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Total Syntheses of (−)-Englerins A/B, (+)-Orientalols E/F, and (−)-Oxyphyllol

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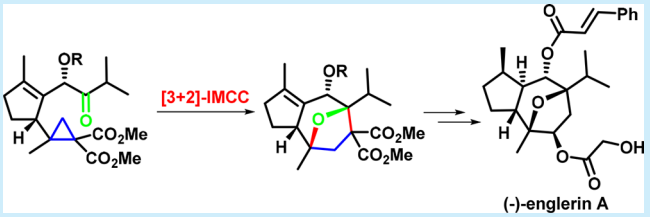
Supporting Information

ABSTRACT: (−)-Englerin A was synthesized in 20 steps from the commercially available material (*R*)-(+)-limonene. In addition, (−)-englerin B, (+)-orientalol E/F and (−)-oxyphyllol were obtained from the intermediate in the route. The key steps include a hydroxyl-directing stereoselective and regioselective intramolecular cyclopropanation and a multigram-scale stereoselective formal intramolecular [3 + 2] cross cycloaddition ([3 + 2]-IMCC) of a cyclopropane 1,1-diester with a carbonyl. A precursor of 7,10-diastereoisomer of englerins was also obtained.



(−)-Englerin A (**1**) and B (**2**) were isolated by Beutler and coworkers in 2008 from stem/root bark of *Phyllanthus engleri*,[1] and it was proven that **1** was an excellent selective inhibitor of renal cancer (Figure 1). Orientalols E/F[2] and oxyphyllol[3] are

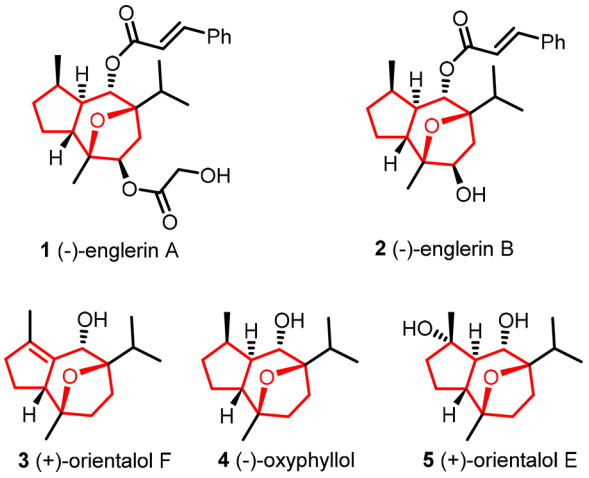


Figure 1. Englerin A and selected structurally related natural products.

three structurally related natural products, the biological activities of which were not well studied due to their extremely low content in nature. These five natural products belong to a family of guianolide sesquiterpenes, which is characterized by a bicyclo[5.3.0]decane (hydroazulene) skeleton and an embedded oxa-[3.2.1]octane skeleton. In view of their biological activities and novel structures, englerins have been attracting attention from the synthetic and medicinal communities since their isolations.[4−8]

So far, since the first total synthesis of (+)-englerin A by Christmann et al. in 2009,[9] over 20 (formal) total syntheses of this englerin family (including their enantiomers and racemates) have been reported. The key strategies include ring-closing metathesis (Christmann et al.,[9,10] Parker et al.,[11] Hatakeyama et al.,[12] Metz et al.,[13−15] Shen et al.[16]), gold-catalyzed [2 + 2 + 2] cycloaddition (Echavarren et al.,[17,18] Ma et al.[19]), 1,3-dipolar [3 + 2] cycloaddition (Nicolaou/Chen et al.,[20] Hashimoto/Anada et al.,[21] Iwasawa et al.[22]), [4 + 3] cycloaddition (Theodorakis et al.,[23,24] Sun/Lin/Xu et al.,[25,26] Mascarenas/Lopez et al.[27]), intramolecular cross-coupling (Cook et al.[28]), Michael-addition/radical cyclization (Chain et al.[29]), ring contraction (Maier et al.[30]) and Nazarov cyclization (Iwabuchi et al.[31]).

We herein report the total syntheses of (−)-englerins A/B, (+)-orientalols E/F and (−)-oxyphyllol via a formal IMCC (intramolecular cross cycloaddition) strategy of cyclopropanes. This formal IMCC strategy, which we have recently developed on the basis of intermolecular formal cycloadditions of donor−acceptor cyclopropanes,[32] can provide a general and highly efficient construction of bridged skletons.[33−44]

(−)-Englerin A was selected as an example for the retrosynthetic analysis (Scheme 1). Our retrosynthesis of (−)-englerin A started from the cleavage of the two ester groups to diol **6**. Diol **6** could be prepared either from compound **7** or **11**. Compound **7** or **11** can be obtained via the key formal [3 + 2]-IMCC of **8** or **12** respectively. Compound **8** or **12** can be prepared from the same intermediate **9** through northern cyclopropanation of carbon−carbon double bond *a* or southern cyclopropanation of carbon−carbon double bond *b* respectively. Trienol **9** can be prepared from a known compound **10**, which has been obtained from commercially available (*R*)-(+)-limonene in two steps.[45]

Our initial attempts to the northern cyclopropanation of carbon−carbon double bond *a* failed and no cyclopropanations

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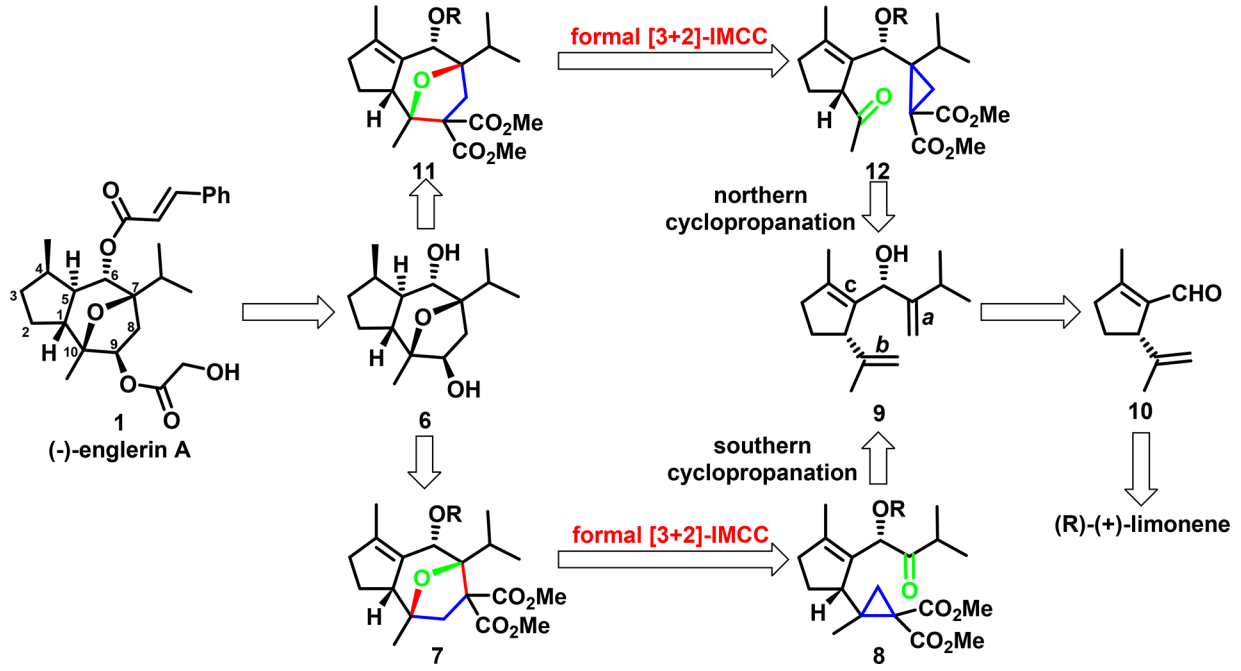
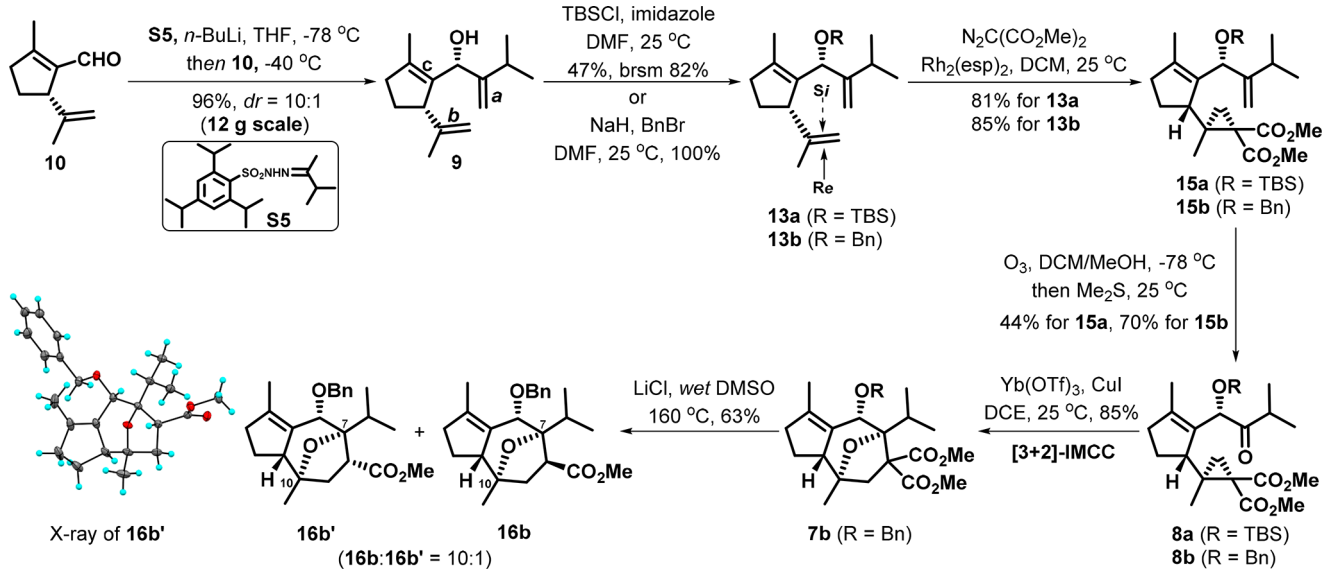
Scheme 1. Retrosynthetic Analysis of (−)-Englerin A



Scheme 2. Intermolecular Cyclopropanation of Double Bond *b*



were observed (see Supporting Information SI). However, we successfully carried out the southern cyclopropanation of carbon−carbon double bond *b* via both intermolecular and intramolecular pathways.

Aldehyde **10** was converted into alcohol **9** by a Shapiro reaction[46] in 96% yield (*dr* = 10:1). Protection of the hydroxyl group in **9** afforded **13a** or **13b** (Scheme 2). The southern intermolecular cyclopropanation of **13a** or **13b** afforded **15a** or **15b** respectively. The steric hindrance probably played a key role for the chemoselective cyclopropanation. A single-crystal X-ray analysis of **15a** confirmed the absolute stereochemistry of the quaternary carbon in cyclopropane as R configuration (see SI). This result implies that the Rh-carbene attacked the *Re* face of the double bond *b*. After ozonolysis of double bond *a*, $Yb(OTf)_3$/CuI-catalyzed formal [3 + 2]-IMCC of the obtained **8b** was successfully carried out to afford cycloadduct **7b** (85%), while **8a** gave a complex result. Krapcho decarboxylation of **7b** afforded **16b**/**16b′** (**16b**:**16b′** = 10:1), a single crystal X-ray analysis of the minor diastereoisomer **16b′** showed that the stereochemistries of C7 and C10 were opposite from those of the natural products. This result implies an S_N2-like mechanism of the formal [3 + 2]-IMCC, which is in accordance with our previously reported results.[33]

As the intrinsic stereoselectivity of the southern intermolecular cyclopropanation preferred the *Re* face, we considerd an intramolecular cyclopropanation strategy as a rational one to match the desired stereochemistry (Scheme 3). In this strategy, benefiting from its suitable stereochemistry, the hydroxyl group could be considered as a stereochemistry-directing group. Thus, we planned to connect the Rh-carbene moiety to the hydroxyl group. After a three-step isolation-free sequence composed of a Mukaiyama esterification,[47] a Regitz diazotization[48] and a

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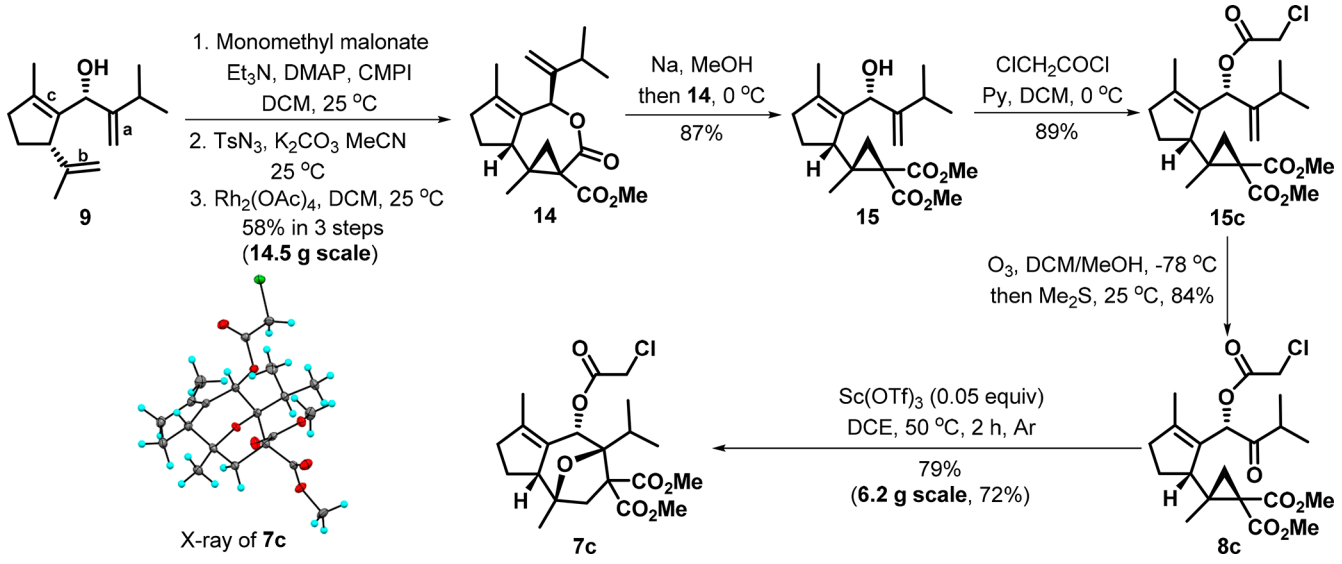
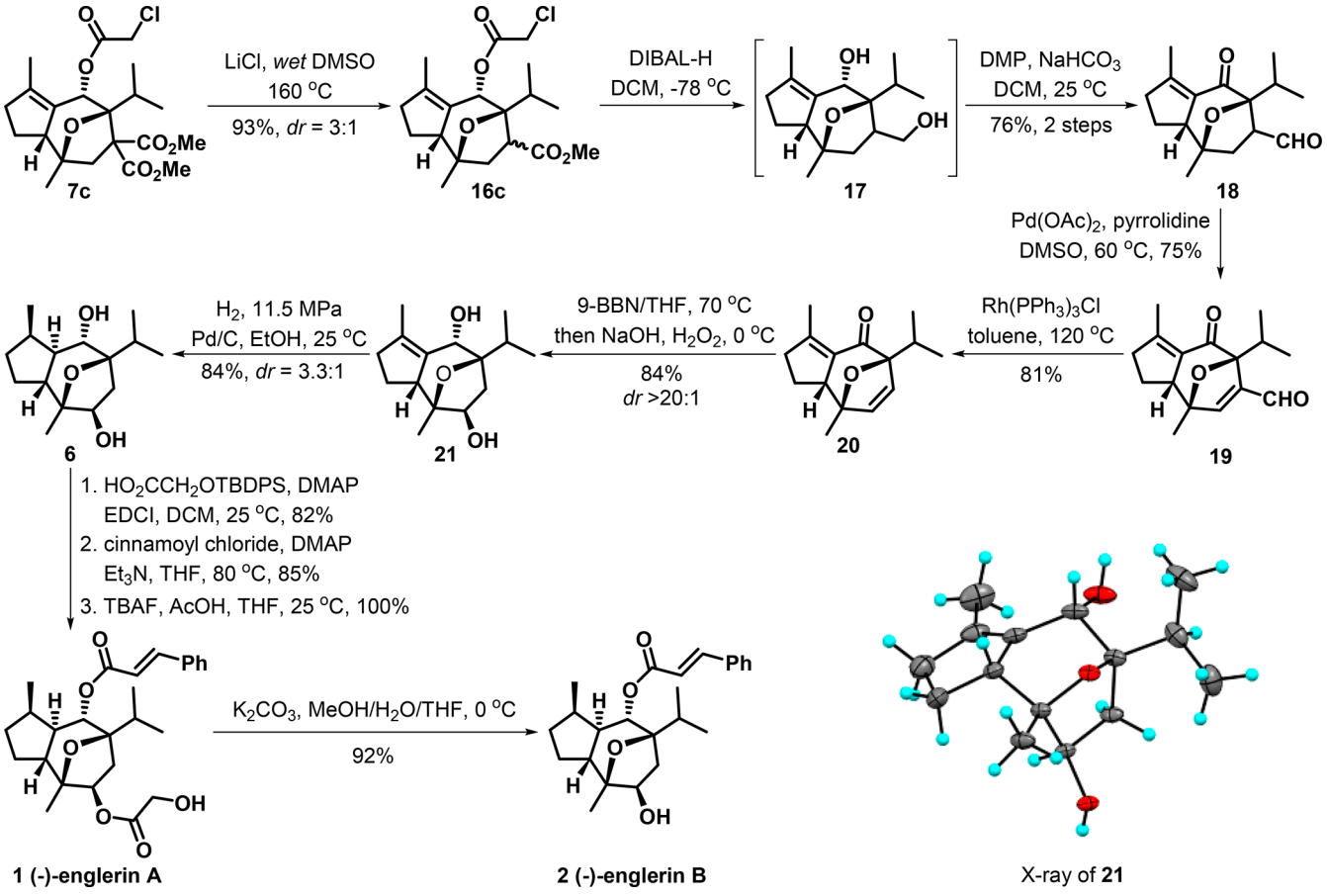
Scheme 3. Intramolecular Cyclopropanation of Double Bond *b* and Formal [3 + 2]-IMCC



Scheme 4. Completion of the Total Syntheses of (−)-Englerins A and B



chemoselective intramolecular cyclopropanation of double bond *b*, **9** was successfully converted to lactone **14** in 58% overall yield. Treatment of lactone **14** with sodium methoxide led to transesterification product **15** in 87% yield. We have tried several protecting groups for protection of the hydroxyl group in compound 15. However, in most of the subsquent [3 + 2]-IMCC, instead of the desired [3 + 2] cycloadducts, the deprotected product was recovered. To our delight, a chloroacetyl group was proven to be a successful one. After several attempts, chloroacetyl chloride was selected for the protection of hydroxyl group. Subsequent ozonolysis of the double bond *a*, the formal [3 + 2]-IMCC precursor **8c** was obtained in 75% yield over two steps. The Lewis acid-catalyzed formal [3 + 2]-IMCC of **8c** proceeded smoothly in most cases (see SI). Under the catalysis of 0.05 equiv of $Sc(OTf)_3$, with DCE as a solvent at 50 °C, the cycloadduct **7c** was obtained in

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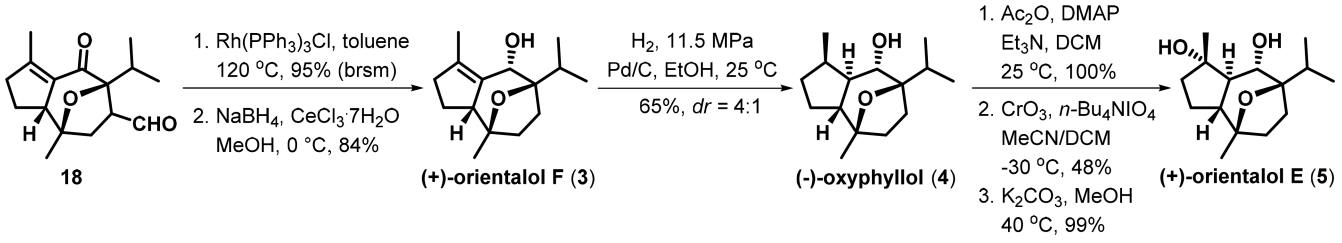
Scheme 5. Completion of Total Syntheses of (+)-Orientalols E/F and (−)-Oxyphyllol



79% yield. This reaction was run on a 6.2 g (14.4 mmol) scale in 72% yield. To our great delight, a single-crystal X-ray analysis of **7c** unambiguously confirmed its absolute configuration, which is in accordance with that of the natural products.

With **7c** in hand, we then started to carry out the subsequent decorations (Scheme 4). Krapcho decarboxylation of **7c** afforded monoester **16c** in 93% yield and with a 3:1 *dr*. Following the reduction of the two ester groups in **16c** with DIBAL-H, diol **17** was obtained as a single diastereoisomer. Without purification, aldehyde **18** was obtained (76%, 2 steps) under the global oxidation of **17** with Dess−Martin periodinane. An enamine Saegusa oxidation[49] was adopted to give α,β-unsaturated aldehyde **19** (75%), and a Tsuji−Wilkinson decarbonylation of which afforded **20** (81%). The intermediate **20** was the enantiomer of the intermediate in total synthesis of *ent*-englerin A by Sun/Lin et al.[25] Hydroboration−oxidation of **20** gave the diol **21** in 84% yield and with *dr* > 20:1. The absolute configuration of **21** was determined by X-ray crystallographic analysis.[50] After a dozen of failed attempts (e.g., Raney Ni[19,22] and Ir^{I}-based catalyst[20,25]), the hydroxyl-directing Pd/C-hydrogenation[21] of **21** was finally accomplished, and **6** was obtained in 84% yield and with 3.3:1 *dr*. After the double esterifications and desilylation, we finally achieved (−)-englerin A (**1**) in 70% yield (3 steps). Under a mild saponification condition, (−)-englerin B (**2**) was obtained in 92% yield.

From the intermediate **18**, we also synthesized (+)-orientalol F (**3**), (−)-oxyphyllol (**4**) and (+)-orientalol E (**5**) (Scheme 5). After a Tsuji-Wilkinson decarbonylation and Luche reduction, (+)-orientalol F (**3**) was obtained in 80% yield over two steps. Pd/C-hydrogenation of **3** afforded (−)-oxyphyllol (**4**) (65% yield, *dr* 4:1). Using a protocol similar to that reported by Sun/Lin et al.,[25] we obtained (+)-orientalol E (**5**) (48% over 3 steps). All the data of the synthesized products were in accordance with those reported in the literature.

In conclusion, we achieved the total syntheses of (−)-englerin A, (−)-englerin B, (+)-orientalol F and (−)-oxyphyllol, as well as the first total synthesis of (+)-orientalol E, from the commercially available and inexpensive (*R*)-(+)-linonene. The key steps include the hydroxyl-directing stereoselective and regioselective intramolecular cyclopropanation, and the multi-gram-scale stereoselective formal [3 + 2]-IMCC of a cyclopropane 1,1-diester with a carbonyl for construction of a core oxa-[3.2.1]octane bicyclic skeleton. A precursor of 7,10-diastereoisomer of englerins was also obtained. Additionally, benefiting from the broad structural diversities being provided by the IMCC, we strongly believe that this synthetic strategy will also show its potential applications to drug discovery in the future. Further research includes construction of structurally diverse libraries via this synthetic strategy and study of their biological activities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00552.

Detailed experimental procedures and characterization data (PDF)

Accession Codes

CCDC 1485699, 1564694, 1812332, and 1812334 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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(50) CCDC 1485699 (**7c**), 1812332 (**15a**), 1812334 (**16b′**) and 1564694 (**21**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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