Natural Products

Deutsche Ausgabe: DOI: 10.1002/ange.201602235
Internationale Ausgabe: DOI: 10.1002/anie.201602235

Short, Enantioselective Total Synthesis of Highly Oxidized Taxanes

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Dedicated to Professor K. C. Nicolaou on the occasion of his 70th birthday

Abstract: *In the realm of natural product chemistry, few isolates have risen to the level of fame justifiably accorded to Taxol (**1**) and its chemical siblings. This report describes the most concise route to date for accessing the highly oxidized members of this family. As representative members of taxanes containing five oxygen atoms, decinnamoyltaxinine E (**2**) and taxabaccatin III (**3**), have succumbed to enantioselective total synthesis for the first time in only 18 steps from a simple olefin starting material. The strategy holistically mimics nature's approach (two-phase synthesis) and features a carefully choreographed sequence of stereoselective oxidations and a remarkable redox-isomerization to set the key trans-diol present in **2** and **3**. This work lays the critical groundwork necessary to access even higher oxidized taxanes such as **1** in a more practical fashion, thus empowering a medicinal chemistry campaign that is not wedded to semi-synthesis.*

The spectacular clinical success of taxanes combined with their stunning complexity has motivated and inspired scores of chemists over the past several decades.[1–3] Indeed, Taxol (**1**, Figure 1) can be treated as a barometer to measure progress and advances in the science of chemical synthesis. This iconic natural product has been prepared on ten separate occasions (seven total syntheses[4–12] and three formal syntheses[13–16]), thus elegantly demonstrating the feasibility of its reconstitution by purely chemical means. Notwithstanding the beauty of these landmark accomplishments, they are eight to nine orders of magnitude less efficient than biological production. To be sure, mere milligrams were produced all together by total synthesis, whereas metric tons of Taxol are accessed every year through a plant cell culture process developed by Bristol-Myers Squibb and Phyton Biotech, Inc. This gap in efficiency is therefore an exciting opportunity for invention and exploration in chemical synthesis.[17] As a first step for addressing this profound challenge, a strategy for emulating the two-phase biosynthesis[18] of terpenes in the laboratory was delineated and demonstrated in the context of simple eudesmane terpenes.[19] Since then, this strategy has enabled simplified approaches to representative members of the germacrene,[20,21] steroid,[22–24] and ingenane terpene families.[25] The two-phase approach to ingenanes has been particularly significant from an industrial standpoint as it enabled the scalable preparation of not only the parent natural product but also analogues, with improved biological profiles, which are unavailable through semi-synthesis or synthetic biology approaches.[26]

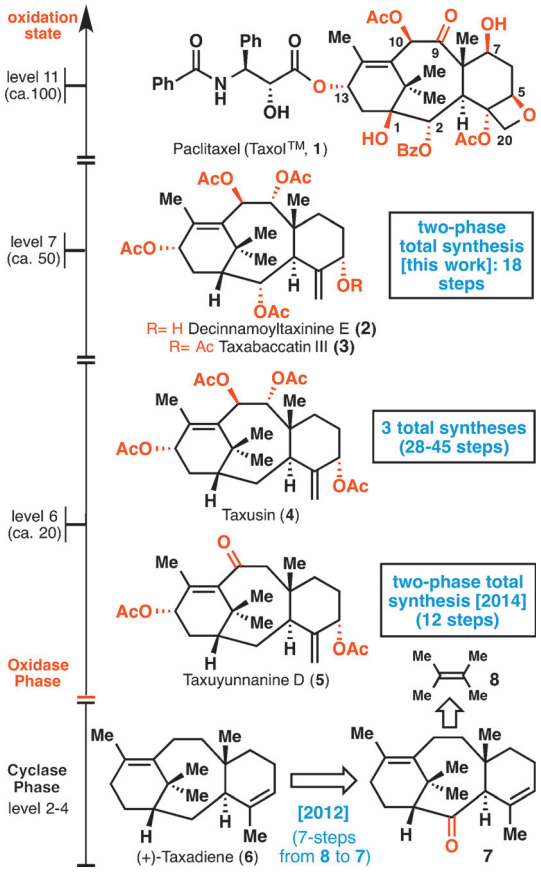

Figure 1. Taxol (**1**) and taxane family members ordered in sequential oxidation levels. Bz = benzoyl.

Two-phase terpene synthesis[27] is critically reliant on two strategic choices: 1) the selection of an oxidized hydrocarbon bearing the minimum oxidation pattern required to effectively build the carbon skeleton of a terpene family (cyclase phase) and 2) a plan which maximizes divergent access to a broad array of oxidized natural products in the family by the deliberate use of C–H functionalization logic (oxidase phase). In the case of the taxanes, of which hundreds are known,[28] this approach simplifies the retrosynthetic blueprint as family members can be simply abbreviated as mathematical sets

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Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201602235.

rather than discreet targets. As illustrated in Figure 1, Taxol can be viewed as a "level 11" taxane because of the presence of nine oxidized carbon atoms and two degrees of unsaturation; over 100 natural products at this oxidation state have been isolated. Similarly, decinnamoyltaxinine E (**2**),[29] taxabaccatin III (**3**),[30] taxusin (**4**),[31–36] taxuyunnanine D (**5**),[37,38] and taxadiene (**6**)[39–41] can be viewed as level 2–7 taxanes and represent over 100 additional natural products. In this report, the first enantioselective total syntheses of **2** and **3** are presented. As the most advanced embodiment of two-phase chemical synthesis to date, this route builds highly complex taxanes containing five oxidized carbon atoms and two degrees of unsaturation in only 18 steps from a simple olefin feedstock (tetramethylethylene; **8**).

The chemical cyclase phase of taxane synthesis was reported in 2010 and featured a highly efficient, triply convergent, enantioselective, and scalable approach which was amenable to outsourcing.[42] Ready access to the taxane skeleton enabled the first simple access to synthetic taxadiene (**6**)[41] from taxadienone (**7**). Whereas the former is nature's cyclase phase endpoint, the latter served as our laboratory's departure point for highly oxidized members of the family.[38,41] Notably, synthetic **6** has since been dispersed to multiple laboratories for use in their independent studies. Of the eight oxygen atoms adorning the Taxol skeleton, three of them are derived from oxidation of weak allylic C–H bonds (C5, C10, C13). Thus, initial efforts focused on deciphering the exact reagent choice and oxidation choreography needed for their installation. This effort resulted in the first total synthesis of a level 6 taxane, taxuyunnanine D (**5**)[38] in 2014 in only five steps from **7** (12 steps from **8**). Level 7 taxanes were targeted next, such as **2** and **3**, neither of which have been prepared before. To put this challenge in the proper context, it is worth briefly reviewing the elegant total syntheses of the related level 6 taxane, taxusin (**4**). This simpler natural product has been the subject of numerous studies culminating in three total syntheses from the groups of Holton (49 steps, chiral pool),[32] Paquette (40 steps, chiral pool),[35,36] and Kuwajima (27 steps, racemic; 28 steps, enantioselective).[33,34] These target-oriented approaches demonstrated the feasibility of chemically accessing a single taxane, but they would not be viable blueprints for a medicinal chemistry program which minimizes steps and maximizes divergency. This might be due to reliance on a retrosynthetic strategy oriented to specific strategic bond disconnections triggered by specific oxidation patterns found in a specific target. In stark contrast, we outline below an enantioselective pathway to **2** and **3** and it represents a step-change in convenience to access highly functionalized taxanes because it targets the entire family in a unified fashion.

Commencing with **7**, Bouveault–Blanc reduction (Na, *i*PrOH) selectively afforded the alcohol **9** in 63% yield (gram-scale; Figure 2). Based on prior studies,[38] it was expected that palladium-catalyzed allylic oxidation would take place smoothly to install the C5 oxygenation. Instead, the C2 alcohol interfered and produced a cyclic ether (**SI-10**; see the Supporting Information for details) which could not be utilized further in the synthesis. A simple workaround approach was pursued by Sharpless vanadium-catalyzed epoxidation to deliver **10**, with immediate exposure to hydroxide, thus affording the crystalline triol **11** in 67% yield (gram-scale, structure confirmed by X-ray crystallography)[51]. Acetylation of the secondary alcohols (Ac_2O, 89%, gram-scale) set the stage of **12** for chromium(V)-mediated installation of the C13 oxygenation. This C–H oxidation, invented specifically for this oxidation but finding utility in related contexts,[26] could be used to robustly access the enone **14** (50% yield, gram-scale) along with **13**[51] (29%, structure verified by X-ray crystallography). As with the synthesis of **14**, this reagent[43] proved essential and was unique in its ability to enable access to C13 oxidized taxane intermediates.

Installation of the C10 oxidation relied on a radical-based C–H functionalization as described previously.[38] Thus, exposure of **14** to NBS in the presence of benzoyl peroxide furnished an allylic bromide which could be smoothly converted into the silyl ether **15** by solvolysis with AgOTf and TMSOH (79% yield, one-pot). The free tertiary alcohol (**15**), which served as a bystander to two C–H oxidations, could now be eliminated using the Burgess reagent and the crude olefin was subjected to a strategic reduction using DIBALH to set the proper stereochemistry of **16** at C13 (81% yield, one pot). In preparation for installation of the challenging C9 oxygen atom, the triol was protected as the tri-MOM ether and the allylic silyl ether was selectively oxidized directly using IBX (85% yield, one-pot) to afford **17**. The net conversion of enone **17** into the *trans*-diol **22** proved to be an incredibly challenging undertaking with a surprisingly simple solution. First, subjection of **17** to Et_2NLi followed by the Vedejs reagent (MoOPh)[44] delivered the α-hydroxy enone **18**, which was directly exposed to $Cu(OAc)_2$[45] to form the dione **19** in 77% yield (along with 12% recovered enone **17**). The unusual aluminum-based reducing agent LiAlH(O*t*Bu)*s*Bu_2[46] (2.5 equiv) was then employed to stereo- and siteselectively produce **20**. Over a short period of time in CH_2Cl_2 this compound fortuitously isomerized into the α-hydroxy ketone **21**, a species which could be isolated and crystallized (structure verified by X-ray crystallography).[51] In the optimized route **21** was carried forward in the same flask and exposed to sodium amalgam[47] at room temperature to produce the coveted *trans*-diol **22** in 72% yield from **19**. It is worth reflecting on the fact that this taxane **22**, bearing an additional layer of complexity (C2 oxidation) relative to **4**, could be procured in only 16 steps from **8**. With all of the proper stereochemistry and oxygenation in place all that remained was to remove the sturdy MOM ethers and replace them with acetates. To this end, acetylation of the 9,10-diol using Ac_2O (85% yield) delivered **23**. Mild MOM ether removal using CBr_4[48] produced the triol **24** which could be acetylated to produce (+)-**2** (71% yield, +23°, $CHCl_3$, $c = 0.15$). (+)-Decinnamoyltaxinine E [(+)-**2**] can be further acetylated in the presence of $Cu(OTf)_2$ and Ac_2O[49] to afford (+)-**3** (87% yield, +14°, $CDCl_3$, $c = 0.14$) thus completing the first synthesis of these complex, level 7 taxanes.

It is instructive to reflect on some of the challenges encountered in this total synthesis. The very first step, reduction of **7** to **9**, was strategically timed as the stereochemistry was difficult to set at any other stage stereoselec-

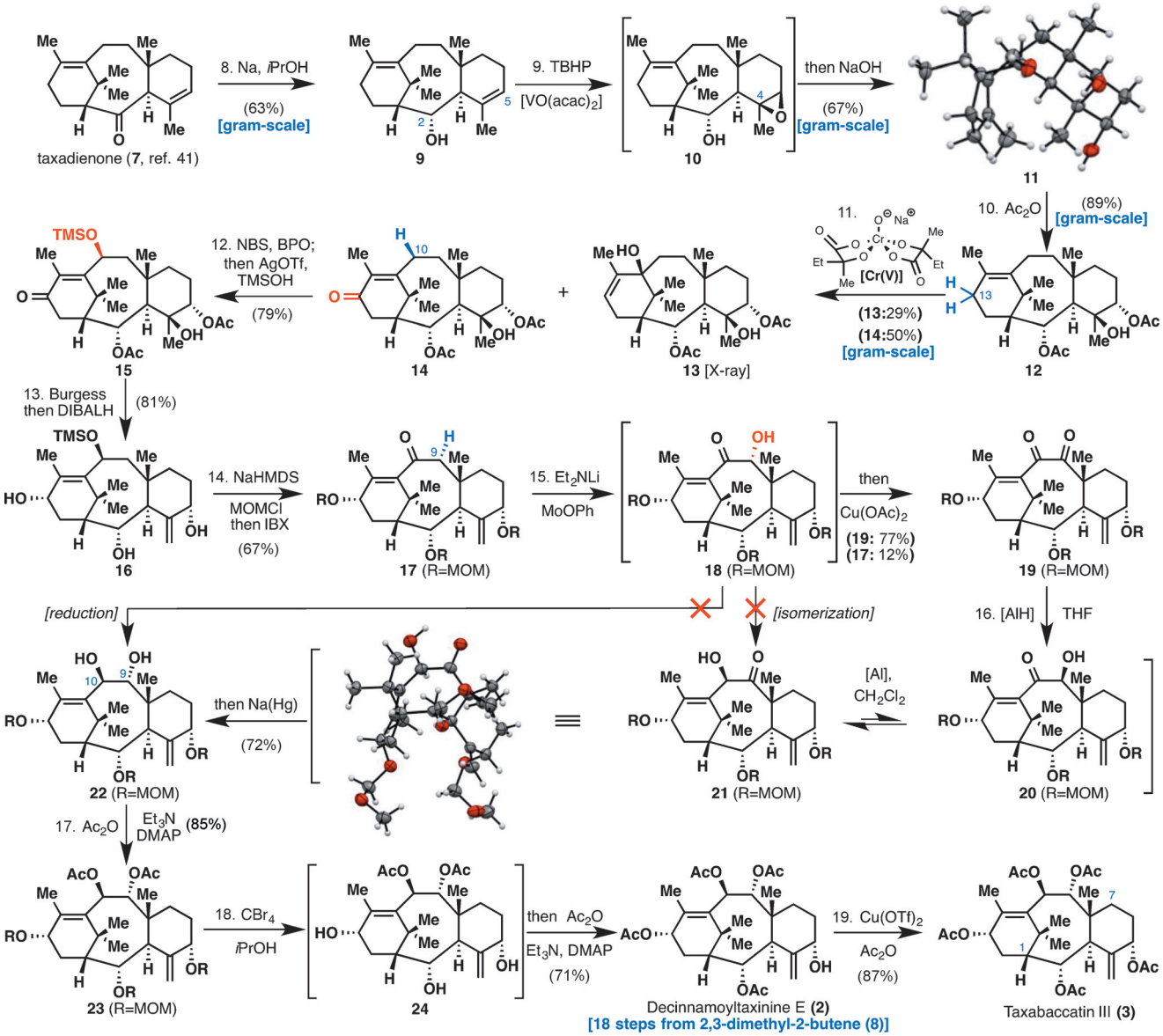

Figure 2. Reaction conditions: 8. Na (5×7 equiv, each portion added every 30 min), *i*PrOH, 80 °C, 3 h, 63 % (11 % *epi*-**9**, see the Supporting Information); 9. $VO(acac)_2$ (0.05 equiv), TBHP (1.1 equiv), DCE, 0→23 °C, 2 h; then aq. NaOH (3 M, 8.3 equiv), DMSO, 140 °C (sealed tube), 4 h, 67 %; 10. Ac_2O (6 equiv), Et_3N (8 equiv), DMAP (0.2 equiv), THF, 60 °C, 10 h, 89 %; 11. Cr^V (4 equiv), 15-crown-5 (5 equiv), MnO_2 (20 equiv), *t*BuOMe, 90 °C (sealed tube), 36 h, **14** 50 %, **13** 29 %; 12. NBS (1.05 equiv), BPO (0.2 equiv), CCl_4, 80 °C, 15 min; then TMSOH (excess), 2,6-*tert*-butylpyridine (5 equiv), AgOTf (5 equiv), toluene, 23 °C, 1.5 h, 79 %; 13. Burgess reagent (2 equiv), toluene, 80 °C, 1 h; then DIBALH (15 equiv), toluene, −78→23 °C, 15 min, 81 %; 14. KHMDS (12 equiv), MOMCl (12 equiv), THF, −78→23 °C, 30 min; then IBX (26 equiv), DMSO, 80 °C, 20 h, 67 %; 15. Et_2NLi (2 equiv), MoOPh (4 equiv), THF, 23→−20→23 °C, 20 min; then $Cu(OAc)_2$ (40 equiv), MeOH, 23 °C, 5 h, **19** 77 %, **17** 12 %; 16. $LiAlH(OtBu)sBu_2$ (2.5 equiv), THF, 23 °C, 1 min; then H_2O (66 equiv), evaporated to dryness and CH_2Cl_2, 23 °C, 8 h; Na (Hg) (2.2 equiv), MeOH, 23 °C, 30 min, 72 %; 17. Ac_2O (10 equiv), Et_3N (10 equiv), DMAP (1 equiv), THF, 60 °C, 9 h, 85 %; 18. CBr_4 (50 equiv), *i*PrOH, 82 °C, 8 min; then Ac_2O (360 equiv), Et_3N (96 equiv), DMAP (100 equiv), 23 °C, 30 min. acac = acetylacetonate, BPO = benzoyl peroxide, DCE = 1,2-dichloroethane, DIBALH = diisobutylaluminum hydride, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, DMSO = dimethylsulfoxide, HMDS = hexamethyldisilazide, IBX = *o*-iodoxybenzoic acid, MOM = methoxymethyl, NBS = *N*-bromosuccinimide, TBHP = *tert*-butylhydroperoxide, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, TMS = trimethylsilyl.

tively (see the Supporting Information for details). As mentioned above, C5 oxidation necessitated the use of a diol as a redox-mask for an allylic alcohol. Next, C–H oxidation at C13 using our chromium(V)-based reagent was successful only on a handful of substrates. For example, the MOM-protected version of **12** failed to deliver more than 5 % oxidized product. For a complete summary of the substrates evaluated to identify the correct choreography for this C–H oxidation, see the Supporting Information.

Puzzlingly, and in contrast to studies on the C2 deoxy series,[38] if the tertiary alcohol at C4 was dehydrated, the resulting allylic acetate could not be oxidized at either C13

(using Cr) or C10 (radical based systems). The choice of MOM ethers (**17**) for shielding the C2, C5, and C13 alcohols was based solely on the stability of downstream intermediates and execution of the key C9 oxidation (Bz, silyl, and unprotected variants all failed). Oxygenation of the enolate derived from **17** proved quite challenging (MoOPh is the only oxidant that succeeded) and required the use of a nonhindered base (Et_2NLi) and precise control of temperature (for the >40 different reaction conditions attempted see the Supporting Information). As illustrated in the Supporting Information, direct reduction of **18** to the *trans*-diol **22** was unworkable after trying over 60 different reduction conditions. Isomerization of **18** into **21** was also fruitless despite literature precedent for such transformations on related systems using KO*t*Bu.[6,7,13] Oxidation to **19** followed by controlled reduction to **20** led directly to **21** after isomerization. The choice of reducing agent [LiAlH(O*t*Bu)*s*Bu_2] was critical as reagents such as DIBALH led to over-reduction and $NaBH_4$ did not react. The residual aluminum salts present after addition of water accelerated the isomerization of **20** into **21** (as monitored by NMR spectroscopy, see the Supporting Information for illustration).

Dozens of reducing agents screened for both **20** and **21** delivered either only the undesired *cis*-diol or led to decomposition. The pivotal reduction of **21** to *trans*-diol **22** could only be achieved using sodium amalgam (see the Supporting Information for list of conditions). Finally, gentle removal of the MOM ethers required the use of CBr_4/*i*PrOH, presumably as a means to slowly release HBr, as conventional reagents (Brønsted acid, BBr_3, catechol borane bromide, TMSI) all led to undesired outcomes.

As this overarching strategy brings us closer to **1** it is worth reflecting on the inherent wisdom of selecting **7** (level 4 taxane) as a synthetic cyclase phase end point. Since introduction of the C9,C10 alcohols proved so challenging, a revised cyclase phase endpoint harboring an additional point of unsaturation was also explored. Thus, as depicted in Figure 3, the unsaturated dione **25** was targeted and constructed in only six steps from **8** (see the Supporting Information for preparation). The structure and the extremely hindered nature of the C9,C10 olefin was verified by X-ray crystallography.[51] Despite several hundred experiments on **25** and derivatives thereof we were unable to oxidize this olefin in either the presence or absence of oxygen at either C2, C13, or C5 (**26**). While frustrating, this spectacular failure bolsters the original design of **7** as the ideal synthetic cyclase phase endpoint.

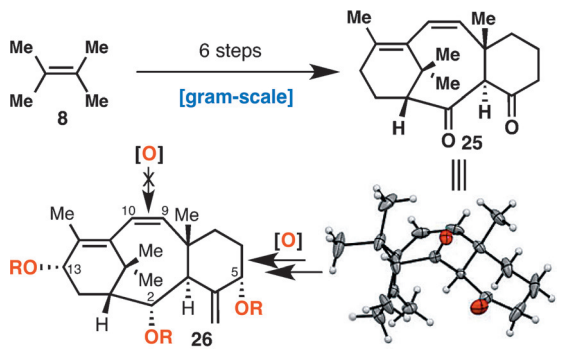

Figure 3. Exploration of an alternative cyclase phase endpoint for taxane synthesis.

With the completion of short total syntheses of two representative level 7 taxanes a light can be seen at the end of the tunnel: a scalable total synthesis of **1**. While much remains to be learned and more challenges await prior to its eventual completion, it is tempting to speculate how it will take place. It is clear that two unactivated C–H bonds remain to be functionalized: C1 and C7. Although precedent exists for the oxidation of C1 using an electrophilic dioxirane,[50] the latter C–H bond is a significant hurdle to overcome. Meanwhile, the two-phase strategy for the preparation of complex terpenes has enabled access to taxanes never before accessible through synthesis. Since most of the members of this family differ only by the identity and location of ester side chains this route will permit access to dozens of natural and unnatural cogeners. This synthesis represents a short step-count relative to the myriad of previous studies, and will thus hopefully contribute to the budding mindset that even the most complex natural products can be the subject of modern medicinal chemistry efforts via total synthesis.

Acknowledgements

We are grateful to Dr. Yoshihiro Ishihara and Dr. Minetaka Isomura for helpful discussions and Lily Maloney for experimental assistance. We thank Dr. D.-H. Huang and Dr. L. Pasternack for NMR spectroscopic assistance, and Professor A. Rheingold (UCSD) for X-ray crystallographic analysis. Financial support for this work was provided by the NIH/NIGMS (GM-097444), Bristol-Myers Squibb (unrestricted research support) and Bestsyn Technologies (postdoctoral fellowship to Y.J.).

Keywords: natural products · oxidations · terpenes · total synthesis · X-ray diffraction

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 8280–8284
Angew. Chem. **2016**, *128*, 8420–8424

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[51] CCDC 1435374 (**11**), 1435375 (**13**), 1435471 (**21**), and 1435376 (**25**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Received: March 3, 2016
Published online: May 30, 2016

