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# The first enantiospecific synthesis of (−)-koumidine via the intramolecular palladium-catalyzed enolate driven cross coupling reaction. The stereospecific introduction of the 19-(*Z*) ethylidene side chain

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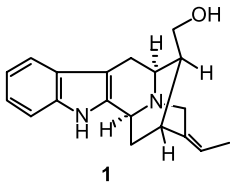
**Abstract**—The stereospecific synthesis of (−)-koumidine was realized by replacement of triphenylphosphine with tricyclohexylphosphine in the enolate driven palladium-catalyzed cross coupling process.


Many sarpagine indole alkaloids have been isolated from species of *Alstonia*,[1–3] and contain a C(19)-*E*-ethylidene function.[1–3] However, in the koumidine series this olefinic moiety (C-19) is found in the *Z* configuration, as shown in Figure 1. Koumidine (**1**) was isolated in 1982,[4] and the correct structure later reported by Cordell et al.[5] and Sakai et al.[6] Three syntheses of this indole alkaloid **1** have appeared in the past twenty years. Magnus and co-workers reported the first total synthesis of (+)-koumidine, the antipode of this natural product.[7] Sakai et al.[8–11] reported the partial synthesis of this alkaloid from ajmaline as well as from gardnerine. However, the stereospecific introduction of the *Z*-olefinic group at C(19) into the koumidine skeleton has not yet been reported. The solution to this problem forms the basis of this letter.




**1**

**Figure 1.**

Recently, an intramolecular enolate driven palladium-catalyzed cross coupling reaction has been developed.[12–15] The cyclization of the $N_b$ alkylated tetracyclic ketone **2** to provide the *E*-ethylidene function in pentacyclic ketone **3** had been realized in 80% yield, as illustrated in Scheme 1.[12,13] This process served as the key step in an efficient synthesis of (+)-vellosimine **4** ($R_1=H$, $R_2=H$), which contains the *E*-ethylidene side chain.[12,13] A number of sarpagine alkaloids and their enantiomers have been synthesized recently via this palladium-mediated process as a pivotal step. Similar coupling conditions had been employed previously in traditional Heck coupling processes;[16] however, the mechanism of this intra-molecular cross coupling process was different, and similar to that present in the α-arylation of carbonyl compounds.[17–19] The intermolecular process has been well studied over the past few years by Hartwig et al.[20,21] and Buchwald et al.[22] Following our work in the indole area,[12] another intramolecular version of this process with amino-tethered aryl halides/vinyl halides and ketones as substrates was reported by Solé et al.[23–25] In the alkaloid area, prior to our work, no reports of an effective palladium mediated enolate driven cross coupling process had appeared. This process in the alicyclic area was first reported by Piers et al. in the early 1990's.[14,15] An interesting example was recently reported by Liu and Hartwig[26] in regard to the α-arylation of azlactones. This α-vinylation reaction offered the advantage of

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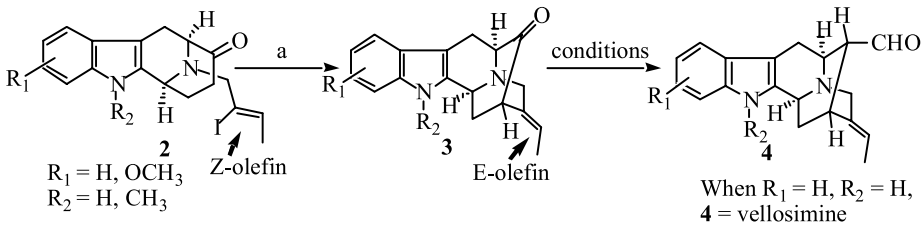
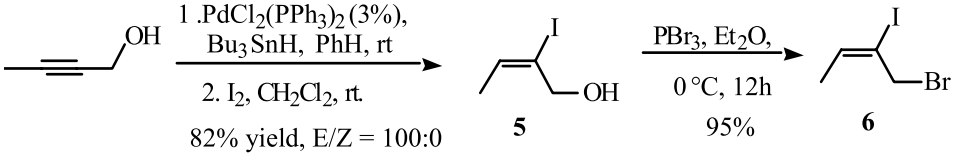



**Scheme 1.** *Reagents and conditions*: (a) $Pd(OAc)_2$, $PPh_3$, $Bu_4NBr$, $K_2CO_3$, DMF–$H_2O$ (9:1), 70°C.[12,13]




**Scheme 2.**

stereospecific introduction of the olefinic moiety into **1** and was, therefore, explored in order to extend the method to the *Z*-ethylidene side chain in the koumidine series.

Incorporation of the *Z*-ethylidene function into the koumidine skeleton required the use of *E*-1-bromo-2-iodo-2-butene **6**, which could be easily prepared by the reported procedure (Scheme 2).[27,28] The tributyltin functionalized olefin was treated with iodine in $CH_2Cl_2$ to provide the desired iodoolefin **5** in 82% overall yield.[12,13,27,28] The hydroxyl group in iodoolefin **5** was smoothly converted into the bromide moiety in **6** on stirring **5** with $PBr_3$ (95%).

D-(+)-Tryptophan methyl ester had been earlier converted into the $N_b$-benzyl tetracyclic ketone **7** (>98% ee) on large scale in a two pot process via the asymmetric Pictet–Spengler reaction/Dieckmann cycloadditon protocol (Scheme 3).[29,30] The $N_b$-benzyl group in **7** was then removed to provide the $N_b$-H tetracyclic ketone **8** via catalytic hydrogenation in 94% yield. The *E*-1-bromo-2-iodo-2-butene **6** was stirred with this $N_b$-H ketone **8** in the presence of $K_2CO_3$ to afford the alkylated ketone **9**, which was set up for the intramolecular Pd-catalyzed cross coupling (α-vinylation) reaction.

The alkylated ketone **9** was stirred under conditions analogous to those required (entry 1, Table 1) for the preparation of the pentacycle **3**. Surprisingly, no coupling product was detected. The reaction mixture was complex, and the dealkylated material **8** comprised the major portion of the mixture in a yield of approximately 30%. Certainly, the process required tuning to minimize the undesired side reactions and facilitate the desired coupling process. Based on our previous results,[31,32] replacement of triphenylphosphine with a different ligand was explored.

After a few attempts, it was found that replacement of triphenylphosphine with tricyclohexylphosphine (entry 2, Table 1) provided the desired intramolecular cross coupling to furnish olefin **10** in 62% yield, accompanied by 25% of the dealkylated $N_b$-H tetracyclic ketone **8**. No alkyne, which would form by elimination of HI, was observed. However, in previous cases **2** ($Ph_3P$, *Z*-olefin), some alkyne as well as **8** had formed. When tri-*t*-butylphosphine was employed (entry 3, Table 1), the process furnished a complex mixture of compounds; the desired pentacyclic ketone **10** was not observed. When the bidentate ligand dppp (entry 4, Table 1) was employed, complete dealkylation was observed; no cross coupling product was found. No significant difference was observed when $K_3PO_4$ was employed as the base (entry 6, Table 1). The reaction temperature was also critical (entries 2, 8 and 9, Table 1). When the temperature was decreased to 45°C, the reaction proceeded very slowly; over a 24 h period, only a small amount of the desired coupling product **10** and dealkylated product **8** were isolated. However, when the temperature was held at 60°C, the dealkylated product **8** became the major material, and was isolated in a yield of 68%. The desired coupling process to furnish **10** had occurred in less than 15% yield. The mechanism of the dealkylation process remains under study. However, a few control experiments have been carried out, and are also listed in Table 1. In the absence of base (entry 10, Table 1), the starting material **9** and the dealkylated product **8** were the only two materials which were observed after a 24 h period. Certainly, the base required for the generation of the enol was not involved in the dealkylation process. The dealkylation process, presumably, must undergo formation of a Pd species, since no dealkylation occurred and the starting material

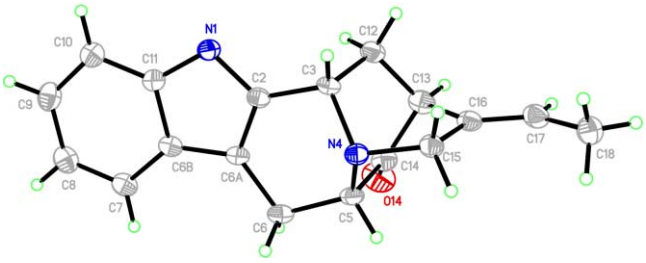
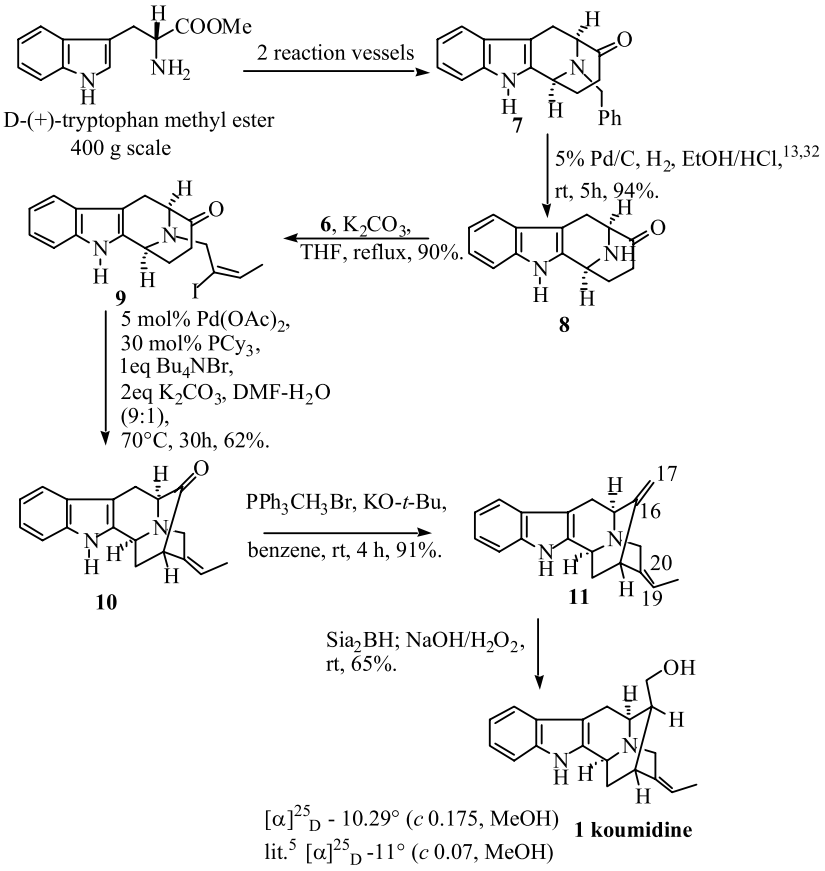



**Figure 2.** ORTEP drawing of pentacycle **10**.




**Scheme 3.**

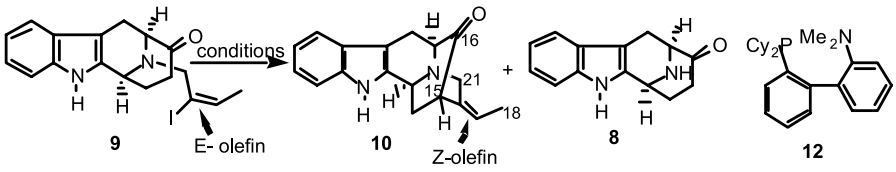
**9** was the only material observed when **9** was heated in DMF in the absence of the Pd catalyst and base (entry 11, Table 1). Presumably, after the oxidative addition, the $N_b$ nitrogen could coordinate to the Pd in competition with nucleophilic attack by the enolate, so generated. Thus, the dealkylation could occur from this complex. Recently, four-membered azapalladacycles have been isolated and characterized by Solé et al.[23] during studies of the intramolecular α-arylation of ketones. Consequently, excess amine, such as DBU, was added to the reaction mixture (entry 5, Table 1); however, no significant change was observed. A ligand **12** recently developed by Buchwald, which contains an additional coordinating amine function, was also employed (entry 12, Table 1). This reaction process furnished a more complex mixture and provided the desired coupling product in only 50% yield. A considerable amount of the dealkylated product **8** (~30%) was still isolated. Furthermore, replacing $K_2CO_3$ with the more soluble $Cs_2CO_3$ and increasing the temperature to 90°C had only a small effect on the reaction process (entry 7, Table 1). Presumably, under these conditions more enolate was formed but the yields were not improved. Clearly, further work was required to speed up attack of the enolate and retard the coordination of the amine to the Pd-intermediate.

It is noteworthy under the conditions reported by Solé et al.[24] [20% $Pd(PPh_3)_3$, *t*-BuOK, THF, reflux for 30 min], the desired coupling product **10** was produced in a yield of about 50–60%. However, as described in their paper, a large amount of $Pd(PPh_3)_3$ (20%) was employed for this process. In our case, difficulties arose on trying to remove the triphenylphosphine by-products from the desired **10** during the purification.

The structure of the pentacycle **10** was established by NMR studies. Although the $^1H$ and $^{13}C$ NMR spectra of the pentacycles **3** and **10** are similar, the signals at C-15 and C-21 in the $^{13}C$ NMR spectra can be employed to distinguish between the two. These two carbon signals appeared at 50.57 ppm (C-15) and 52.74 ppm (C-21), respectively, in **10**, and 44.55 ppm (C-15) and 55.24 ppm (C-21) in **3**. Similar phenomena were observed among the related natural products koumidine, gardnerine and normacusine B.[3,5] Eventually crystals of **10** were grown and the structure of **10** was established unambiguously by single crystal X-ray analysis (see ORTEP drawing of this crystal structure (Fig. 2)).

The pentacyclic ketone **10** was then converted into koumidine **1** in two steps. First, the ketone carbonyl in **10** was converted into the olefin **11** on stirring **10** with methyltriphenylphosphonium bromide in benzene in the presence of potassium *t*-butoxide. This Wittig reaction provided **11** in a yield of 91%. Hydroboration took place at the less hindered C16–C17 double bond (relative to the C19–C20 site) in regiospecific, stereospecific manner and this was followed by oxidative workup to furnish the natural product (–)-koumidine. This

**Table 1.**




| Entry[a] | Ligand | Base | $T$ (°C)[a] | **10** (%) | **8** (%) |
|---|---|---|---|---|---|
| 1 | $Ph_3P$ | $K_2CO_3$ | 70 | 0 | 20–30 |
| **2** | **$Cy_3P$** | **$K_2CO_3$** | **70** | **62** | **25** |
| 3 | $tBu_3P$ | $K_2CO_3$ | 70 | 0 | 0 |
| 4 | dppp | $K_2CO_3$ | 70 | 0 | 0 |
| 5 | $Cy_3P$ | $K_2CO_3$, DBU | 70 | 58 | 23 |
| 6 | $Cy_3P$ | $K_3PO_4$ | 70 | 60 | 20–30 |
| 7 | $Cy_3P$[b] | $Cs_2CO_3$ | 90 | ~58 | 20–30 |
| 8 | $Cy_3P$ | $K_2CO_3$ | 45 | <5 | <5 |
| 9 | $Cy_3P$ | $K_2CO_3$ | 60 | <15 | 68 |
| 10 | $Cy_3P$ | None | 70 | 0 | ~45 |
| 11 | None | None | 70 | 0 | 0 |
| 12 | **12** | $K_2CO_3$ | 70 | 50 | 30 |

*Standard conditions*: $Pd(Ac)_2$(0.1 equiv.),[c] $Cy_3P$ (0.5 equiv.), $K_2CO_3$ (2 equiv.), $Bu_4NBr$ (1 equiv.), $DMF/H_2O$ (9:1), 70–72°C, 24 h.
[a] Bath temperature.
[b] 10 equiv. $Cs_2CO_3$, $DMF:H_2O = 6:1$.
[c] On slightly larger scale (500 mg **9**), 0.05 equiv. $Pd(Ac)_2$ was sufficient to provide the desired coupling product **10** in a similar yield.

hydroboration/oxidation had been realized by employing diisoamylborane as the hydroborating reagent originally by Magnus et al.,[7] which had proven successful during the synthesis of (*E*) 16-epiaffinisine.[33]

Therefore, the olefin **11** was treated with freshly prepared diisoamylborane, and then followed by stirring with $NaOH/H_2O_2$ to provide (−)-koumidine **1** in a yield of 65%. The spectral data ($^1H$ and $^{13}C$ NMR) and the optical rotation $[\alpha]_D^{25} = -10.29°$ (*c* 0.175, MeOH) [lit.[5] $[\alpha]_D^{25} = -11°$ (*c* 0.07, MeOH)] of the synthetic material **1** were in excellent agreement with that reported in the literature.[3,5,7]

In conclusion, the Pd catalyzed intramolecular α-vinylation (an enolate driven cross coupling reaction) has been extended to the case of *E*-iodo-2-butene but required judicious replacement of triphenylphosphine with tricyclohexylphosphine as the ligand. The natural product (−)-koumidine was synthesized concisely (from D-(+)-tryptophan methyl ester) in 7 reaction vessels in an overall yield of 21%.[34,35]

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34. **9**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.05 (1H, bs), 7.50 (1H, d, $J=7.6$ Hz), 7.35 (1H, d, $J=7.7$ Hz), 7.24–7.12 (2H, m), 6.47 (1H, q, $J=7.1$ Hz), 4.06 (1H, bs), 3.74 (1H, d, $J=6.5$ Hz), 3.46 (1H, d, $J=13.8$), 3.19 (1H, m), 3.03 (1H, d, $J=6.5$ Hz), 2.76 (1H, d, $J=17.0$ Hz), 2.56–2.51 (2H, m), 2.11–2.04 (2H, m), 1.56 (3H, d, $J=7.1$ Hz); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 210.14, 139.33, 135.84, 132.09, 126.79, 122.06, 119.71, 118.19, 110.95, 106.87, 101.26, 64.39, 55.91, 49.67, 34.46, 30.49, 20.71, 16.90; EIMS ($m/e$, relative intensity) 406 ($M^+$, 80), 349 (100), 251 (45), 169 (55); HRMS ($m/e$) for $C_{18}H_{19}N_2OI$ calcd: 406.0542. Found: 406.0555. This material was employed directly in the next step.
**10**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.93 (1H, bs), 7.47 (1H, d, $J=7.1$ Hz), 7.28 (1H, d, $J=7.1$ Hz), 7.07–7.18 (2H, m), 5.49 (1H, m), 4.28 (1H, d, $J=9.5$ Hz), 3.92 (1H, d, $J=17.3$ Hz), 3.76 (1H, d, $J=17.3$ Hz), 3.58 (1H, d, $J=6.0$ Hz), 3.33 (1H, dd, $J=15.6$, 1.2 Hz), 3.04 (1H, dd, $J=15.6$, 6.4 Hz), 2.97 (1H, dd, $J=3.8$, 1.1 Hz), 2.38 (1H, t, $J=10.3$ Hz), 2.15–2.20 (1H, m), 1.63 (3H, d, $J=6.9$ Hz); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 216.89, 136.30, 135.98, 132.81, 126.90, 122.00, 121.38, 119.70, 118.52, 110.89, 105.35, 64.51, 52.74, 50.75, 50.57, 37.37, 22.44, 13.00; EIMS ($m/e$, relative intensity) 278 ($M^+$, 10), 250 (75), 249 (95), 182 (6), 169 (100), 168 (40). HRMS ($m/e$, relative intensity) required for $C_{18}H_{18}N_2O$: 278.1419. Found: 278.1398. This material was used directly in the next step. The structure was confirmed by single crystal X-ray analysis.[35]
**11**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.83 (1H, bs), 7.48 (1H, d, $J=8.3$ Hz), 7.28 (1H, d, $J=8.4$ Hz), 7.14–7.09 (2H, m), 5.20 (1H, m), 4.82 (2H, dd, $J=5.9$, 3.3 Hz), 4.13 (1H, d, $J=8.2$ Hz), 3.83–3.68 (3H, m), 3.19 (1H, dd, $J=15.4$, 5.6 Hz), 3.00 (1H, dd, $J=15.4$, 1.3 Hz), 2.88 (1H, dd, $J=3.74$, 1.8 Hz), 2.15 (1H, td, $J=11.7$, 1.6 Hz), 1.86 (1H, dt, $J=11.8$, 3.3 Hz), 1.58 (3H, d, $J=6.8$ Hz); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 153.19, 138.50, 137.61, 136.23, 127.64, 121.35, 119.32, 118.14, 115.28, 110.89, 105.02, 104.8, 57.1, 53.69, 50.5, 43.8, 37.58, 26.54, 12.63; EIMS ($m/z$, relative intensity) 276 ($M^+$, 90), 275 (100), 169 (60), 168 (65). HRMS ($m/e$, relative intensity) required for $C_{19}H_{20}N_2$: 276.1626. Found: 276.1613. This material was used directly in the next step.
**1**: $[\alpha]_D=-10.29°$ ($c$ 0.175, MeOH), lit. $[\alpha]_D=-11°$ ($c$ 0.07, MeOH); $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.36–7.33 (1H, d, $J=7.7$ Hz), 7.23–7.20 (1H, d, $J=7.8$ Hz), 7.02–6.90 (2H, m), 5.35–5.33 (1H, m), 4.19–4.16 (1H, dd, $J=10.1$, 3.0 Hz), 3.83–3.78 (1H, d, $J=16.2$ Hz), 3.68–3.63 (1H, d, $J=16.5$ Hz), 3.65–3.61 (1H, dd, $J=10.8$, 6.6 Hz), 3.46–3.41 (1H, dd, $J=10.8$, 6.6 Hz), 3.15–3.05 (1H, dd, $J=8.7$, 2.0 Hz), 2.97 (1H, t, $J=16.0$ Hz), 2.93–2.85 (1H, dd, $J=15.8$, 5.7 Hz), 2.42 (1H, d, $J=2.5$ Hz), 2.20 (1H, m), 1.92–1.85 (1H, m), 1.82–1.76 (1H, m), 1.54 (3H, d, $J=6.8$ Hz); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 140.50, 138.26, 137.27, 127.33, 122.40, 119.97, 118.83, 116.20, 112.04, 105.74, 61.01, 54.54, 54.45, 51.31, 43.90, 34.83, 29.09, 23.09, 12.57.
$^1$H NMR (300 MHz, DMSO-$d_8$) $\delta$ 10.75, (1H, s), 7.36–7.33 (1H, d, $J=7.5$ Hz), 7.27–7.25 (1H, d, $J=7.8$ Hz), 7.02–6.90 (2H, m), 5.26–5.23 (1H, m), 4.03 (1H, d, $J=7.5$ Hz), 3.63 (1H, d, $J=16.6$ Hz), 3.52 (1H, d, 16.7 Hz), 3.40 (1H, dd, $J=10.8$, 6.6 Hz), 3.30 (1H, dd, $J=10.8$, 6.6 Hz), 2.90 (1H, t, $J=8.5$ Hz), 2.84 (1H, d, $J=15.8$ Hz), 2.74–2.68 (1H, dd, $J=15.5$, 5.9 Hz), 2.36 (1H d, $J=2.0$ Hz), 2.05 (1H, m), 1.75–1.67 (1H, m), 1.68–1.61 (1H, m), 1.53 (3H, d, $J=6.7$ Hz); $^{13}$C NMR (75 MHz, DMSO-$d_8$) $\delta$ 142.59, 138.10, 136.13, 126.02, 120.40, 118.33, 117.68, 112.75, 111.11, 104.54, 59.10, 53.52, 52.22, 49.15, 42.60, 33.48, 28.38, 22.24, 12.35; EIMS ($m/e$, relative intensity) 294 ($M^+$, 65), 293 (62), 277(15), 263 (25), 169 (100), 168 (90). HRMS ($m/e$) calcd for $C_{19}H_{22}N_2O$: 294.1714. Found: 294.1732. The spectral data for **1** were in excellent agreement with that of the natural product.[3,5,7]
35. Cao, H.; Deschamps, J.; Cook, J. M., see manuscript in preparation for coordinates. The coordinates are available from the Cambridge Crystallographic Data Center (CCDC 219730), 12 Union Road, Cambridge, CB2 1EZ, UK.