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An Acid-Catalyzed Epoxide Ring-Opening/Transesterification Cascade Cyclization to Diastereoselective Syntheses of (±)-β-Noscapine and (±)-β-Hydrastine

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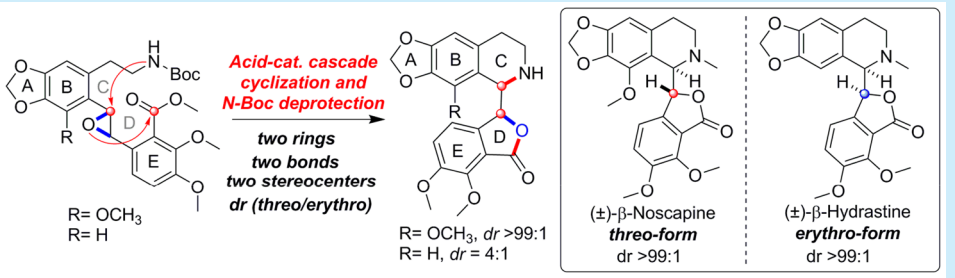
Supporting Information



ABSTRACT: An acid-catalyzed stereoselective epoxide ring-opening/intramolecular transesterification cascade cyclization reaction and *N*-Boc deprotection was found to be a successful strategy to construct the phthalide tetrahydroisoquinoline skeleton in one pot. Based on this strategy, the unified and highly diastereoselective routes for the total syntheses of (±)-β-Noscapine and (±)-β-Hydrastine were exploited.

Phthalide tetrahydroisoquinoline alkaloids, such as Noscapine (**1**),[1] Hydrastine (**2**),[2] Bicuculline (**3**),[2a,3] and Cordrastine (**4**),[4] are known to possess interesting and diverse biological properties (Figure 1).[5] Structurally, the alkaloids comprise a 1,2,3,4-tetrahydroisoquinoline and a phthalide ring and these two units are linked together by two chiral centers at their C-1 and C-3′ carbons to form either *erythro*- or *threo*-isomer (Figure 1). (−)-α-Noscapine [(−)-**α-1**], originally isolated from *Papaver somniferum L.*,[6] is a classical non-addictive antitussive agent without significant toxicity[7a] and also displays other potential clinical utilities[7] for the treatment of stroke, anxiety, especially and cancer. Clinically used (−)-**α-1** can be provided through extraction from plant resources.[8] For the intriguing structure and important bioactivity, Noscapine (**1**) has become an attractive target for chemical synthesis and much effort has been made toward the development of efficient routes to Noscapine (**1**).[4b,9−12] The first route was reported by Robinson and Perkin,[9] who constructed a C-1−C-3′ bond through direct condensation between Cortanine and Meconine, which were produced by degradation of natural (−)-**α-1**. Based on Robinson−Perkin strategy, several other approaches[4b,10] were reported, such as zinc-promoted[4b] coupling and electrochemical reductive coupling.[10]

Alternatively, Kerekes and Bognár[11] and Szántay et al.[12] synthesized phthalide isoquinoline skeletons through the Bischler−Napieralski reaction. Despite these remarkable achievements, an inherent drawback associated with all of the above-mentioned strategies was the lack of regioselectivity and/or stereoselectivity. Thus, the development of novel strategies for regioselective and stereoselective construction of a phthalide tetrahydroisoquinoline core is still in great demand. Recently, we proposed a unified acid-catalyzed epoxide ring-opening/intramolecular transesterification cascade cyclization strategy for the regioselective and stereoselective synthesis of phthalide tetrahydroisoquinoline alkaloids, in which the C and D rings are constructed simultaneously in one step (Scheme 1). Herein, we described the total syntheses of (±)-β-Noscapine [(±)-**β-1**] and (±)-β-Hydrastine [(±)-**β-2**], based on this cascade strategy.

Our retrosynthetic analysis of (±)-β-Noscapine was outlined in Scheme 2. We envisioned that the phthalide tetrahydroisoquinoline core (**5a**) might be introduced by an acid-catalyzed epoxide ring-opening/transesterification cascade cyclization of the epoxide **6a**, which could be derived from (*E*)-stilbene **7a** by epoxidation.[13] Moreover, the stilbene **7a**

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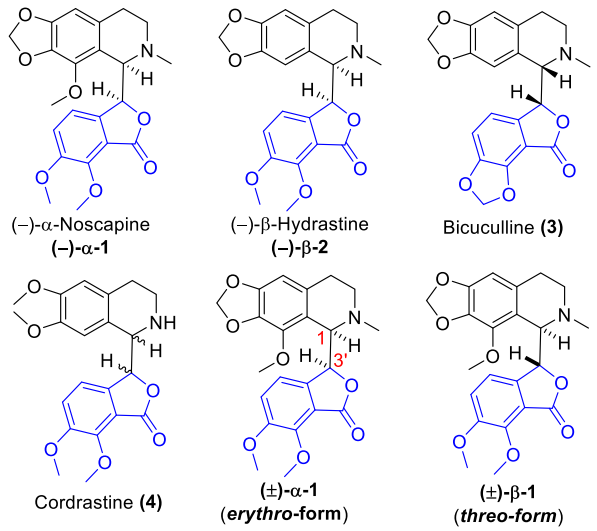
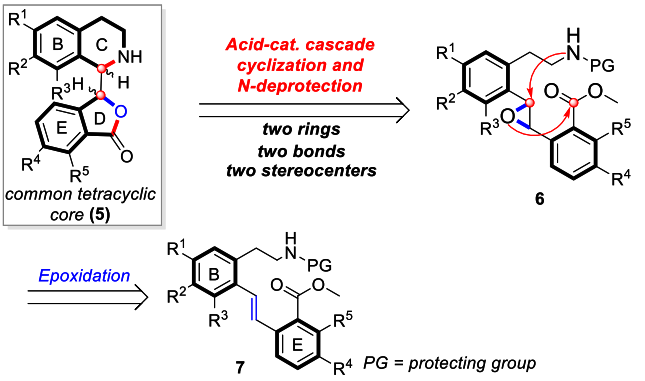
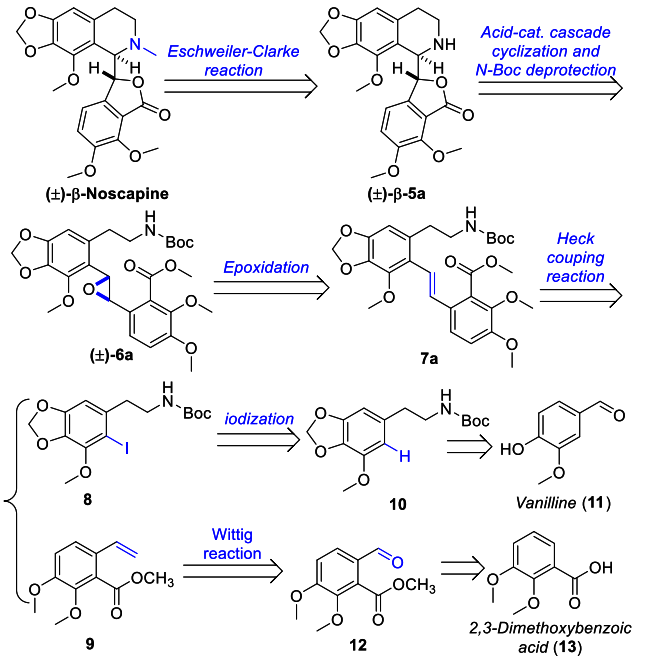


Figure 1. Phthalide-tetrahydroisoquinoline-containing alkaloids and *erythro*- and *threo*-form of Noscapine (**1**).

Scheme 1. Our Proposed Common Strategy To Form a Phthalide Tetrahydroisoquinoline Skeleton



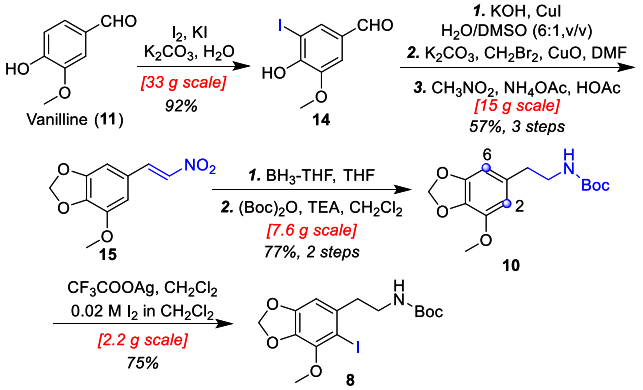
Scheme 2. Retrosynthetic Analysis of (±)-β-Noscapine



might be constructed from monoiodide **8** and substituted styrene **9** by a Pd-catalyzed Heck coupling reaction. The monoiodide **8** could be synthesized by a selective monoiodization of *N*-Boc protected phenethylamine **10**, which could be obtained from commercially available vanilline (**11**). In addition, the styrene **9** could be afforded via the Wittig reaction from **12**, which could be derived from commercially available 2,3-dimethoxybenzoic acid (**13**).[14]

Consequently, our synthetic studies commenced with the preparation of monoiodide **8** (Scheme 3). The vanilline **11** was

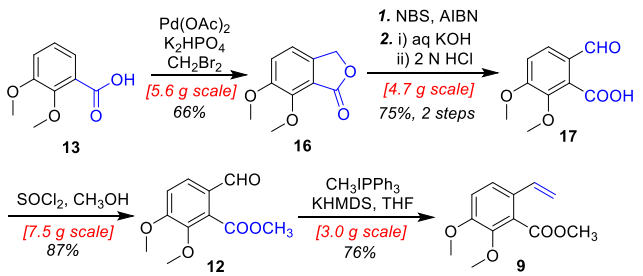
Scheme 3. Synthesis of Monoiodide 8



subjected to the I_2/KI condition,[15] leading to the formation of iodovanilline **14** in 92% yield. A three-step sequence involving the hydrolysis of iodide in **14**, the subsequent dioxolane ring closure with CH_2Br_2,[15] and the Henry reaction,[16] provided the desired precursor **15** in 57% overall yield. The precursor **15** underwent a reduction of olefin and nitro group with BH_3-THF complex, followed by *N*-Boc protection to generate carbamate **10** in 77% yield over two steps. Without further purification, the selective monoiodination of compound **10** with I_2/CF_3COOAg[17] was examined, but it failed to provide the expected monoiodide **8**; only the diiodination product at both C-2 and C-6 was obtained in quantitative yield. Alternatively, the temperature- and iodine-concentration-controlled iodination was performed using 0.02 M I_2 in CH_2Cl_2 at −15 °C to generate monoiodide **8** regioselectively in 75% isolated yield. Note that this seven-step sequence required only one chromatographic purification, which allowed the preparation of **8** with an overall yield of 30% in gram scale.

Next, we then turned our attention to synthesize the key intermediate **9** (Scheme 4). The transformation of commercially available 2,3-dimethoxybenzoic acid **13** to phthalide **16** was achieved by modified Pd(II)-catalyzed *ortho* alkylation of benzoic acid with CH_2Br_2[18] in 66% yield. Two successive steps

Scheme 4. Synthesis of Substituted Styrene 9



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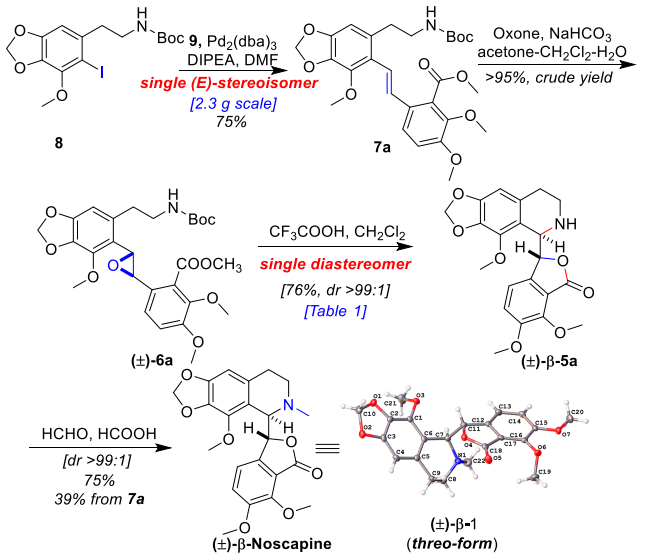
involving a radical bromination on benzyl position of **16** with NBS and AIBN, and a hydrolysis in the presence of aqueous KOH, thus yielded *ortho*-formyl functionalized product **17** in 75% yield. Methyl esterification of **17** was easily achieved by treatment with $SOCl_2$/MeOH in excellent yield. Finally, the resulting **12** was converted to corresponding substituted styrene **9** in 76% yield via the Wittig reaction.[14] Notably, compound **9** were readily prepared in gram scale through this five-step sequence in 33% overall yield.

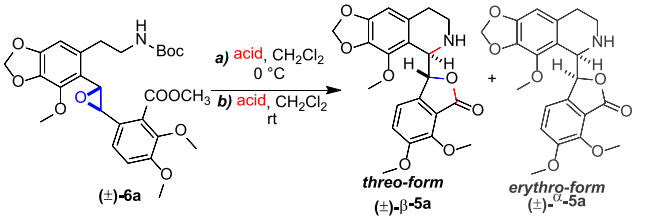
With substantial amounts of the key intermediates **8** and **9** in hand, we moved on to install a phthalide tetrahydroisoquinoline core (Scheme 5). The Pd-catalyzed Heck coupling

Scheme 5. Completion of the Synthesis of (±)-β-Noscapine



reaction of the monoiodide **8** and substituted styrene **9** turned out to be highly stereoselective, thus providing a 75% yield of (*E*)-stilbene **7a** as the only stereoisomer. Epoxidation of (*E*)-alkene **7a** with DMDO[13] proceeded smoothly to give epoxide **6a**. Inspired by the acid-catalyzed ring-opening reaction of epoxides with amines[19] and Lewis acid-mediated selective deprotection of *N*-Boc,[20] we expected that an acid-catalyzed expoxide ring-opening/intramolecular transesterification cascade cyclization reaction and the deprotection of *N*-Boc would occur regioselectively and stereoselectively to install the challenging phthalide tetrahydroisoquinoline core **5a** in one pot. Initially, we treated epoxide **6a** with $AlCl_3$ in CH_2Cl_2, leading to the isolation of **5a** as a single diastereomer (with a diastereomeric ratio (dr) of >99:1) in 34% yield (see Table 1, entry 1). Extensive screening of Lewis acids, such as $FeCl_3$, $ZnCl_2$, $Zn(OTf)_2$, $RuCl_3{\cdot}xH_2O$, $BF_3{\cdot}Et_2O$, $TiCl_4$, $Ti(i\text{-}PrO)_4$ and $Ti(n\text{-}BuO)_4$ failed to improve the yield (see Table 1, entries 2–9). Ultimately, trifluoroacetic acid (CF_3CO_2H) proved to be effective to promote this cascade reaction to afford **5a** in 76% yield (see Table 1, entry 12). The *N*-methylation of **5a** occurred under classic Eschweiler–Clarke reaction conditions,[21] thus yielding **(±)-β-1** in a yield of 75% with unaltered diastereoselectivity (dr > 99:1). The structure of **(±)-β-1** was unambiguously confirmed by X-ray single-crystal diffraction. Notably, without purification of **5a** and **6a**, **(±)-β-1** was prepared from **7a** in the three-step yield of 39% (see the Supporting Information).

Table 1. Optimization of the Acid-Catalyzed Cascade Cyclization and *N*-Boc Deprotection in One Pot



entry	acid	method[a]	yield[b] (%)	diastereomeric ratio, dr[c]
1	$AlCl_3$	A	34	>99:1
2	$FeCl_3$	A	42	>99:1
3	$ZnCl_2$	A	33	>99:1
4	$Zn(OTf)_2$	A	30	>99:1
5[d]	$RuCl_3{\cdot}xH_2O$	A	–	–
6	$BF_3{\cdot}Et_2O$	A	25	>99:1
7	$TiCl_4$	A	29	>99:1
8[d]	$Ti(i\text{-}PrO)_4$	A	–	–
9[d]	$Ti(n\text{-}BuO)_4$	A	–	–
10	CF_3CO_2H	A	0[e]	–
11	CF_3CO_2H	B	ND[f]	–
12	**CF_3CO_2H**	**B**[g]	**76**	**>99:1**

[a]Method A: (a) **6a** (0.05 mmol), acid (0.2 equiv), CH_2Cl_2 (7.0 mL), 0 °C, 3.0 h; (b) acid (2.0 equiv), rt, 3.0 h. Method B: (a) **6a** (0.05 mmol), CF_3CO_2H (5.0 equiv), CH_2Cl_2 (7.0 mL), 0 °C, 3.0 h; b) CF_3CO_2H (20 equiv), rt, 3.0 h. [b]Isolated yield. [c]The dr (*β*/*α* or *threo*/*erythro*) was determined by ^1H NMR. [d]No reaction. [e]Starting material was recovered. [f]**6a** was completely converted, the product was *N*-Boc **5a** (see Scheme SI-5 and Table S1 in the Supporting Information). [g]For entry 12, (a) CF_3CO_2H (30 equiv) was used; (b) CF_3CO_2H (120 equiv) was used.

To further examine the scope of this cascade cyclization in constructing the phthalide tetrahydroisoquinoline alkaloid, (±)-*β*-Hydrastine [**(±)-β-2**] was synthesized by using a similar strategy. As outlined in Scheme 6, commercially available 3,4-methylenedioxyphenethylamine **18** was converted to iodide **19** in 84% yield over two steps, namely, *N*-Boc protection and I_2/CF_3COOAg-mediated iodination.[17] Next, the Pd-catalyzed Heck coupling reaction[22] of **19** and **9** was performed to generate (*E*)-stilbene **20** as the only stereoisomer, which was converted to the phthalide tetrahydroisoquinoline scaffold **21** as a pair of diastereomers [dr (*α*/*β* or *threo*/*erythro*) = 4:1] by DMDO-mediated epoxidation[13] and the subsequent one-pot acid-catalyzed epoxide ring-opening/intramolecular transesterification cascade cyclization and *N*-Boc deprotection. Pleasingly, Eschweiler–Clarke methylation of this mixture afforded easily chromatographically separable Hydrastine in 57% yield, leading to the isolation of both (±)-*α*-Hydrastine [**(±)-α-2**, 46%] and the desired (±)-*β*-Hydrastine [**(±)-β-2**, 11%] as the single diastereomers. Finally, a late-stage epimerization of **(±)-α-2** at C-3′ under MeOK/MeOH conditions afforded its *β*-configured epimer [**(±)-β-2**] as a diastereomerically pure product in a yield of 65%. The structure and stereochemistry of (±)-*β*-Hydrastine [**(±)-β-2**] were confirmed by X-ray crystallographic analysis.

Mechanistically, as shown in Scheme 7, this pivotal cascade reaction probably occurs via an acid-catalyzed regioselective and stereoselective ring opening of epoxide in a S_N1-like mechanism[19b,23] and transesterification sequence. Probably, in the initial step, the proton will coordinate to the oxygen atom in the trans-epoxide **6a** (or **22**) to form an oxonium ion **6a-I**

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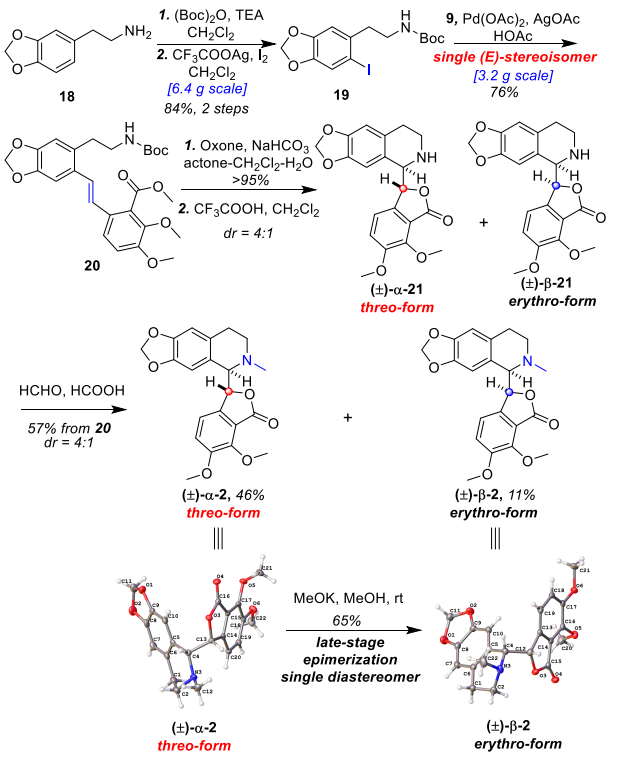
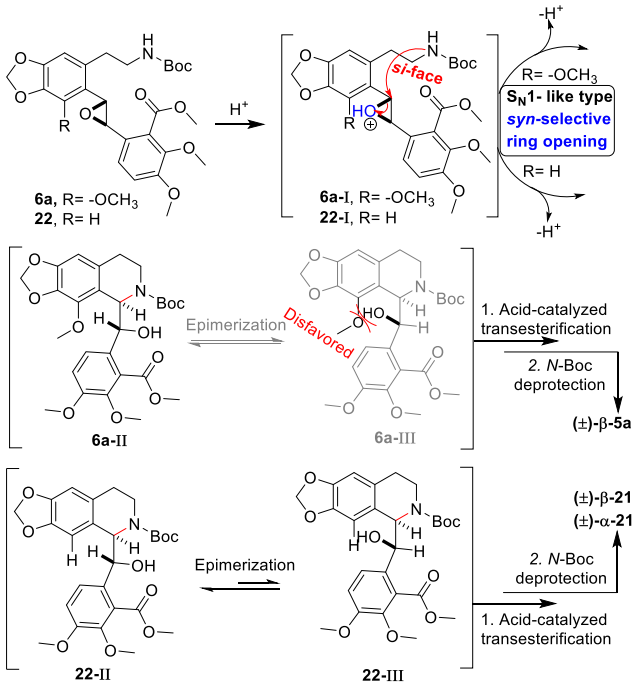
Scheme 6. Completion of the Synthesis of (±)-β-Hydrastine



Scheme 7. Postulated Mechanism for Acid-Catalyzed Cascade Cyclization and *N*-Boc Deprotection in One Pot



(or **22-I**), which, in turn, undergoes rupture of the C−O bond and intramolecular amino nucleophilic substitution from the *si*-face to afford **6a-II** (or **22-II**). Such a *syn*-opening[23,24] approach causes the retention of configuration at C-1. The diastereoselectivity of this cascade reaction could be interpreted as the epimerization of **6a-II** and **22-II** at C-3′. Namely, the steric repulsion between hydroxyl and methoxyl in **6a-III** is the main cause of the inability of **6a-II** to epimerize to produce its epimer **6a-III**, thus resulting in (±)-β-**5a** as a single diastereomer (dr > 99:1). However, the hydroxyl group in **22-II** is sterically less hindered to epimerize to produce its epimer **22-III**, thus resulting in the above-mentioned diastereoselectivity (dr = 4:1). At the experimental stage, the detectable intermediates **6a-II**, **22-II**, and **22-III**, as well as the easily chromatographically obtainable intermediates *N*-Boc protected (±)-β-**5a**, (±)-α-**21**, and (±)-β-**21** (see Scheme SI-5 in the Supporting Information) strongly supported our proposed reaction mechanism.

In summary, we have disclosed a diastereoselective synthetic approach to form the phthalide tetrahydroisoquinoline alkaloids (±)-β-Noscapine and (±)-β-Hydrastine. The synthesis featured a novel and unprecedented acid-catalyzed epoxide ring-opening/intramolecular transesterification cascade annulation reaction and *N*-Boc deprotection in one pot as the key step to construct the phthalide tetrahydroisoquinoline scaffolds. The synthetic strategy applied in the present synthesis offers a new access to those phthalide-tetrahydroisoquinoline-containing alkaloids. We anticipate that the synthetic strategy described herein may find more applications in the diastereoselective and/or enantioselective total syntheses of other related natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02715.

Experimental procedures, spectroscopic data, and X-ray crystallographic data for (±)-β-**1**, (±)-α-**2**, and (±)-β-**2** (PDF)

Accession Codes

CCDC 1944137 [(±)-β-**1**], CCDC 1944152 [(±)-α-**2**], and CDCC 1944153 [(±)-β-**2**] 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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Author Contributions

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Notes

The authors declare no competing financial interest.

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