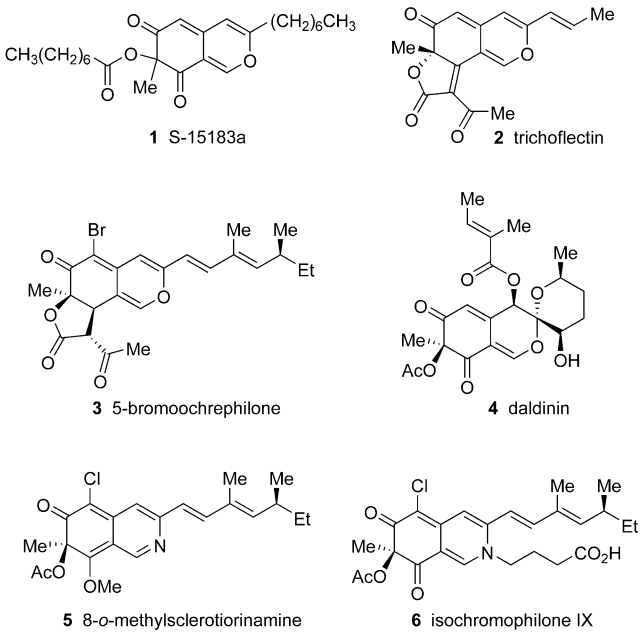
Natural Product Synthesis

Synthesis of Azaphilones and Related Molecules by Employing Cycloisomerization of *o*-Alkynylbenzaldehydes**

*Jianglong Zhu, Andrew R. Germain, and John A. Porco, Jr.**

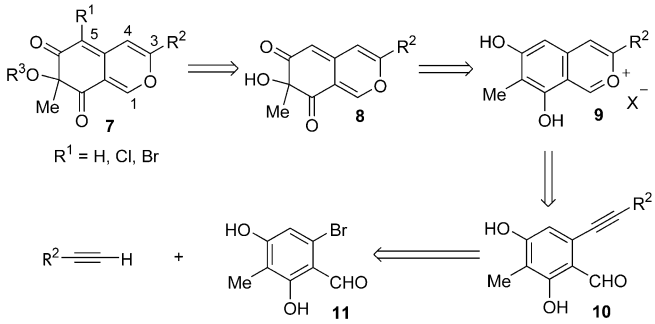
The azaphilones are a structurally diverse family of natural products containing a highly oxygenated bicyclic core and a quaternary center (see **1**–**6**, Scheme 1).[1] These molecules



Scheme 1. Representative azaphilone natural products.

exhibit a wide range of biological activities, including gp120-CD4,[1c] Grb2-SH2,[1d] and sphingosine kinase inhibition.[1e] The potent biological activities of this class of compounds may be related to reaction of the 4*H*-pyran nucleus with amines to produce the corresponding vinylogous 4-pyridones (see **6**).[2] A number of synthetic efforts concerning azaphilones have been reported.[3] In general, pyronoquinones[3a] and pyrylium salts[3b,c] have been employed as precursors. Herein we report an approach to the synthesis of the azaphilones involving cycloisomerization of *o*-alkynylbenzaldehydes to 2-benzopyrylium salts and subsequent oxidation to the 6*H*-isochromene ring system.

Our retrosynthetic analysis for the azaphilones is shown in Scheme 2. Core structure **7** may be prepared by acylation of



Scheme 2. Retrosynthetic analysis for the azaphilone core structure.

tertiary carbinol **8**, which may be derived from oxidation of 2-benzopyrylium salt **9**.[3c,4] We planned to prepare **9** by transition-metal-catalyzed cycloisomerization[5,6] of *o*-alkynylbenzaldehyde **10**. This approach takes advantage of readily available alkynes to construct azaphilones with diverse side chains at C3. Alkynylbenzaldehyde **10** may be obtained by Sonogashira coupling of 2-bromobenzaldehyde **11**.

S-15183a (**1**), a sphingosine kinase inhibitor isolated from *Zopfiella inermis* SANK 15183,[1e] was chosen as our initial target and the basis for model experiments. Nitration of commercially available 2,4-dimethoxy-3-methylbenzaldehyde (**12**) with $Cu(NO_3)_2$ in acetic anhydride afforded **13** in which the aldehyde was protected in situ as the geminal diacetate (85%).[7] Compound **13** was then reduced (Pd/C, H_2) and brominated to afford *o*-bromoaniline **14** (92%). Deamination of **14** and in situ deprotection of the geminal diacetate produced 6-bromo-2,4-dimethoxy-3-methylbenzaldehyde (**15**; 87%). Demethylation of **15** proceeded smoothly with BBr_3 to afford 2-bromobenzaldehyde **11** (95%). Sonogashira coupling of **11** with 1-nonyne afforded the desired *o*-alkynylbenzaldehyde **16** (92%, Scheme 3).[8]

We next investigated cycloisomerization reactions of *o*-alkynylbenzaldehyde **16**. Recent reports have highlighted the utility of Lewis acids for alkyne activation,[5,6,9,10] including formal [4+2] benzannulations of *o*-alkynylbenzaldehydes and alkynes/alkenes by employing gold(III) catalysis.[5e–g,6] It was envisaged that substrates such as **16** could be converted directly into 2-benzopyrylium salts in the presence of a catalytic amount of a carbophilic Lewis acid and stoichiometric amounts of a proton source. A number of Lewis acid catalysts were investigated for the cycloisomerization (Table 1). Among these Lewis acids, gold(III) acetate ($Au(OAc)_3$)[11] was found to be optimal and led to formation of 2-benzopyrylium salt **17** in 1 min at room temperature with 1,2-dichloroethane/trifluoroacetic acid (10:1) as the solvent

[*] J. Zhu, A. R. Germain, Prof. Dr. J. A. Porco, Jr.
Department of Chemistry
Center for Chemical Methodology and Library Development
Boston University, 590 Commonwealth Avenue
Boston, MA 02215 (USA)
Fax: (+1) 617-353-6466
E-mail: porco@chem.bu.edu

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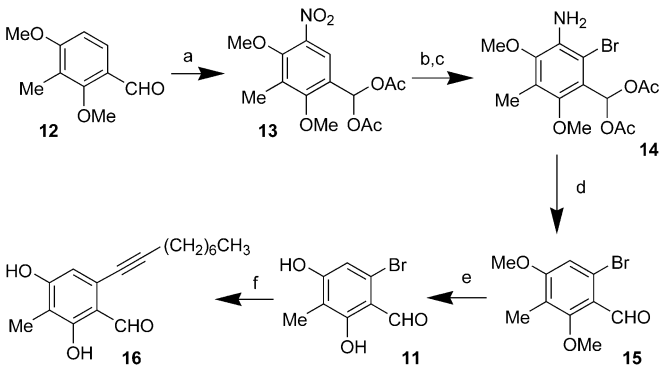
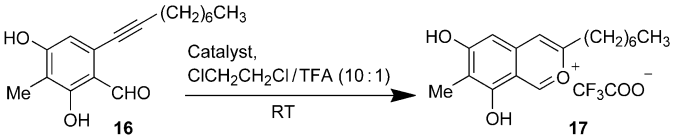


Scheme 3. a) $Cu(NO_3)_2 \cdot 3H_2O$, Ac_2O, RT, 85%; b) Pd/C, H_2, THF, RT; c) Br_2, HOAc, RT, 92% for two steps; d) $NaNO_2$, conc. HCl, THF/H_2O, −5 °C; H_3PO_2, 0 °C→40 °C, 87%; e) BBr_3, CH_2Cl_2, −78 °C→RT, 95%; f) $[PdCl_2(PPh_3)_2]$, 1-nonyne, CuI, Et_3N, DMF, 60 °C, 92%. THF = tetrahydrofuran, DMF = *N*,*N*-dimethylformamide.

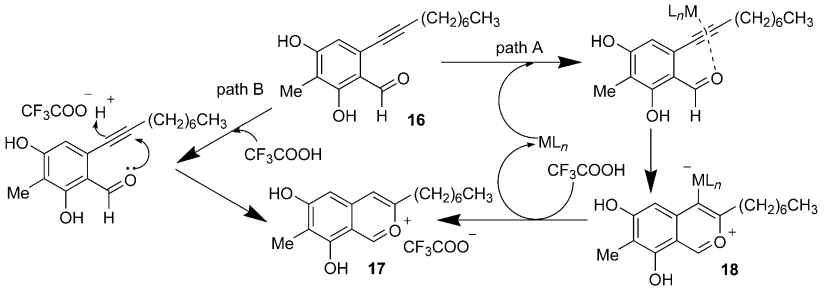
Table 1: Lewis acid catalyzed formation of 2-benzopyrylium salt **17**.[a]



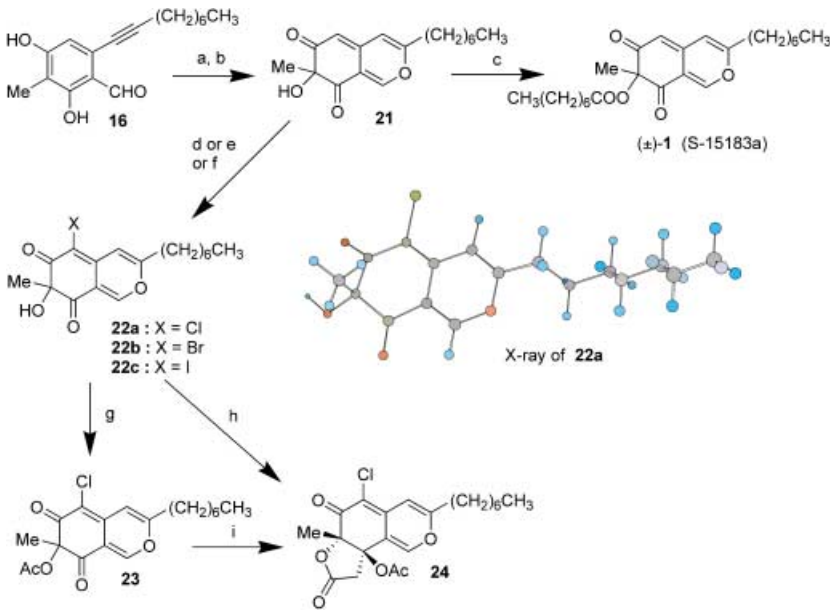
Entry	Catalyst (equiv)	*t* [min]	Conversion [%][b]
1[c]	None	20	< 1
2	$AuCl_3$ (0.05)	20	75
3	$AuBr_3$ (0.05)	20	48
4	$Au(OAc)_3$ (0.05)	1	100
5	$Cu(OTf)_2$ (0.05)	20	41
6	$[CuOTf]_2$·toluene (0.025)	20	74
7	$AgNO_3$ (0.05)	20	94

[a] Reactions were conducted on a 0.1-mmol scale in $ClCH_2CH_2Cl$ (1.0 mL) and CF_3COOH (0.1 mL). [b] Reactions were quenched with CH_3CN/H_2O and conversion was determined by reversed-phase HPLC analysis of the recovered starting material with benzophenone used as an internal standard. See the Supporting Information for a detailed procedure. [c] Less than 1% conversion was observed after 20 min at 40 °C.

(entry 4).[12,13] In comparison, $AuCl_3$ (entry 2) led to 75% conversion in 20 minutes (entry 2). In the absence of Lewis acid catalyst, less than 1% conversion was observed at 40 °C (entry 1). However, 2-benzopyrylium salt **17** was formed completely in 2 h at 60 °C by using trifluoroacetic acid (TFA) as the solvent. The 2-benzopyrylium salt **17** may thus be formed by two possible pathways (Scheme 4). Lewis acid activation of the triple bond of *o*-alkynylbenzaldehyde **16** should provide metal ate complex **18**[5e] which may be protonated to afford **17** (path A). In the absence of a Lewis acid catalyst, the protic acid may also activate the alkyne for attack by the aldehyde carbonyl group to afford **17** directly (path B).[5b] Although Lewis acid catalysis was not necessary for cycloisomerization of **16** into **17**, subsequent experiments revealed that Lewis acid catalysis is advantageous for cycloisomerization of certain *o*-alkynylbenzaldehyde substrates (see below). This methodology may be a general approach for the preparation of 2-benzopyrylium salts.[14]



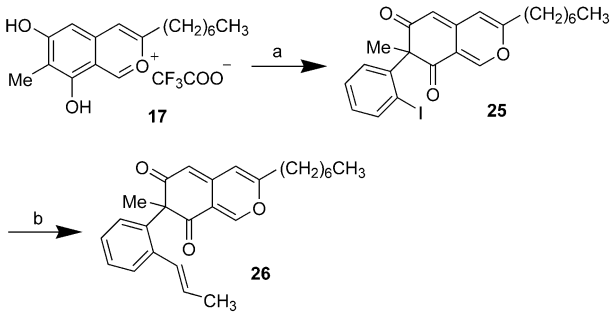
Scheme 4. Proposed mechanism for cycloisomerization. M = metal, L = ligand.



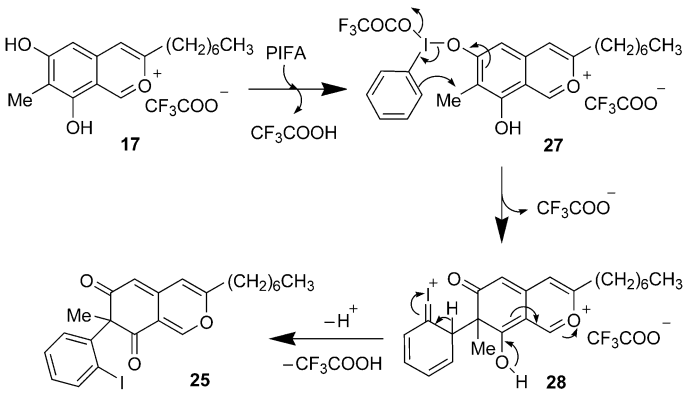
Scheme 5. a) $Au(OAc)_3$ (5 mol%), $ClCH_2CH_2Cl/CF_3COOH$ (10:1), RT; b) IBX, tetrabutylammonium iodide (5 mol%), RT, then sat. $Na_2S_2O_3$, 84% (two steps); c) $CH_3(CH_2)_6COCl$, iPr_2NEt, DMAP, CH_2Cl_2, RT, 61%; d) NCS, CH_3CN, RT, 83%;[24] e) NBS, CH_3CN, RT, 88%; f) NIS, CH_3CN, RT, 66%; g) Ac_2O (4.0 equiv), Et_3N (2.0 equiv), DMAP, CH_2Cl_2, RT, 73%; h) Ac_2O (4.0 equiv), Et_3N (5.0 equiv), DMAP, RT, CH_2Cl_2, 42%; i) Ac_2O (4.0 equiv), Et_3N (5.0 equiv), DMAP, CH_2Cl_2, RT, 47%. DMAP = 4-dimethylaminopyridine, NCS = *N*-chlorosuccinimide, NBS = *N*-bromosuccinimide, NIS = *N*-iodosuccinimide.

Previous studies on the oxidation of 2-benzopyrylium salts related to **17** to form the azaphilone nucleus have typically involved the use of lead tetraacetate.[3a–c] However, after screening alternative oxidants we found that *o*-iodoxybenzoic acid (IBX)[15] in 1,2-dichloroethane/TFA cleanly afforded the desired azaphilone **21** in 84% yield after reductive workup (Scheme 5). A key to this transformation was the use of tetrabutylammonium iodide as a phase-transfer catalyst and apparent IBX activator.[16,17] Acylation of **21** afforded (±)-S-15183a (**1**; 61%) whose

^{1}H NMR, ^{13}C NMR, and mass spectra were found to be identical to those of an authentic sample. Since a number of azaphilone natural products contain chlorine or bromine at the C5 position, we next investigated halogenation of **21**. It was found that chloroazaphilone **22a** could be obtained in 83% yield when azaphilone **21** was treated with *N*-chlorosuccinimide in CH_3CN. The structure of **22a** was confirmed by single-crystal X-ray structure analysis. Similarly, bromination



Scheme 6. a) PIFA, RT, then sat. $Na_2S_2O_3$, 46%; b) $Pd(OAc)_2$, (*o*-tolyl)$_3$P, (*E*)-tributyl-1-propenylstannane, DMF, 80°C, 81%.



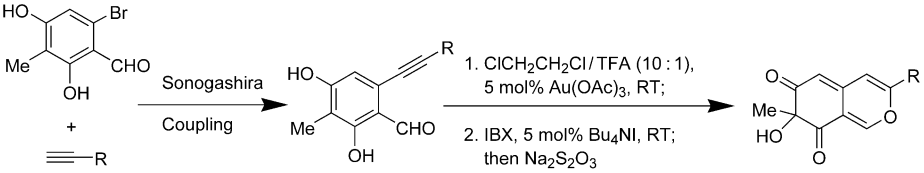
Scheme 7. Proposed mechanism for the formation of **25**.

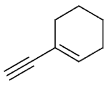
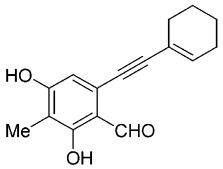
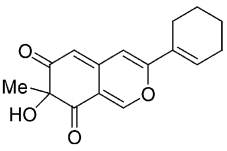
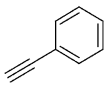
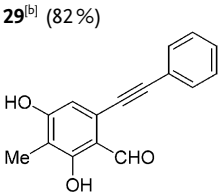
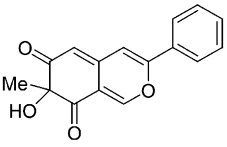
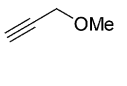
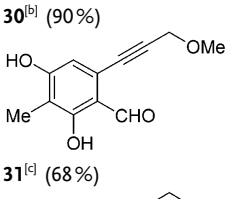
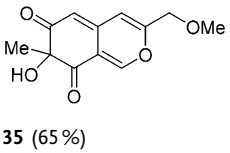
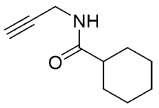
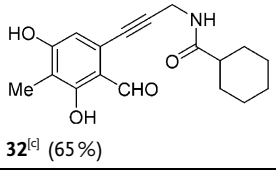
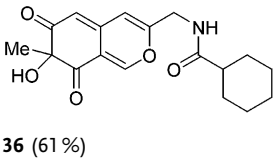
or iodination of alcohol **21** with *N*-bromosuccinimide or *N*-iodosuccinimide, respectively, afforded bromoazaphilone **22b**[1c] (88%) and iodoazaphilone **22c** (66%). These results reaffirm that halogenation of the azaphilone nucleus may be performed at a late stage.[18] Attempted acylation of **22a** led to acetate **23** or angular azaphilone **24**, which is related to trichoflectin (**2**)[1b] and 5-bromoochrephilone (**3**),[1c] depending on the reaction conditions employed.

Interestingly, treatment of 2-benzopyrylium salt **17** with the hypervalent iodine reagent (bis(trifluoroacetoxy)-iodo)benzene (PIFA) did not afford the desired azaphilone but provided C-arylated azaphilone **25** (46%; Scheme 6). A proposed mechanism for this transformation is shown in Scheme 7. Reaction of 2-benzopyrylium salt **17** with PIFA affords intermediate **27**, which may undergo [3,3] sigmatropic rearrangement to dearomatized intermediate **28**.[19] Rearomatization and elimination of trifluoroacetic acid affords C-arylated azaphilone **25**. Preliminary experiments showed that **25** may undergo further functionalization by Pd-catalyzed cross-coupling to afford novel styrenyl azaphilone **26** (81%; Scheme 6).

The cycloisomerization–oxidation sequence was next applied to the synthesis of several unnatural azaphilones (Table 2). Sonogashira coupling of 2-bromobenzaldehyde **11** with 1-ethynylcyclohexene and phenylacetylene with P*t*Bu$_3$ employed as the ligand[20] cleanly afforded the desired *o*-alkynylbenzaldehydes **29** and **30**, respectively (entries 1 and 2). In contrast, microwave conditions[21] were required for efficient coupling with methyl propargyl ether and propargyl cyclohexyl amide to prepare substrates **31** and **32**, respectively (entries 3 and 4). $Au(OAc)_3$-catalyzed cyclo-

Table 2: Synthesis of several unnatural azaphilones.

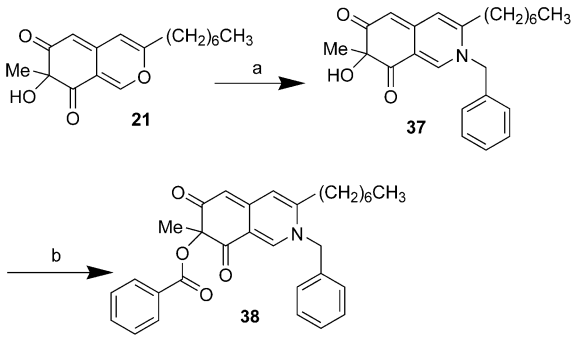


Entry	Alkyne	*o*-Alkynylbenzaldehyde (yield[a])	Azaphilone (yield[a])
1		 **29**[b] (82%)	 **33** (65%)
2		 **30**[b] (90%)	 **34** (82%)
3		 **31**[c] (68%)	 **35** (65%)
4		 **32**[c] (65%)	 **36** (61%)

[a] Yield of isolated product. [b] Method A: $[PdCl_2(PhCN)_2]$, CuI, P*t*Bu$_3$·HBF$_4$, *i*Pr$_2$NH, 1,4-dioxane, RT. [c] Method B: $[PdCl_2(PPh_3)_2]$, CuI, Et$_3$N, 1,2-dimethoxyethane, microwave (300 W, 120°C, 25 min).

isomerization of the resulting *o*-alkynylbenzaldehydes in 1,2-dichloroethane/TFA (10:1) at room temperature produced the corresponding 2-benzopyrylium salts.[22] Oxidation of the 2-benzopyrylium salts with IBX in the presence of tetrabutylammonium iodide afforded the corresponding C3-functionalized azaphilones **33**–**36** (61–82%).

As a prelude to the anticipated use of the azaphilones as scaffolds in a chemical library synthesis, we conducted the functionalization sequence shown in Scheme 8. Reaction of



Scheme 8. a) Benzylamine (1.2 equiv), CH_3COOH (3.6 equiv), THF, RT, 90%; b) benzoyl chloride (1.5 equiv), Et_3N (1.0 equiv), DMAP (0.5 equiv), CH_2Cl_2, RT, 86%.

azaphilone **21** with benzylamine in THF in the presence of acetic acid[23] proceeded smoothly to afford the corresponding vinylogous 4-pyridone **37**, which underwent acylation with benzoyl chloride to produce vinylogous 4-pyridone ester **38**. These experiments demonstrate access to three orthogonal diversification points on the azaphilone core structure.

In conclusion, an approach to the synthesis of diverse azaphilones has been developed by employing gold(III)-catalyzed cycloisomerization of *o*-alkynylbenzaldehydes into 2-benzopyrylium salts and subsequent oxidation to form the azaphilone ring system by using IBX in conjunction with a phase-transfer catalyst. Preliminary results suggest that the azaphilones may be functionalized to afford highly functionalized vinylogous 4-pyridones. Further studies including asymmetric synthesis of select azaphilone targets and preparation of azaphilone-based chemical libraries are in progress and will be reported in due course.

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Keywords: alkynes · azaphilones · cycloisomerization · gold · Lewis acid catalysis

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[13] It is possible that gold(III) acetate may undergo ligand exchange with trifluoroacetic acid to form gold(III) trifluoroacetate. For preparation of gold(III) triflate by exchange of $AuBr_3$ with triflic acid, see: N. E. Drysdale, R. E. Bockrath, WO 9409055, **1994**.

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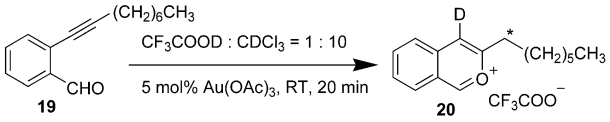

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[22] In contrast, formation of the 2-benzopyrylium salts from *o*-alkynylbenzaldehydes **31** or **32** in CF_3CO_2D (60 °C) was extremely slow and was accompanied by severe side reactions, as observed by ^{1}H NMR analysis.

[23] Control experiments revealed that acetic acid was required to buffer the benzylamine and prevent decomposition of azaphilone **21**.

[24] CCDC 219685 (**22a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

