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Communication

The Suzuki-Miyaura reaction in the chemical transformations of vindoline★

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Vindoline and its analogues are important constituents of the Madagascan periwinkle *Catharanthus roseus*, and some of them are valuable chemotherapy drugs used in treatment for some types of cancer, including leukaemia, lymphoma, breast and lung cancer. The search for semi-synthetic congeners of natural substances is still an important task for organic chemistry. In this communication we report the synthesis of five new vindoline derivatives, 15-(2-methoxyphenyl)vindoline 11**, 15-(3-methoxyphenyl)vindoline** 12**, 15-(2-nitrophenyl)vindoline** 13**, 15-(3-cyanophenyl)vindoline** 15**, and 15-(4-cyanophenyl)vindoline** 16 **using the Suzuki-Miyaura reaction as the key step. X-Ray analysis of compound** 16 **is also reported.**

Keywords: alkaloids, natural products, bioorganic chemistry, chemotherapy

INTRODUCTION

Vinblastine **1** and vincristine **2,** bisindole alkaloids from leaves of the Madagascan periwinkle *Catharanthus roseus* (L.) G. Don (Fig. 1), have attracted considerable attention because of their unique structural features, potent biological activity and, unfortunately, limited availability from plant sources (Taylor & Farsnsworth, 1975; Brossi, 1990). Both alkaloids are clinically useful anticancer pharmaceuticals used routinely for the treatment of a number of human cancers (Leveque *et al*., 1996). Since these compounds are accessible only in small amounts from plant material, several research groups have been engaged in their synthesis (Van der Heijden *et al*., 2004). The leading idea for the most successful synthetic approaches was chemical or biochemical coupling of two monoindole alkaloids: catharanthine and vindoline **3**. This approach was based on the biogenetic findings that (hetero)dimeric indole alkaloids are produced in plants by coupling of the monomeric counterparts to form an intermediate anhydrovinblastine from which vinblastine **1** and vincristine **2** are synthesized.

The same transformation can be performed synthetically and the Polonovski-Potier reaction between vindoline and catharanthine *N*-oxide was of-

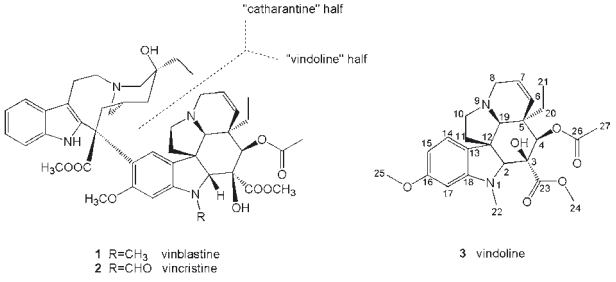

Figure 1. Structures of bis- and monoindole alkaloids.

★This paper is dedicated to Professor Tadeusz Chojnacki from the Institute of Biochemistry and Biophysics, Polish Academy of Sciences in Warsaw on the occasion of the 50th anniversary of his scientific activity and 75th birthday.

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Abbreviations: DME, 1,2-dimethoxyethane; HR MS, high resolution mass spectrometry; MS, mass spectrometry; SPE, solid phase extraction; TLC, thin layer chromatography; TMS, tetramethylsilane.

ten used for this purpose (Kutney *et al.*, 1976; Langlois *et al.*, 1976). Vindoline **3** is by far more available from natural sources than the bisindoles, being also a subject of total synthesis (Ishikawa *et al.*, 2006). It constitutes the most functionalized fragment of the (hetero)dimeric molecule and although it lacks the cytotoxic activity itself, it is often considered as a starting point to generate different semi-synthetic derivatives of possibly comparable anti-cancer activity to the leading structures, but of lower toxicity and side effects. Besides the Polonovski-Potier reaction, there are also several other synthetic and biosynthetic procedures for the introduction of the desired substituent at C15 position in vindoline (Hirata *et al.*, 1997; Tabakovic *et al.*, 1997; Berrier *et al.*, 1998; Danieli *et al.*, 1998; Sundberg *et al.*, 1998; Choi *et al.*, 2005). Recently, a very convenient and effective way for direct arylation of vindoline using the Suzuki-Miyaura reaction as the key step was published (Fekete *et al.*, 2005).

Stimulated by the ready availability of a variety of arylboronic acids with various substitution patterns, we decided to explore the possibility of introducing other aryl frameworks into the vindoline molecule. The palladium-catalyzed Suzuki-Miyaura cross-coupling reaction offers an attractive methodology for direct alkylation, alkenylation or arylation of the electrophilic aromatic ring (for a recent review see: Suzuki, 1999; Kotha *et al.*, 2002; Littke & Fu, 2002; Schröter *et al.*, 2005). Encouraged by the positive results in the arylation of some pyridines (Błachut *et al.*, 2006), we applied similar conditions to the vindoline derivative.

MATERIALS AND METHODS

Vindoline **3** was obtained in this laboratory by solid phase extraction (SPE) from *Catharanthus roseus* (L.) G. Don dried leaves imported from India (Ruszkowska *et al.*, 1994; 2003). Melting points were determined on a Boetius hot-plate microscope and are uncorrected. Optical rotation was measured on a Perkin-Elmer 247 MC polarimeter. All organic extracts were dried over anhydrous sodium sulfate. Flash chromatography was performed using Merck Kieselgel 60, 230–400 mesh ASTM. TLC chromatography was carried out on Merck TLC aluminium silica gel 60 F_{254} sheets. Developed plates were visualized by CAS reagent. The ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at room temperature on a Varian Unity Plus spectrometer operating at 500 MHz for ^1H NMR and at 125 MHz for ^{13}C NMR, using TMS as an internal standard. Following abbreviations were used to describe shape and multiplicity of signals: s – singled, d – doublet, t – triplet, m – multiplet. Mass spectra were recorded on a Waters Micromass LCT mass spectrometer in methanol using electrospray ionization in the positive ion mode. A crystal of compound **16** having dimensions 0.85 × 0.7 × 0.7 mm was placed on a Kuma KM4 κ-axis single crystal diffractometer. Structural data were collected at T = 293 K using MoKα (λ = 0.71073 Å) radiation.

15-Iodovindoline (4)

To a solution of 100 mg of vindoline **3** in DME (5 ml) a portion of 54 mg of *N*-iodosuccinimide was added and the mixture was stirred in a closed vessel for 5 h at room temp. The formed precipitate was isolated by filtration and washed with a small portion of cold DME. The combined filtrates were additionally diluted with 5 ml of CH_2Cl_2 and the resulting solution was extracted with 15 ml of 5% $NaHCO_3$ aq., washed with water (2 × 5 ml) and dried. Crystalline solid that deposited after evaporation of the solvent was combined with the above precipitate to yield 120 mg (94%) of compound **4** in the form of pale yellow crystals.

m.p.: 233°C with decomposition (lit. (Fekete *et al.*, 2005) 233°C decomp.). MS: m/z = 583.3 $[M+H]^+$.

General procedure for the preparation of 15-arylvindolines (11–16)

A mixture of 15-iodovindoline **4** (50 mg in 5 ml of DME), 0.12 mmol of the corresponding phenylboronic acid **5–10**, aqueus solution of K_3PO_4 (36 mg in 0.2 ml H_2O), 1.4 mg of $Pd(OAc)_2$ and 3.9 mg of $(o\text{-tolyl})_3P$ was stirred and heated under argon in a closed vessel at 80°C for 20 h. The reaction mixture was then dried after cooling, the solvent was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel with ethyl acetate-cyclohexane gradient elution to isolate the following compounds:

15-(2-Methoxyphenyl)vindoline (11)

Yield: 25%. $[\alpha]_D^{20}$ = +4.6 (*c* 1.0, $CHCl_3$). δ_H: 9.6 (1H, s, C3OH), 7.28 (1H, m, ArH), 7.16 (1H, m, ArH), 6.96 (2H, m, ArH), 6.87 (1H, s, C14H), 6.17 (1H, s, C17H), 5.85 (1H, m, C7H), 5.53 (1H, s, C4H), 5.24 (1H, d, C6H), 3.81 (3H, s, $C24H_3$), 3.78 (1H, d, C2H), 3.76 (3H, s, $ArOCH_3$), 3.74 (3H, s, $C25H_3$), 3.50 (1H, m, $C8H_2$), 3.40 (1H, m, $C10H_2$), 2.78 (1H, d, $C8H_2$), 2.74 (3H, s, $C22H_3$), 2.67 (1H, s, C19H), 2.46 (1H, m, $C10H_2$), 2.36 (2H, m, $C11H_2$), 2.09 (3H, s, $C27H_3$), 1.71 (1H, m, $C20H_2$), 1.26 (1H, m, $C20H_2$), 0.56 (3H, t, $C21H_3$). δ_C: 172.05 (C23), 170.90 (C26), 158.25 (C-16), 157.24 (C2′), 152.95 (C18), 131.73 (ArC), 130.52 (C6), 128.21 (ArC), 128.17 (ArC), 125.09 (C13), 124.14 (C14), 123.97 (C7), 120.30 (ArC), 118.70 (C15), 111.19 (ArC), 93.68 (C17), 83.68 (C2), 79.59 (C3), 76.53 (C4), 66.13 (C19), 55.83 ($ArOCH_3$), 55.67 (C25), 52.97 (C12),

52.28 (C24), 52.17 (C10), 51.15 (C8), 43.98 (C11), 42.96 (C5), 38.57 (C22), 30.96 (C20), 21.10 (C27), 7.73 (C21). MS: *m/z* 563.1 (100% $[M+H]^+$), 585.1 (76% $[M+Na]^+$), HR MS: calc. for $C_{32}H_{38}N_2O_7Na$ 585.2577, found 585.2582.

15-(3-Methoxyphenyl)vindoline (12)

Yield: <5%. Compound **12** was separated from vindoline by repeated column chromatography on silica gel with various solvent mixtures (ethyl acetate/cyclohexane, hexane/acetone, methylene dichloride/methanol). MS: *m/z* 457.3 (6% $[vindoline+H]^+$), 479.4 (48% $[vindoline+Na]^+$), 563.4 (20% $[M+H]^+$), 585.4 (100% $[M+Na]^+$), HR MS: calc. for $C_{32}H_{38}N_2O_7Na$ 585.2577, found 585.2532.

15-(2-Nitrophenyl)vindoline (13)

Yield: 7%. $[\alpha]_D^{20}$ = +19.2 (*c* 1.0, $CHCl_3$). δ_H: 9.63 (1H, s, C3OH), 7.85 (1H, m, ArH), 7.57 (1H, m, ArH), 7.40 (1H, m, ArH), 7.26 (1H, m, ArH), 6.91 (1H, s, C14H), 6.08 (1H, s, C17H), 5.86 (1H, m, C7H), 5.50 (1H, s, C4H), 5.24 (1H, d, C6H), 3.81 (3H, s, $C24H_3$), 3.79 (1H, d, C2H), 3.68 (3H, s, $C25H_3$), 3.50 (1H, m, $C8H_2$), 3.44 (1H, m, $C10H_2$), 2.80 (1H, d, $C8H_2$), 2.74 (3H, s, $C22H_3$), 2.67 (1H, s, C19H), 2.51 (1H, m, $C10H_2$), 2.40 (2H, m, $C11H_2$), 2.09 (3H, s, $C27H_3$), 1.63 (1H, m, $C20H_2$), 1.25 (1H, m, $C20H_2$), 0.86 (3H, t, $C21H_3$). δ_C: 171.95 (C23), 170.83 (C26), 157.39 (C-16), 153.97 (C18), 149.87 (ArC), 133.41 (ArC), 132.44 (ArC), 132.28 (ArC), 130.42 (C6), 127.28 (ArC), 124.91 (C13), 124.10 (C7), 123.88 (C14), 123.26 (C15), 95.82 (ArC) 93.03 (C17), 83.50 (C2), 79.46 (C3), 76.36 (C4), 67.02 (C19), 55.26 (C25), 52.93 (C12), 52.36 (C24), 52.27 (C10), 51.12 (C8), 43.89 (C11), 42.94 (C5), 38.18 (C22), 29.70 (C20), 21.08 (C27), 7.83 (C21). MS: *m/z* 578.4 (12% $[M+H]^+$), 600.3 (100% $[M+Na]^+$), HR MS: calc. for $C_{31}H_{35}N_3O_8Na$ 600.2322, found 600.22314.

15-(3-Nitrophenyl)vindoline (14)

Yield: 36%. $[\alpha]_D^{20}$ = –74.1 (*c* 1.0, $CHCl_3$). δ_H: 9.9 (1H, s, C3OH), 8.29 (1H, m, ArH), 8.10 (1H, m, ArH), 7.80 (1H, m, ArH), 7.51 (2H, t, ArH), 6.96 (1H, s, C-14), 6.17 (1H, s, C-17), 5.90 (1H, m, C-7), 5.45 (1H, s, C-4), 5.25 (1H, d, C-6), 3.84 (3H, s, $COOCH_3$, C-24), 3.82 (3H, s, OCH_3, C-25), 3.79 (1H, d, C-2), 3.52 (1H, m, C-8), 3.46 (1H, m, C-10), 2.85 (1H, d, C-8), 2.78 (1H, s, C-19), 2.77 (3H, s, NCH_3, C-22), 2.58 (1H, m, C-10), 2.35 (2H, m, C-11), 2.09 (3H, s, $OCOCH_3$, C-27), 1.70 (1H, m, C-20), 1.20 (1H, m, C-20), 0.59 (3H, t, C-21). δ_C: 171.79 (C-23), 170.84 (C-6), 157.97 (C-16), 153.89 (C-18), 148.17 (C-3′), 140.63 (C-1′), 135.44 (ArC), 130.30 (C-6), 128.68 (ArC), 124.81 (C-13), 124.33 (ArC), 124.09 (C-14), 124.07 (C-7), 120.91 (ArC), 118.88 (C-15), 93.27 (C-17), 83.38 (C-2), 79.60 (C-3), 76.27 (C-4), 66.74 (C-19), 55.73 (C-25), 52.97 (C-12), 52.35 (C-24), 51.66 (C-10), 50.99 (C-8), 43.99 (C-11), 42.90 (C-5), 38.15 (C-22), 30.94 (C-20), 21.08 (C-27), 7.72 (C-21). MS: *m/z* = 578.3 $[M+H]^+$, HR MS: calc. for $C_{31}H_{36}N_3O_8$ 578.2502, found 578.2504.

15-(3-cyanophenyl)vindoline (15)

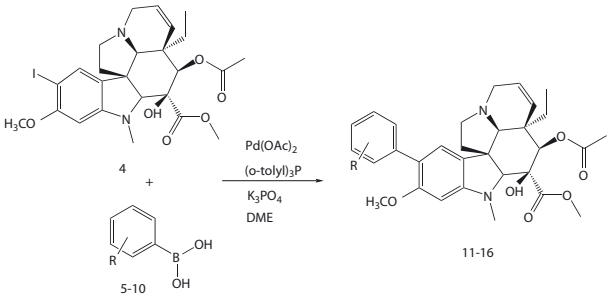
Yield: 78%. $[\alpha]_D^{20}$ = –28.9 (*c* 1.0, $CHCl_3$). δ_H: 7.72 (1H, m, ArH), 7.66 (1H, m, ArH), 7.53 (1H, m, ArH), 7.45 (1H, m, ArH), 7.27 (1H, s, C3OH), 6.90 (1H, s, C14H), 6.16 (1H, s, C17H), 5.89 (1H, m, C7H), 5.47 (1H, s, C4H), 5.26 (1H, d, C6H), 3.82 (3H, s, $C24H_3$), 3.81 (3H, s, $C25H_3$), 3.80 (1H, d, C2H), 3.52 (1H, m, $C8H_2$), 3.46 (1H, m, $C10H_2$), 2.87 (1H, d, $C8H_2$), 2.76 (3H, s, $C22H_3$), 2.75 (1H, s, C19H), 2.56 (1H, m, $C10H_2$), 2.35 (2H, m, $C11H_2$), 2.09 (3H, s, $C27H_3$), 1.68 (1H, m, $C20H_2$), 1.26 (1H, m, $C20H_2$), 0.56 (3H, t, $C21H_3$). δ_C: 171.81 (C23), 170.85 (C26), 157.88 (C-16), 153.80 (C18), 140.19 (C1′), 133.71 (ArC), 132.89 (ArC), 130.28 (C6), 129.53 (C6), 128.74 (ArC), 124.83 (C13), 124.29 (C14), 124.05 (C7), 119.30 (C3′), 119.04 (C15), 112.04 (ArCN), 93.30 (C17), 83.38 (C2), 79.55 (C3), 76.25 (C4), 66.90 (C19), 55.69 (C25), 52.93 (C12), 52.36 (C24), 51.80 (C10), 51.03 (C8), 43.98 (C11), 42.89 (C5), 38.20 (C22), 30.94 (C20), 21.08 (C27), 7.77 (C21). HR MS: calc. for $C_{32}H_{36}N_3O_6$ 558.2604, found 558.2619.

15-(4-Cyanophenyl)vindoline (16)

Yield: 93%. $[\alpha]_D^{20}$ = –94.2 (*c* 1.0, $CHCl_3$). δ_H: 9.61 (1H, s, C3OH), 7.63 (2H, m, ArH), 7.54 (2H, m, ArH), 6.92 (1H, s, C14H), 6.16 (1H, s, C17H), 5.88 (1H, m, C7H), 5.46 (1H, s, C4H), 5.27 (1H, d, C6H), 3.83 (3H, s, $C24H_3$), 3.81 (3H, s, $C25H_3$), 3.79 (1H, d, C2H), 3.52 (1H, m, $C8H_2$), 3.47 (1H, m, $C10H_2$), 2.87 (1H, d, $C8H_2$), 2.76 (3H, s, $C22H_3$), 2.67 (1H, s, C19H), 2.55 (1H, m, $C10H_2$), 2.34 (2H, m, $C11H_2$), 2.09 (3H, s, $C27H_3$), 1.69 (1H, m, $C20H_2$), 1.22 (1H, m, $C20H_2$), 0.56 (3H, t, $C21H_3$). δ_C: 171.96 (C23), 170.02 (C26), 158.24 (C-16), 154.14 (C18), 144.07 (C1′), 130.93 (C2′ and C6′), 130.47 (C6), 129.99 (C3′ and C5′), 124.99 (C13), 124.48 (C14), 124.30 (C7), 119.60 (C4′), 119.57 (C15), 109.52 (ArCN), 93.42 (C17), 83.54 (C2), 79.74 (C3), 76.41 (C4), 66.97 (C19), 55.88 (C25), 53.11 (C12), 52.56 (C24), 51.89 (C10), 51.18 (C8), 44.16 (C11), 43.04 (C5), 38.27 (C22), 30.10 (C20), 21.27 (C27), 7.92 (C21). MS: *m/z* 558.4 (100% $[M+H]^+$), 580.4 (29% $[M = Na]^+$), HR MS: calc. for $C_{32}H_{35}N_3O_6Na$ 580.2423, found 580.2406.

RESULTS

Vindoline **3** was obtained in this laboratory from dried leaves of the Madagascan periwinkle us-



Scheme 1. The Suzuki-Miyaura reaction of 15-iodovindoline 4 and a series of aryl boronic acids 5–10.

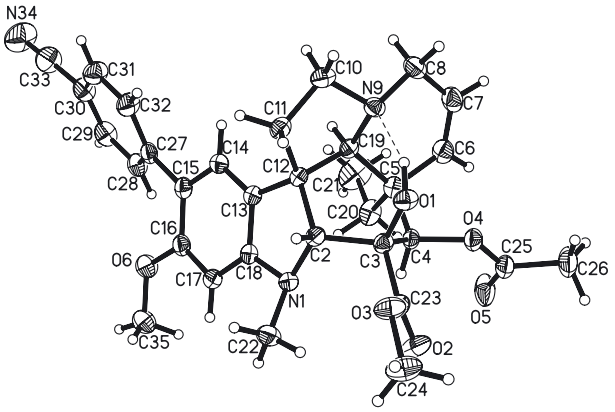


Figure 2. Conformation of molecule 16 and numbering scheme.
Non-hydrogen atoms are shown as 30% probability ellipsoids. The intramolecular O–H···N hydrogen bond is shown as the dashed line.

ing a solid phase extraction method (Ruszkowska *et al.*, 1994) and it was transformed into 15-iodovindoline **4** by a slightly modified method described by Fekete *et al.* (2005). The subsequent series of Suzuki-Miyaura coupling reactions were performed under standard conditions, using 15-iodovindoline **4** and a series of aryl boronic acids **5–10**.

The reactions were carried out under inert atmosphere at 80°C in 1,2-dimethoxyethane:water two phase system. The palladium catalyst was formed *in situ* from $Pd(OAc)_2$ and tri(*o*-tolyl)phosphine. Potassium phosphate (K_3PO_4) was used as the base. After a standard work-up and column chromatography, a series of 15-arylvindolines were prepared. The results are summarized in Table 1.

The yield of the final products varied from 5% (compound **6**) to 93% in the case of 4-cyano-derivative **16**, which observation is in accordance with the substituents' effects on the reactivity of aryl boronic acids (Thimmaiah & Fang, 2007).

The structures of all final compounds were studied on the basis of their spectroscopic data. Moreover, in the case of compound **16** we were able to obtain a monocrystal suitable for rentgenostructural analysis. The crystal of **16** was orthorhombic with the $P2_12_12_1$ space group symmetry. The unit cell parameters were as follows a = 13.522(3), b = 13.612(3), c = 15.425(3) Å, $\alpha = \beta = \gamma = 90°$, V = 2839.1(10) Å^3. 4788 reflections up to $2\theta = 50°$ were collected with $-17 \le h \le 0$, $-17 \le k \le 0$, $-5 \le l \le 21$. Structure was solved using direct methods from SHELXS97 (Sheldrick, 1997). All non-hydrogen atoms were found from the E-maps. Further isotropic and anisotropic least-squares refinement revealed almost all hydrogen atoms. Most of them were used in further cycles of refinement as fixed contributors fulfilling standard geometrical criteria and having their isotropic displacement parameters tied to the respective values of carbon atoms they are bonded to. Such a procedure led to a model with R1 = 0.0405, wR2 = 0.1129, respectively, for 3485 observed independent reflections with $I > 2\sigma(I)$. The conformation of the molecule is shown in Fig. 2. The intramolecular O-H···N hydrogen bond characteristic for vindoline (Ruszkowska *et al.*, 2004) is also depicted. The respective O1–H1, H1···N9 and O1···N9 distances are 0.91(3), 1.83(3), 2.686(2) Å. The O1–H1–N9 angle is 155(3)°. Detailed data for this structure have been deposited with the Cambridge Structural Data Centre under the number CCDC 604437.

Table 1. Chemical yield of Suzuki-Miyaura reaction products.

R	Phenylboronic acid	Product	Yield[b]
2-OCH_3	**5**	**11**	25%
3-OCH_3	**6**	**12**	< 5%
2-NO_2	**7**	**13**	7%
[a]3-NO_2	**8**	**14**	36%
3-CN	**9**	**15**	78%
4-CN	**10**	**16**	93%

[a] also obtained by Fekete *et al.* (2005); [b] isolated yield

CONCLUSION

In this communication we demonstrated that the Suzuki-Miyaura reaction is a powerful tool for the direct arylation of sensitive and complicated natural products. Vindoline **3** was iodinated and subjected to a series of cross-coupling reactions catalyzed by a palladium-phosphine complex. Several new compounds were obtained with the yield up to 93%. Their structures were established on the basis of their spectroscopic data and, in the case of 15-(4-cyanophenyl)vindoline **16**, a rentgenostructural analysis was performed.

All derivatives will be screened for possible biological activity.

REFERENCES

Berrier C, Jacquesy JC, Jouannetaud MP, Lafitte C, Vidal Y, Zunino F, Fahy J, Duflos A (1998) *Tetrahedron* **54**: 13761–13770.

Błachut D, Wojtasiewicz K, Czarnocki Z (2006) *Synthesis* **17**: 2855–2864.

Brossi A, ed (1990) Antitumor Bisindole Alkaloids from *Catharanthus roseus* (L.), *The Alkaloids*, vol 37, Academic Press.

Choi Y, Ishikawa H, Velcicky J, Elliott GI, Miller MM, Boger DL (2005) *Org Lett* **7**: 4539–4542.

Danieli B, Lesma G, Martinelli M, Passarella D, Silvani A (1998) *J Org Chem* **63**: 8586–8588.

Fekete M, Kolonits P, Novak L (2005) *Heterocycles* **65**: 165–171.

Hirata K, Duangteraprecha S, Morihara E, Honda M, Akagi T, Nakae M, Katayama H, Miyamoto K (1997) *Biotechnol Lett* **19**: 53–57.

Ishikawa H, Elliott GI, Velcicky J, Choi Y, Boger DL (2006) *J Am Chem Soc* **128**: 10596–10612.

Kotha S, Lahiri K, Kashinath D (2002) *Tetrahedron* **58**: 9633–9695.

Kutney JP, Hibino T, Jahngen E, Okutani T, Ratcliffe AH, Treasurywala AM, Wunderly S (1976) *Helv Chim Acta* **59**: 2858–2882.

Langlois N, Gueritte F, Langlois Y, Potier P (1976) *J Am Chem Soc* **98**: 7017–7024.

Leveque D, Wihlm J, Jehl F (1996) *Bull Cancer* **83**: 176–186.

Littke AF, Fu GC (2002) *Angew Chem Int* **41**: 4176–4211.

Ruszkowska J, Macierewicz B, Wróbel JT (1994) P 164 944; C 07D 519/04.

Ruszkowska J, Chrobak R, Wróbel JT, Czarnocki Z (2003**)** *Adv Exp Med Biol* **527**: 643–646.

Ruszkowska J, Chrobak R, Maurin JK, Czarnocki Z (2004) *Acta Cryst* **C60**: 377–380.

Sheldrick GM (1997) SHELXL97 Program for the solutions of crystal structures. University of Goettingen, Germany.

Schröter S, Stock C, Bach T (2005) *Tetrahedron* **61**: 2245–2267.

Sundberg RJ, Hong J, Smith SQ, Sabat M, Tabakovic I (1998) *Tetrahedron* **54**: 6259–6292.

Suzuki A (1999) *J Organomet Chem* **576**: 147–168.

Tabakovic I, Gunic E, Juranic I (1997) *J Org Chem* **62**: 947–953.

Taylor WI, Farnsworth NR, eds, (1975) *The Catharanthus Alkaloids*, Marcel Dekker Inc., New York.

Thimmaiah M, Fang S (2007) *Tetrahedron* **63**: 6879–6886.

Van der Heijden R, Jacobs DI, Snoeijer W, Hallared D, Verpoorte R (2004) *Curr Med Chem* **11**: 607–628.