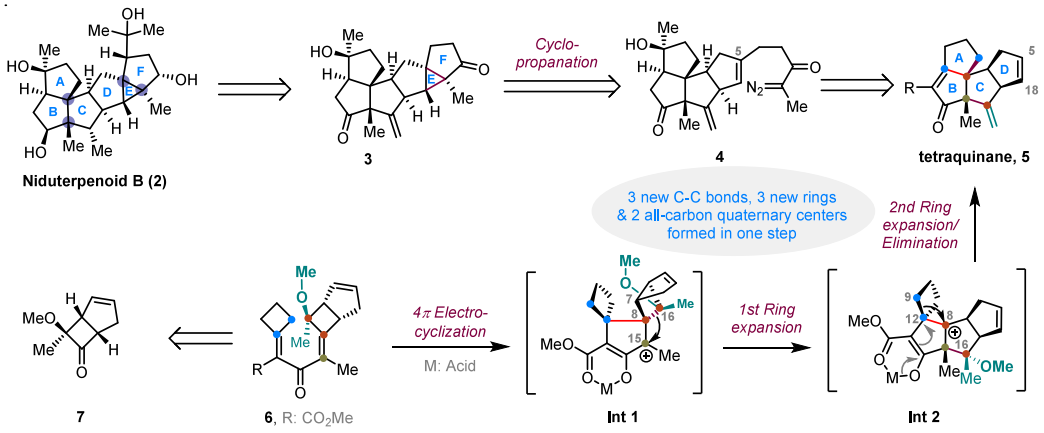

Figure 2. Retrosynthetic analysis of niduterpenoid B.

installed at a late stage and the tetraquinane (A–D rings) would be introduced early in the synthetic sequence (Figure 2). We envisaged synthesizing target molecule **2** from intermediate **3** through global functional transformations to introduce the required motifs and functional groups. Having simplified our target to **3**, we sought to identify an intramolecular cyclopropanation as the key reaction to rapidly assemble the 3/5 bicyclic framework and multisubstituted cyclopropane motif from diazoketone **4**.[4,13] Compound **4** could be accessed from tetraquinane **5** by installation of the diazoketone motif at the C5 position of the alkene. Ultimately, tetraquinane **5** was recognized as a strategic intermediate that could be accessed from dienone **6** through a cascade process.[10a] In the pivotal 4π electrocyclization/double ring expansions/elimination cascade, we proposed that conrotatory cyclization of **6** would give rise to allylic carbocation species **Int 1**, featuring contiguous cyclobutanyl groups on the newly formed B ring. Subsequent methoxy-controlled regioselective double ring expansions through migrations of the C16–C8 (to C15) bond and C9–C12 (to C8) bond and elimination of the methoxy group would give the desired compound **5**. Notably, we aimed to introduce the OMe group as a handle to control the desired migrating behavior.[14] The n–σ* noncovalent interaction between the lone pair of OMe and the C16–C8 antibonding (σ*) orbital increases the HOMO orbital energy of the C16–C8 bond and lowers the energy barrier with the empty p orbital of C15 in carbocation **Int 1**, making the C16–C8 bond preferentially migrate. Practically, the rationally designed **6** would be readily prepared from multisubstituted cyclobutanone **7**,[15] 2-phosphonopropionate, and cyclobutanone in a modular manner.

Our synthesis commenced with the preparation of dienone **6** (Scheme 1) from known compound **7**, which was synthesized *via* [2 + 2] cycloaddition of cyclopentadiene with *in situ* generated methoxy(methyl)ketene from 2-methoxypropionyl chloride and Et_3N. Under modified Mattay's conditions,[15b] **7** was obtained on a decagram scale with an 85% yield and a diastereomeric ratio (d.r.) of 7.5:1. Horner–Wadsworth–Emmons (HWE) reaction of **7** with triethyl 2-phosphonopropionate yielded ester **8** in 90% yield, presenting a Z/E ratio of

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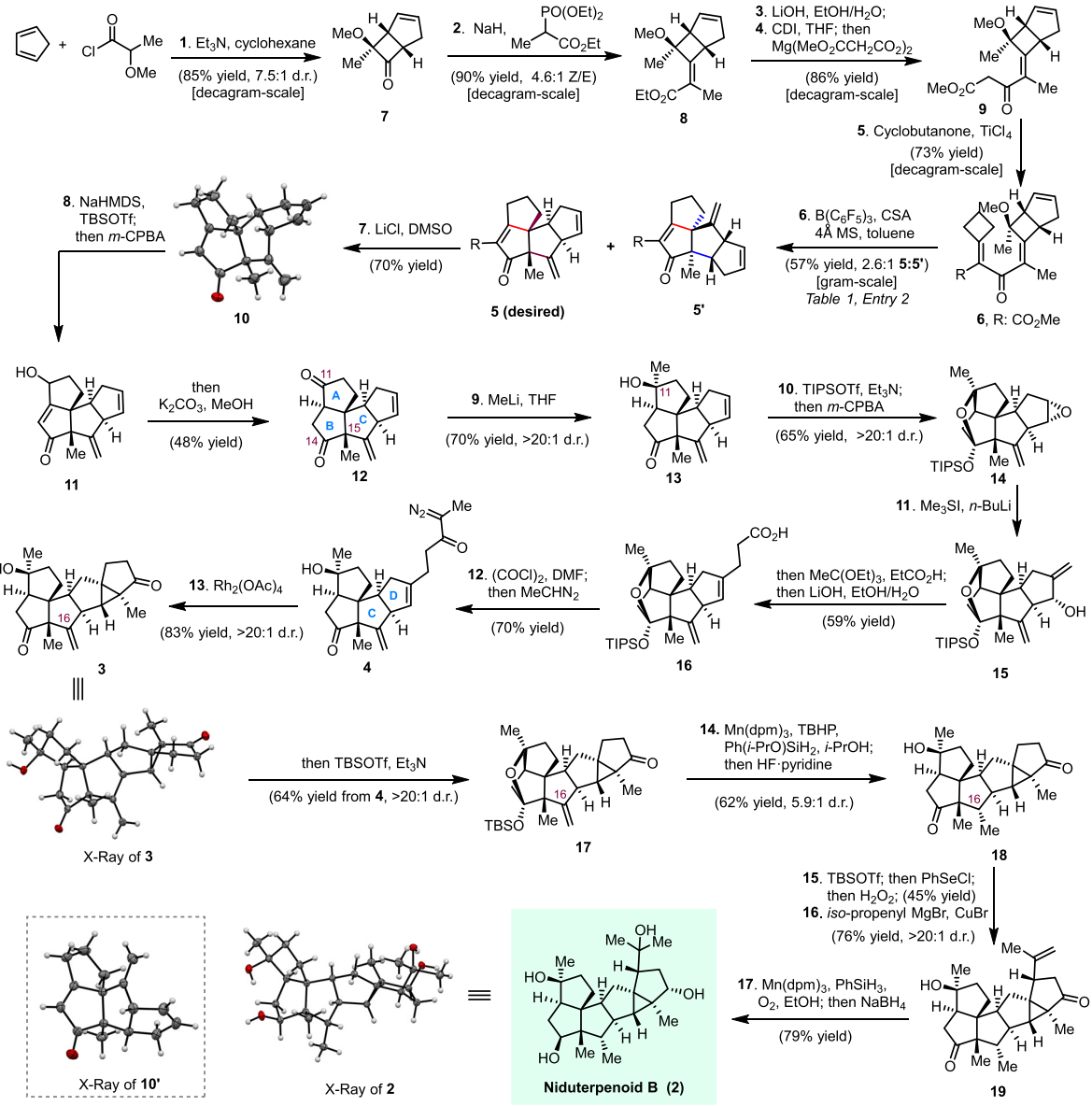
Scheme 1. Total Synthesis of Niduterpenoid B



4.6:1. Hydrolysis of **8**, followed by activation of the resulting acid with CDI, which subsequently reacted with magnesium methyl malonate, furnished *β*-ketone ester **9** in 86% yield. Knoevenagel condensation of **9** with cyclobutanone under $TiCl_4$/pyridine conditions provided dienone **6** in a 73% yield. This four-step sequence enabled decagram-scale access to cascade precursor **6**.

Next, we explored the feasibility of the tandem 4*π* electrocyclization/double ring expansions/elimination reaction. However, the allylic OMe in **6** is acid-sensitive, and its position at the sterically hindered *oxa*-quaternary center typically poses a significant challenge, often leading to the failure of the Nazarov cyclization, as previously reported. Initially, under Lewis acids, such as $TiCl_4$, $InCl_3$, and $AgSbF_6$ conditions, compound **6** was completely consumed with no desired product **5** observed. After systemic optimization of various reaction parameters, including Lewis acid, additive, solvent, and temperature (for more details, see Supplementary Table S1), a novel coordination system with $B(C_6F_5)_3$,[16] CSA and 4Å molecular sieves (MS) was discovered for this cascade reaction. This system enabled the formation of the desired product **5** in 36% yield, along with an undesired product **5′** and other side products (Table 1, entry 1).[17] The structures and stereochemistry of **5** and **5′** were confirmed by X-ray crystallography of these decarboxylation derivatives **10** and **10′**, respectively (Scheme 1).[17] Moreover, compound **5** could be prepared in 41% yield on a gram scale (entry 2). No desired product **5** was formed without $B(C_6F_5)_3$ (entry 3). The use of CSA proved to be essential because $B(C_6F_5)_3$ only provided **5** in 8% yield (entry 4), and omitting CSA led to lower efficiency (entry 5). Without the methoxy group, a substrate like **6c** (for details, see Table S2 and Figure S2) yielded only incorrect stereochemistry (at C16) product **5c′** and an undesired skeleton like **5c-1**, further demonstrating its critical role in controlling the regioselectivity of the cascade reaction.[17]

Notably, the highly congested tetraquinane **5**, featuring multiple functional groups that allow further manipulation, was rapidly prepared on gram-scale in only 5 steps from commercially materials. This transformation (**6**→**5**) exemplifies the precise stereoselective construction of polycyclic

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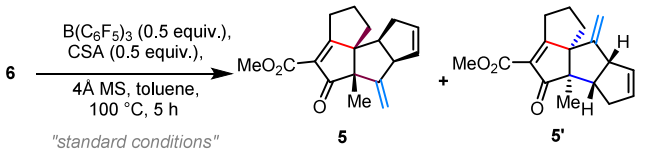
Table 1. Cascade Reaction Discovery and Optimization



Entry	Variations from the "standard conditions"[a]	Yield (%)[b] 5	5′
1	none	36	14
2[c]	3 g-scale of **6**	**41**	**16**
3	No $B(C_6F_5)_3$	0	0
4	$B(C_6F_5)_3$ (1 equiv.), toluene, 120 °C, 12 h	8	trace
5	No CSA	10	<5

[a]Reaction conditions: **6** (0.10 mmol), $B(C_6F_5)_3$ (0.05 mmol), CSA (0.05 mmol), 4Å MS (50 mg), toluene (1.0 mL), 100 °C, 5 h. [b]Isolated yields. [c]Reaction conditions: **6** (3.0 g, 9.6 mmol), $B(C_6F_5)_3$ (5.9 mmol), CSA (6.5 mmol), 4Å MS (3.0 g), toluene (100 mL), 100 °C, 5 h.

structures with densely packed stereocenters in a complex system.

With a scalable route established to access **5**, the stage was set for constructing the 3/5 bicyclic skeleton (E−F rings). Krapcho decarboxylation of **5** with LiCl in wet DMSO provided **10** in 70% yield. Subsequently, γ-hydroxylation of ketone **10** smoothly occurred through chemo- and regioselective epoxidation of its silyl enol ether derivative with *m*-CPBA to afford allyl alcohol **11**, which was isomerized with K_2CO_3 to produce 1,4-diketone **12** in 48% yield.[18] A substrate-controlled highly regio- and stereoselective 1,2-addition of **12** with excess MeLi was realized from the convex face (A/B rings), furnishing the tertiary alcohol **13** with the desired stereochemistry (at C11) in 70% yield as a single isomer. The unreacted C14-carbonyl group of **12** was sterically inaccessible due to the adjacent congested quaternary carbon (C15) and the angular A/B/C rings systems.[19] Furthermore, an *in situ* ketal might be formed at C14 carbonyl after MeLi addition into C11 carbonyl, and therefore, it was not being attacked by MeLi. Protection of γ-hydroxyl ketone **13** with TIPSOTf, followed by *m*-CPBA epoxidation, gave epoxide **14** in high yield and selectivity. Conversion of epoxide **14** to carboxylic acid **16** was achieved through the following sequences: (a) regioselective ring-opening of epoxide **14** with dimethylsulfonium methylide under modified Alcaraz's condition;[20] (b) Johnson−Claisen rearrangement of allylic alcohol **15** with triethyl orthoacetate, followed by *in situ* hydrolysis of the resulting ester with LiOH. Treatment of freshly prepared diazoethane with acyl chloride, derived from acid **16** and oxalyl chloride, produced the diazoketone **4** in 70% yield. To our delight, cyclopropanation occurred smoothly in a diluted toluene solution of catalytic amounts of $[Rh(OAc)_2]_2$, affording the desired product **3** in 83% yield as a single isomer. The stereochemistry and structure of **3** were confirmed by X-ray crystallography. The high diastereoselectivity in cyclopropanation could be attributed to steric hindrance on the *concave* face of the C/D rings, which makes the *convex* face more accessible. This key transformation forges two C−C bonds—with complete control over the C5, C18 quaternary centers—while forming the requisite 3/5 bicyclic ring system (E−F rings) of the target sesterterpenoid.

Achieving stereoselective hydrogenation of the exocyclic double bond in **3** to install the methyl group (*exo* at C16) posed quite the challenge.[17] The undesired diastereomer **18′** (*endo* at C16) was found to be selectively accessible from **3** under Shenvi's reduction conditions.[21] We hypothesized that altering the structure and conformation of the substrate might influence the diastereoselectivity of hydrogenation. Therefore, treatment of alcohol **3** with TBSOTf resulted in the formation of bridged ketal **17**, featuring an additional bridged ether ring on the concave of the A/B ring system and an *exo*-oriented OTBS group. To our delight, hydrogenation of **17** under Shenvi's conditions provided the expected product **18** as the major diastereomer after removal of the silyl ether group. Consequently, treatment of ketal **17** with Mn $(dpm)_3$, Ph(*i*-PrO)SiH_2, and *t*-BuOOH in *i*-PrOH, followed by *in situ* adding HF·pyridine, exclusively afforded **18** in 62% yield (5.9:1 d.r.).

Desaturation of ketone **18** was achieved through silyl enolization/selenization/oxidation/elimination transformations using Luo's conditions.[22] Then 1,4-additon of the unsaturated ketone with *iso*-propenyl magnesium bromide in the presence of CuBr·SMe_2 provided desired product **19** as a single diastereomer in 76% yield. Finally, Mukaiyama hydration of terminal alkene **19**, followed by reduction of diketone with $NaBH_4$, afforded niduterpenoid B (**2**) in high yield with excellent diastereoselectivity. The structure and stereochemistry of niduterpenoid B (**2**) were confirmed by X-ray crystallography.[17] The spectroscopic data of synthetic niduterpenoid B (**2**) were consistent with those of the isolated one.[11]

The enantioenriched (+)-niduterpenoid B was also prepared from chiral cyclobutanone (−)-**7** according to the above synthesis. (−)-**7** was obtained through a two-step sequence: Corey−Bakshi−Shibata (CBS) reduction of (±)-**7** using (*R*)-(+)-2-Me-CBS catalyst, and oxidation of resulting chiral alcohol with Dess-Martin periodinane.[17,23] The optical rotation value of synthetic (+)-**2** ($[\alpha]^{20}_D$ = +24 (*c* 0.1, MeOH)) was consistent with that of the isolated compound ($[\alpha]^{25}_D$ = +16 (*c* 0.1, MeOH)), thus confirming the absolute configuration of natural occurring (+)-niduterpenoid B.[11]

In conclusion, we successfully accomplished the total syntheses of hexacyclic terpenoid niduterpenoid B (**2**) for the first time. Highlights of this work include the following: (1) the rapid, stereoselective construction of congested angular/fused 5/5/5/5 tetracyclic skeleton (A−D rings) bearing vicinal all-carbon quaternary centers through the methoxy-controlled tandem 4π electrocyclization/double ring expansions/elimination in a predicable efficient manner; and (2) the assembly of a challenging angular 5/3/5 tricyclic skeleton (D−F rings) with vicinal all-carbon quaternary centers *via* a highly diastereoselective Rh-catalyzed intramolecular cyclopropanation. This innovative approach demonstrates the power of structural reorganization strategy in the rapid construction of complex polyfused/spirocyclic ring system as well as multiple quaternary stereocenters. The efficiency of our route highlights the benefits of employing such a reorganization strategy in the synthesis of complex molecules. This synthetic framework should provide a versatile platform for the preparation of designed niduterpenoid analogs and further discovery of novel ERα inhibitor for breast cancer treatment.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c09555.

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Experimental procedures, additional data, and X-ray crystallography data for the structures of **S4**, **S1**, **S5**, **10**, (+)-**10**, (−)-**3**, **2**, **3**, **S8**, **S6**, **10′**, and **5′′** (PDF)

Accession Codes

CCDC 2359716−2359726 and 2361452 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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