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# Facile Synthesis of Tetrahydro-1*H*-isoindolones via a Sequential Three-Component Copper-Catalyzed Coupling/ Propargyl-Allenyl Isomerization/[4 + 2] Cyclization Reaction

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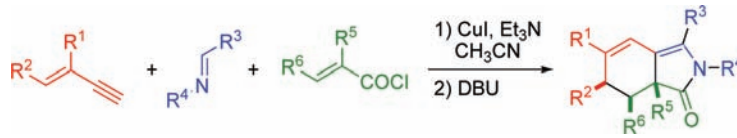
## ABSTRACT




**An interesting sequential three-component copper-catalyzed coupling/propargyl-allenyl isomerization/[4 + 2] cyclization reaction, providing a facile synthesis of highly substituted tetrahydro-1*H*-isoindolones from conjugated vinylic alkynes, imines, and α,β-unsaturated enoic acid chlorides is reported. The most attractive feature of this transformation is that three stereogenic centers could be generated in one step with high diastereoselectivity.**

Multicomponent reactions (MCRs) have attracted considerable attention due to the fact that complex molecules can be easily prepared from simple compounds in one reaction sequence.[1] Allenes show unique reactivity in organic synthesis[2] and many studies have been performed on their preparation and reactivity.[3] [4 + 2] cycloaddition of ene/yne-allenes provides a convenient route for the construction of complex ring systems.[4] Müller et al. pioneered the Sonogashira coupling/propargyl-allenyl isomerization reactions for the synthesis of a variety of useful compounds including chalcones, pyrazolines, pyrroles, fluorescent spirocycles, and some other pharmaceutically interesting het-

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[§] Prof. Huang passed away on March 6, 2010. He had been fully in charge of this project. At this moment, Prof. Luling Wu is finishing all the projects with the help from Prof. Shengming Ma.

(1) (a) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (b) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302. (c) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467. (d) Ikeda, S. I. *Acc. Chem. Res.* **2000**, *33*, 511. (e) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (f) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103.

(2) (a) Patai, S. *The Chemistry of Ketenes, Allenes, and Related Compounds*; John Wiley & Sons: New York, 1980. (b) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; John Wiley & Sons: New York, 1984. (c) Landor, S. R. *The Chemistry of Allenes*; Academic Press: New York, 1982; Vols. 1−3. (d) Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry*; Wiley-VCH: Weinheim, Germany, 2004; Vols. 1−2.

(3) (a) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (b) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701. (c) Ma, S. *Acc. Chem. Res.* **2009**, *42*, 1679. (d) Ma, S. *Eur. J. Org. Chem.* **2004**, 1175. (e) Ma, S. *Aldrichimica Acta* **2007**, *40*, 91. (f) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31. (g) Yamamoto, Y.; Radhakrishnan, U. *Chem. Soc. Rev.* **1999**, *28*, 199. (h) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067. (i) Marshall, J. *Chem. Rev.* **2000**, *100*, 3163.

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erocycles.[5] Previously, we also established a series of sequential reactions wherein an allene intermediate, generated in situ, would undergo [4 + 2] cycloaddition reaction under mild conditions, providing an efficient synthesis of structurally complex polycycles with 2,3-dihydrofuran units,[6] structurally diverse fused dihydroisobenzofuran derivatives,[7] and polysubstituted pyridines and isoquinolines.[8]

The hydroisoindolone core is present in both synthetic and naturally occurring compounds that exert a wide range of pharmacological activities.[9] For example, naturally occurring fungal metabolites such as cytotoxic cytochalasin B[10] and recently discovered anti-HIV cytochalasin L-696,474[11] both contain the hydroisoindolone skeleton (Figure 1).

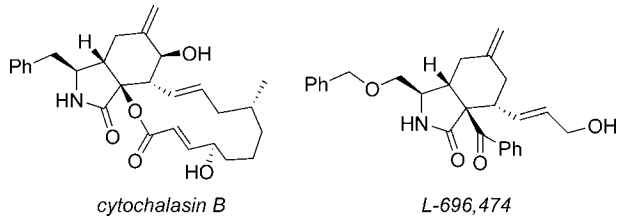
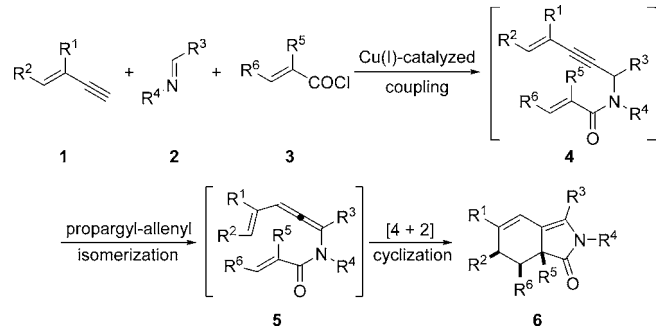



**Figure 1.** Several hydroisoindolone derivatives reported as biologically active compounds and pharmaceutical products.

While numerous methods have been reported for the synthesis of isoindolone derivatives, they are generally limited with respect to stereoselectivity and the types and locations of substituents. In our continuous efforts to design sequential reactions via allene intermediates,[12] we report here a sequential three-component copper-catalyzed coupling/propargyl-allenyl isomerization/[4 + 2] cyclization reaction: the intermediate *N*-(alk-4-en-2-ynyl)alk-2-enamides **4** which would be generated from copper-catalyzed coupling of vinylalkynes **1**, imines **2**, and α,β-unsaturated enoic acid chlorides **3**,[13] may undergo subsequent propargyl-allenyl isomerization reaction in the presence of a base leading to the vinylallenes **5**. An intramolecular [4 + 2] cycloaddition may then proceed to furnish the highly substituted tetrahydro-1*H*-isoindolones **6** (Scheme 1). Thus, by our strategy, three

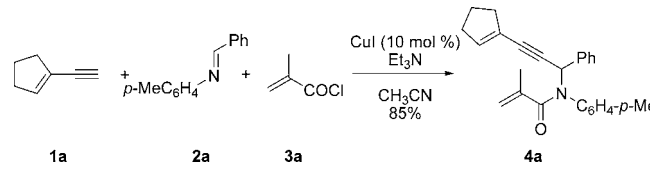
**Scheme 1**




new carbon−carbon bonds and one carbon−nitrogen bond could be formed in a single stroke with the efficient assembly of two rings from readily available starting materials. Furthermore, because of the rigidity of the intermediate vinylallenes **5**, this intramolecular [4 + 2] cyclization was anticipated to lead to polycycle **6** in a highly diastereoselective manner.[14]

We initiated our study by attempting the reaction of **1a**, **2a**, and **3a** (1.2:1:1.2) (Scheme 2). After being stirred at room

**Scheme 2**




temperature for 1 h in the presence of CuI and $Et_3N$, the reaction gave *N*-(alk-4-en-2-ynyl)alk-2-enamide **4a** in 85% yield and no vinylallene or Diels−Alder product was detected.

Subsequently, different bases were tested to promote the propargyl-to-allenyl isomerization and [4 + 2] cycloaddition reaction (Table 1). Weak bases such as triethylamine or $K_2CO_3$ could not trigger the reaction, while a stronger

(4) (a) Ma, S.; Lu, P.; Lu, L.; Hou, H.; Wei, J.; He, Q.; Gu, Z.; Jiang, X.; Jin, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 5275. (b) Jiang, X.; Kong, W.; Chen, J.; Ma, S. *Org. Biomol. Chem.* **2008**, *6*, 3606. (c) Padwa, A.; Meske, M.; Murphree, S. S.; Watterson, S. H.; Ni, Z. *J. Am. Chem. Soc.* **1995**, *117*, 7071. (d) Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843. (e) Padwa, A.; Filipkowski, M. A.; Meske, M.; Watterson, S. H.; Ni, Z. *J. Am. Chem. Soc.* **1993**, *115*, 3776. (f) Kanematsu, K.; Sugimoto, N.; Kawaoka, M.; Yeo, S.; Shiro, M. *Tetrahedron Lett.* **1991**, *32*, 1351.

(5) (a) Braun, R. U.; Ansorge, M.; Müller, T. J. J. *Chem.—Eur. J.* **2006**, *12*, 9081. (b) Braun, R. U.; Zeitler, K.; Müller, T. J. J. *Org. Lett.* **2001**, *3*, 3297. (c) D'Souza, D. M.; Kiel, A.; Herten, D. P.; Müller, T. J. J. *Chem.—Eur. J.* **2008**, *14*, 529. (d) Braun, R. U.; Zeitler, K.; Müller, T. J. J. *Org. Lett.* **2000**, *2*, 4181. (e) D'Souza, D. M.; Rominger, F.; Müller, T. J. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 153. (f) D'Souza, D. M.; Rominger, F.; Müller, T. J. J. *Chem. Commun.* **2006**, 4096.

(6) Shen, R.; Huang, X. *Org. Lett.* **2008**, *10*, 3283.

(7) Shen, R.; Huang, X.; Chen, L. *Adv. Synth. Catal.* **2008**, *350*, 2865.

(8) Sha, F.; Huang, X. *Angew. Chem., Int. Ed.* **2009**, *48*, 3458.

(9) (a) Jiang, J.; Devita, R. J.; Kumar, S.; Mills, S. G.; Tschirret-Guth, R. A. Int. Patent WO 2007002457, 2007. (b) Kuethe, J. T.; Yin, J.; Huffman, M. A.; Journet, M. Int. Patent WO 2007008564, 2007. (c) Rudd, J. A.; Ngan, M. P.; Wai, M. K. *Eur. J. Pharmacol.* **1999**, *366*, 243. (d) Walling, E. A.; Drafft, G. A.; Ware, B. R. *Arch. Biochem. Biophys.* **1988**, *264*, 321.

(10) (a) Haidle, A. M.; Myers, A. G. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12048. (b) Thilly, W. G.; Liber, H. L.; Wogan, G. N. *Front. Biol.* **1978**, *46*, 53.

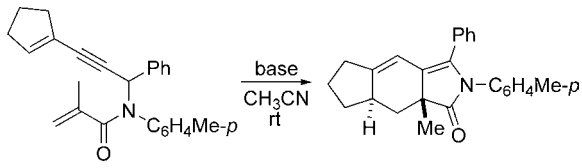
(11) Linghan, R. B.; Hsu, A.; Silverman, K. C.; Bills, G. F.; Dombrowski, A.; Goldman, M. E.; Darke, P. L.; Huang, L.; Koch, G.; Ondeyka, J. G.; Goetz, M. A. *J. Antibiot.* **1992**, *45*, 686.

(12) (a) Shen, R.; Zhu, S.; Huang, X. *J. Org. Chem.* **2009**, *74*, 4118. (b) Huang, X.; Zhu, S.; Shen, R. *Adv. Synth. Catal.* **2009**, *351*, 3118. (c) Shen, R.; Chen, L.; Huang, X. *Adv. Synth. Catal.* **2009**, *351*, 2833.

(13) Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2004**, *6*, 1107.

(14) (a) Deutsch, E. A.; Snider, B. B. *J. Org. Chem.* **1982**, *47*, 2682. (b) Deutsch, E. A.; Snider, B. B. *Tetrahedron Lett.* **1983**, *24*, 3701. (c) Keck, G. E.; Kachensky, D. F. *J. Org. Chem.* **1986**, *51*, 2487. (d) Gibbs, R. A.; Bartels, K.; Lee, R. W. K.; Okamura, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 3717. (e) Curtin, M. L.; Okamura, W. H. *J. Org. Chem.* **1990**, *55*, 5278. (f) Krause, N. *Liebigs Ann. Chem.* **1993**, 521.

**Table 1.** Base Effect on the Propargyl-Allenyl Isomerization and Diels−Alder Reaction[a]




**4a** **6a**

| entry | base | time (h) | yield of **6a** |
|---|---|---|---|
| 1 | $Et_3N$ (1.2 equiv) | 12 | NR |
| 2 | $K_2CO_3$ (1.2 equiv) | 12 | NR |
| 3 | *t*-BuOK (1.2 equiv) | 0.5 | unidentified mixture |
| 4 | *t*-BuOK (0.1 equiv) | 0.5 | unidentified mixture |
| 5 | DBU (1.2 equiv) | 0.5 | 91 |
| 6 | DBN (1.2 equiv) | 0.5 | 88 |
| 7 | DBU (0.1 equiv) | 0.5 | 93 |

[a] The reaction was carried out with **4a** (0.28 mmol) in MeCN (1 mL) at rt.

base such as *t*-BuOK gave an unidentified mixture. DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and DBN (1,5-diazabicyclo[4.3.0]non-5-ene) proved to be suitable options, however, and gave **6a** as the sole product in good yields at room temperature. Further study showed that a catalytic amount of DBU was sufficient to promote this reaction.

We then tried to combine these two steps into a one-pot reaction, without the isolation of *N*-(alk-4-en-2-ynyl)alk-2-enamide **4a**. When the copper-catalyzed coupling reaction was complete, DBU was added to the reaction mixture, and after 12 h the tetrahydro-1*H*-isoindolone **6a** was obtained in 80% overall yield. It should be noted that 3.0 equiv of DBU was required to promote the propargyl-allenyl isomerization reaction probably because of the effect of byproduct $Et_3NH^+Cl^-$ in the coupling reaction. Then we carried out the reaction using various vinylalkynes **1**, imines **2**, and α,β-unsaturated enoic acid chlorides **3**. As indicated in Table 2, the reactions proceeded smoothly to afford the corresponding tetrahydro-1*H*-isoindolones **6** in moderate to good yields. $R^1$ and $R^2$ in vinylalkynes **1** can be H, alkyl, and aryl group (Table 2, entries 1, 2, 7, and 8). Various C-aryl/heteroaryl- and N-alkyl/aryl-substituted imines were also successful (entries 1 and 3−6). Similar alkyl and aryl diversity can be incorporated with the α,β-unsaturated enoic acid chloride (entries 1, 9, and 10).

This approach is not limited to the isolated C═N bond of imines. The C═N bond in nitrogen-containing aromatic heterocycles such as quinoline and isoquinoline can also be employed in this reaction. As shown in Scheme 3, the one-pot reaction of quinoline or isoquinoline, vinylalkyne **1b**, and α,β-unsaturated enoic acid chlorides **3a** and **3c** gave

**Scheme 3**

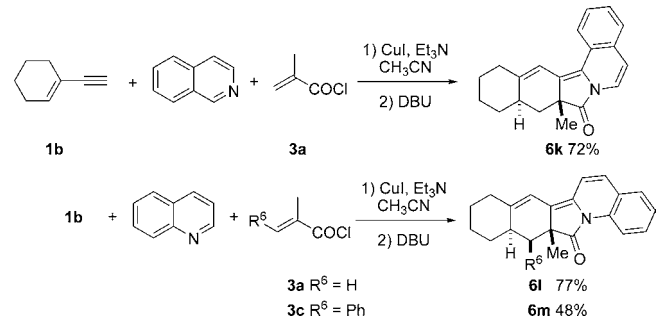
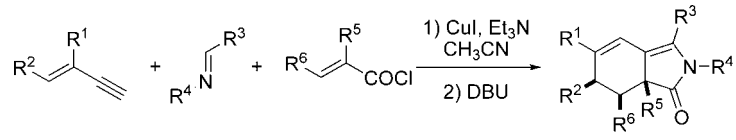



**Table 2.** Synthesis of Tetrahydro-1*H*-isoindolones **6**[a]




**1** **2** **3** **6**

| | **1** | | **2** | | **3** | | |
|---|---|---|---|---|---|---|---|
| entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ | yield of **6** (%) |
| 1 | −$(CH_2)_3$− (**1a**) | | Ph | *p*-tol (**2a**) | Me | H (**3a**) | 80 (**6a**) |
| 2 | −$(CH_2)_4$− (**1b**) | | Ph | *p*-tol (**2a**) | Me | H (**3a**) | 84 (**6b**) |
| 3 | −$(CH_2)_4$− (**1b**) | | *p*-$MeOC_6H_4$ | Bn (**2b**) | Me | H (**3a**) | 92 (**6c**) |
| 4 | −$(CH_2)_4$− (**1b**) | | *p*-tol | *p*-$MeOC_6H_4$ (**2c**) | Me | H (**3a**) | 78 (**6d**) |
| 5 | −$(CH_2)_4$− (**1b**) | | α-furyl | *n*-Pr (**2d**) | Me | H (**3a**) | 81 (**6e**) |
| 6 | −$(CH_2)_4$− (**1b**) | | *p*-$ClC_6H_4$ | allyl (**2e**) | Me | H (**3a**) | 55 (**6f**) |
| 7 | H | Ph (**1c**) | *p*-tol | *p*-$MeOC_6H_4$ (**2c**) | Me | H (**3a**) | 74 (**6g**) |
| 8 | *p*-$MeOC_6H_4$ | H (**1d**) | *p*-$MeOC_6H_4$ | Bn (**2b**) | Me | H (**3a**) | 73 (**6h**) |
| 9 | −$(CH_2)_4$− (**1b**) | | *p*-$MeOC_6H_4$ | Bn (**2b**) | Ph | H (**3b**) | 58 (**6i**) |
| 10 | −$(CH_2)_4$− (**1b**) | | *p*-$MeOC_6H_4$ | Bn (**2b**) | Me | Ph (**3c**) | 41 (**6j**) |

[a] Unless otherwise specified, the reaction was carried out with **1** (1.2 equiv), **2** (1.0 equiv), **3** (1.2 equiv), CuI (0.1 equiv), and $Et_3N$ (1.5 equiv) in MeCN at rt for 1 h and then with DBU (3.0 equiv) for 8−12 h.

fused polycycles **6k**−**m** under the same conditions as those employed with normal imines.

All products were afforded as single stereoisomers and the stereochemistry was revealed by X-ray diffraction of **6g**,[15] **6*l***,[16] and **6m**[17] (Figure 2).

In conclusion, we have realized a highly diastereoselective sequential three-component copper-catalyzed coupling/propargyl-allenyl isomerization/[4 + 2] cyclization reaction, affording bicyclic tetrahydro-1*H*-isoindolones from readily available vinylalkynes, imines, and α,β-unsaturated enoic acid chlorides efficiently. Furthermore, the C═N bond in heteroaromatic compounds such as quinoline and isoquinoline can also be employed in this sequential one-step reaction affording fused polycycles incorporating three adjacent stereocenters with excellent diastereoselectivity. Further explorations in this area are currently underway.

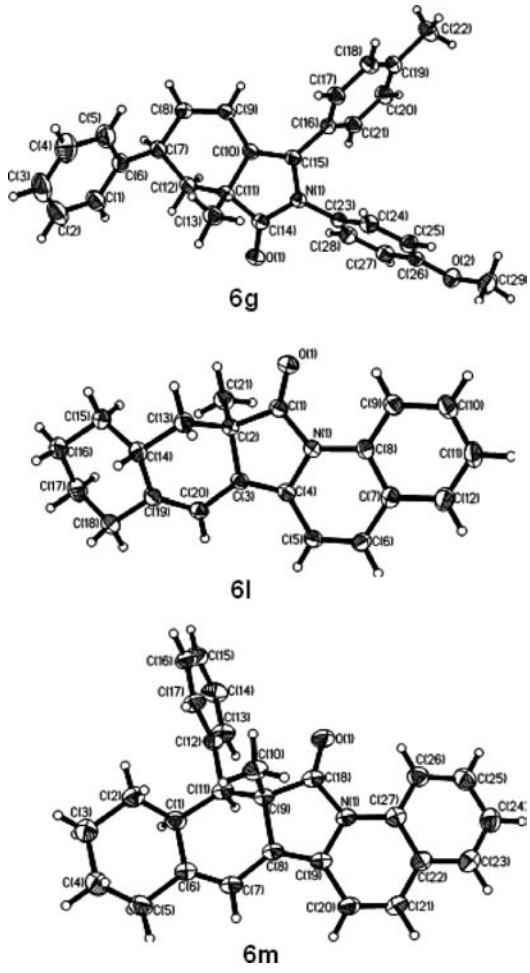



**Figure 2.** ORTEP representations of **6g**, **6*l***, and **6m**.

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**Supporting Information Available:** Spectroscopic data for **4a**, and **6a**−**m**, X-ray crystal data for **6g**, **6*l***, and **6m**, and detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Crystal data for **6g**: $C_{29}H_{27}NO_2$, MW = 421.52, triclinic, space group $P\bar{1}$, final $R$ indices [$I > 2\sigma(I)$], R1 = 0.0385, $w$R2 = 0.0954; $R$ indices (all data), R1 = 0.0587, $w$R2 = 0.0998; $a$ = 10.1023(4) Å, $b$ = 10.2563(6) Å, $c$ = 12.5612(6) Å, α = 78.656(4)°, $\beta$ = 74.978(4)°, $\gamma$ = 68.060(5)°, $V$ = 1158.71(10) Å$^3$, $T$ = 293(2) K, $Z$ = 2, reflections collected/unique 7635/4067 ($R_{int}$ = 0.0149), number of observations [$I > 2\sigma(I)$] 2749, parameters 292. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, CCDC 793327.

(16) Crystal data for **6*l***: $C_{21}H_{21}NO$, MW = 303.39, monoclinic, space group $P2(1)/n$, final $R$ indices [$I > 2\sigma(I)$], R1 = 0.0507, $w$R2 = 0.1128; $R$ indices (all data), R1 = 0.0689, $w$R2 = 0.1214; $a$ = 11.5025(12) Å, $b$ = 9.3758(10) Å, $c$ = 15.0540(16) Å, α = 90°, $\beta$ = 101.188(2)°, $\gamma$ = 90°, $V$ = 1592.6(3) Å$^3$, $T$ = 293(2) K, $Z$ = 4, reflections collected/unique 8873/3299 ($R_{int}$ = 0.0337), number of observations [$I > 2\sigma(I)$] 2405, parameters 210. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, CCDC 793326.

(17) Crystal data for **6m**: $C_{27}H_{25}NO$, MW = 379.48, triclinic, space group $P\bar{1}$, final $R$ indices [$I > 2\sigma(I)$], R1 = 0.0399, $w$R2 = 0.0835; $R$ indices (all data), R1 = 0.0943, $w$R2 = 0.0948; $a$ = 9.0955(10) Å, $b$ = 11.2163(14) Å, $c$ = 11.8083(15) Å, α = 113.640(12)°, $\beta$ = 108.357(11)°, $\gamma$ = 96.114(10)°, $V$ = 1009.2(2) Å$^3$, $T$ = 293(2) K, $Z$ = 2, reflections collected/unique 7886/3670 ($R_{int}$ = 0.0320), number of observations [$I > 2\sigma(I)$] 1893, parameters 263. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, CCDC 793328.