Natural Product Synthesis

Total Synthesis of Lactonamycinone**

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In the previous Communication in this issue, we described an approach to the total synthesis of lactonamycinone (**2**), the aglycone of the antibiotic of lactonamycin (**1**). This effort culminated in a highly concise assembly of the tetracyclic intermediate **3** (see Scheme 1),[1] containing the core functionality, which, in principle, could be exploited in a total synthesis of **2**. As described herein, the first total synthesis of lactonamycinone (**2**) has now been completed. To reach our

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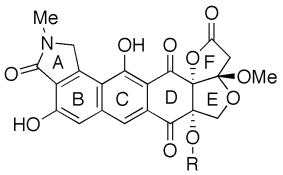
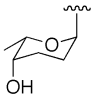
[**] This work was supported by the National Institutes of Health (Grant number: HL25848). A Postdoctoral Fellowship is gratefully acknowledged by C.C. (NIH, Grant Number F32-CA84758). The authors thank Dr. Tekeuchi of The Institute of Microbial Chemistry for kindly providing the ^{1}H NMR spectra of **33** and lactonamycin, Yashuiro Itagaki for high-resolution mass spectral analyses, and Professor Ged Parkin and Dr. David Churchill for crystallographic analysis of compound **8**.

 DOI: 10.1002/anie.200352592



1 R =

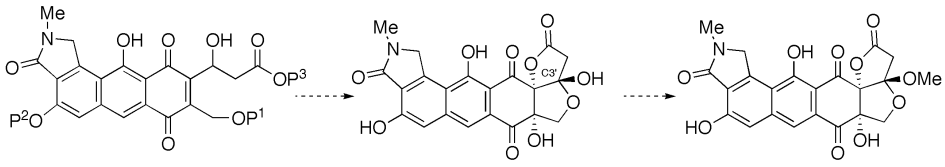


2 R = H

goal, it became necessary to devise a new end-game sequence to overcome a virtually complete breakdown of the chemistry that was workable in several model settings.[2] The new route highlights some important principles, which are likely to prove valuable in any future synthesis of lactonamycinone.

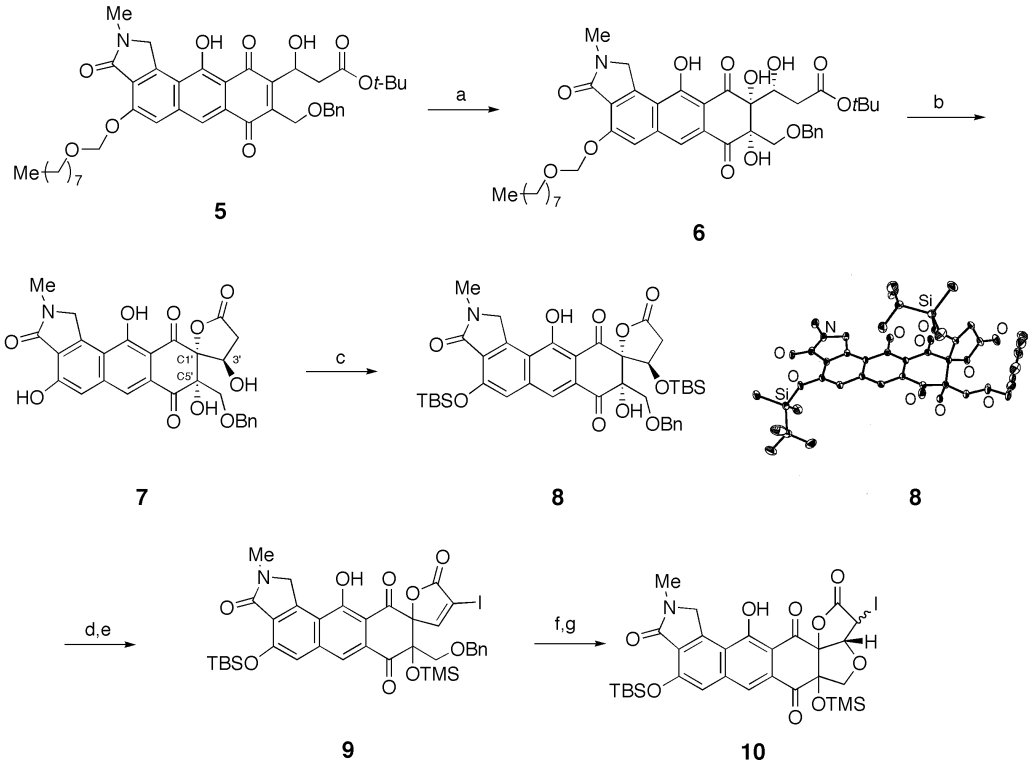
Our original strategy for constructing the E and F rings is summarized in Scheme 1 (**3**→**4**→**2**). Although the protecting groups in the ABC domain are not specified, the concept suggests progression of **3** to hemiacetal **4**. The introduction of the methyl ether at C3′ (in **2**) might involve methanolysis of a system such as **4** through oxonium formation at C3′.

The effort began with a novel and highly diastereoselective dihydroxylation of the quinone moiety of **5** with osmium tetroxide and pyridine. This reaction led to the clean formation (90% yield) of compound **6**, which incorporates the required *cis* relationship of the hydroxy groups at C1′ and C5′ (Scheme 2). The stereochemical sense of this dihydroxylation reaction follows well from Kishi's model, in which OsO_4 approaches the olefin in its lowest-energy conformer (based on minimization of the 1,3-allylic strain) from the face opposite to the hydroxy group.[3] Notably, had the C3′ alcohol been homochiral and of the required absolute configuration, the diol at C1′ and C5′ would have been installed with enantiotopic control. Treatment of **6** with TFA brought about concurrent cleavage of the octyloxymethyl acetal and of the *tert*-butyl ester linkages as well as cyclization to afford lactone **7** in 97% yield. A variety of conditions were screened to



3 **4** **2**

Scheme 1. Proposed construction of the E and F rings.

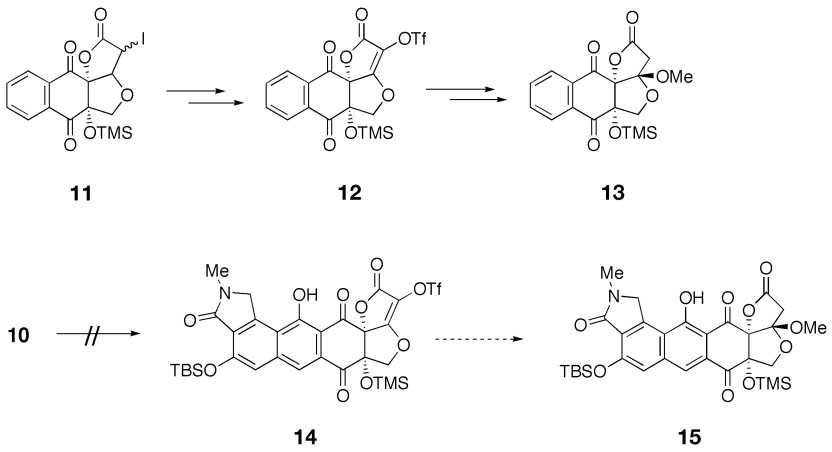


5 **6** **7** **8** **8** **9** **10**

Scheme 2. Reagents and conditions. a) 1) OsO_4, pyridine, THF; 2) $NaHSO_3$, 90%; b) TFA, CH_2Cl_2, H_2O, 97%; c) TBSOTf, 2,6-lutidine, 73%. d) LDA, TMSCl, NIS, THF, −78°C, 61%; e) Cs_2CO_3, THF, 83%; f) BBr_3, CH_2Cl_2, −78°C; g) Al_2O_3, $CHCl_3$, 65% (two steps). TFA = trifluoroacetic acid; TBS = *tert*-butyldimethylsilyl; Tf = trifluoromethanesulfonyl; LDA = lithium diisopropylamide; TMS = trimethylsilyl; NIS = *N*-iodosuccinimide.

oxidize the alcohol at C3′ to the ketolactone. As was the case in our earlier model studies,[2] all attempts were unsuccessful, The inability to execute this seemingly simple operation forced recourse to new methods to install the angular methoxy function. The "C3′" alcohol was converted into its *tert*-butyldimethylsilyl ether derivative with concomitant silylation of one of the phenolic hydroxy groups to give **8**. X-ray crystallographic analysis confirmed this structure and, accordingly, the structures of the precursors throughout the project.[4]

α-Iodination of lactone **8** was achieved through initial formation of an intermediate silyl ketene acetal (not isolated), which was treated with NIS (Scheme 2). Elimination of the β-siloxy group with Cs_2CO_3 furnished vinyl iodide **9** in 51% yield (over two steps). Deprotection of the benzyl ether followed by stirring with weakly acidic alumina yielded tetrahydrofuran **10** in 65% yield (over two steps). The complete hexacyclic ring system of lactonamycin was now in place as a mixture of iodo diastereomers. Interestingly, no intramolecular Michael addition occurs without the activation of the double bond by the iodide substituent.



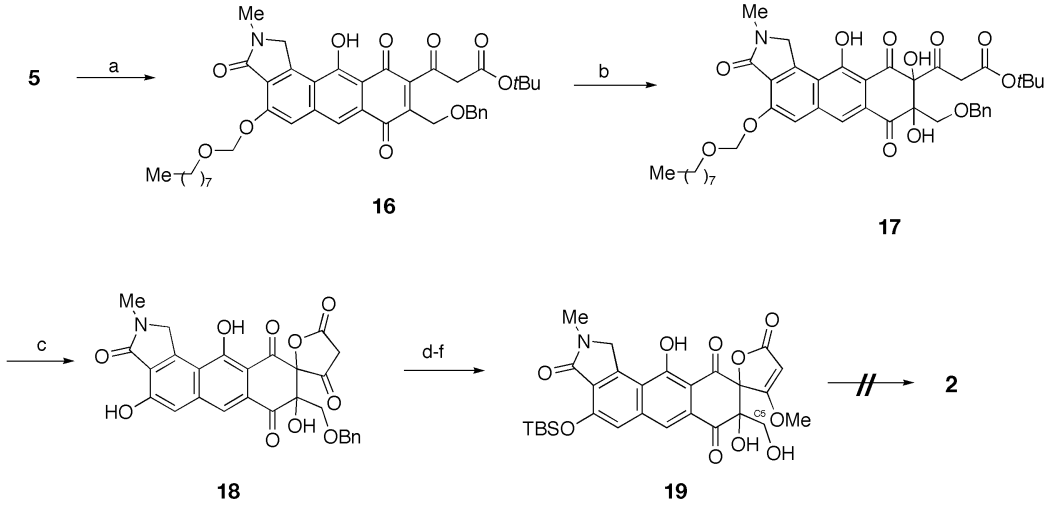
Scheme 3. Failure to adapt model studies **11**→**12**→**13** to **10**→**14**→**15**.

The total synthesis project now appeared to be almost complete. In our model studies, compound **11** had been converted into **13** through methanolysis of the strained double bond of vinyl triflate **12** (Scheme 3).[2] However, various attempts to adapt this chemistry to the case of **10** were unsuccessful. Without presently describing all these initiatives in detail, the overriding difficulty was our inability, in the hexacyclic series, to generate a junction olefin (as in **14**).

Given that the oxidation of the alcohol at C3′ was apparently not feasible at the stage of lactone **7**, it became difficult to install the angular methoxy functional group. It was decided to try to oxidize quinone **5** to the unstable ketoquinone **16** (Scheme 4). Accordingly, the oxidation was conducted with Dess–Martin periodinane[5] at the stage of **5** to afford **16** in 96% yield. Dihydroxylation was now difficult, reflecting electronic depletion of the quinone by the proximal acyl group. However, the transformation was accomplished by using osmium tetroxide coordinated to TMEDA.[6] Reductive cleavage of the osmate ester afforded **17** in 77% yield.

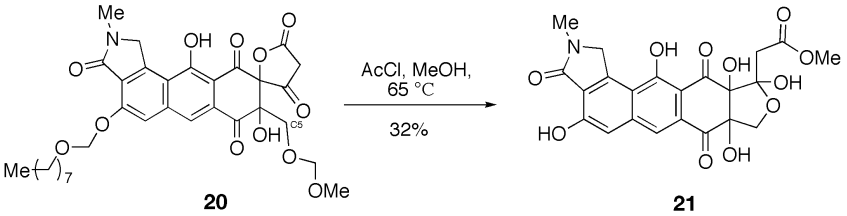
Treatment of **17** with TFA did indeed give rise to ketolactone **18** (along with variable amounts of the decarboxylated product of **18**). Unfortunately, we were unable to cleave the benzyl ether of the labile ketolactone **18**, which was required to trigger the proposed hemiacetal formation. It was found that **18** could be converted into its methyl enol ether **19** (22% over two steps).[7,8] With the added robustness of the vinylogous carbonate ensemble, came the ability to cleave the benzyl ether (see **19**). Unfortunately, all attempts at intramolecular conjugate addition, which would have delivered **2**, failed. Essentially, the vinylogous carbonate double bond in **19** had resisted Michael addition by the now liberated hydroxy group at C5. In fact, methyl tetronate is apparently rather inert to 1,4-additions under acidic conditions.[9]

Given the nonreactivity of methyl enol ether **19**, we revisited the ketolactone concept (see **4**). The main stumbling



Scheme 4. Reagents and conditions. a) Dess–Martin periodinane, CH_2Cl_2, 96%; b) 1) OsO_4, TMEDA, CH_2Cl_2, 2) HCl (1 N), $NaHSO_3$, THF, 77%; c) TFA/CH_2Cl_2, 20–55%; d) TBSOTf, 2,6-lutidine, −78 °C, CH_2Cl_2; e) $TMSCHN_2$, DIPEA, MeCN/CH_2Cl_2, 22% (two steps); f) BBr_3, CH_2Cl_2, −78 °C, 95%. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; DIPEA = *N*,*N*-diisopropylethylamine.

block in obtaining the ketolactone with a free hydroxy group at C5 had been our inability to remove the benzyl ether with the ketolactone moiety in place. As we were unable to deprotect the alcohol from its benzyl ether, it would be necessary to have the latent hydroxy group at C5 protected in an acid-labile form (**20**). Accordingly, in this connection, following protocols very similar to those described above and previously,[1] compound **20**, which contains the acid-labile MOM group on the C5 alcohol, was synthesized. Treatment of this compound with acid did indeed result in liberation of the primary alcohol by cleavage of its protecting group. However, instead of prompting cyclization to lactonamycinone (**2**), the principal product of treatment of **20** with acid in methanol was **21** (Scheme 5). Thus, the hemiacetal cyclization step that we sought had occurred, but was accompanied by opening of the lactone ring. We

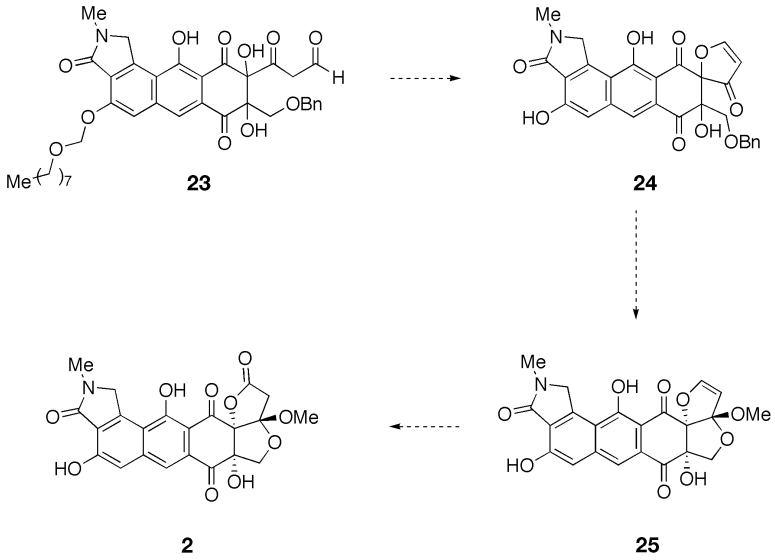


Scheme 5. Failed attempt at lactonamycinone.

cannot speak rigorously as to the timing of these events, but preliminary experiments suggest that lactone degradation precedes hemiacetal formation.

At this point, a new approach was needed to overcome the limitations encountered in the previous routes. In compound **10**, the hexacyclic ring system had been reached; however, all efforts to introduce the angular methoxy were unsuccessful. Methyl enol ether **19** contains the required methoxy functional group and the correct oxidation state at C3′, but the cyclization of the E ring did not occur, apparently due to the stable nature of the vinylogous system. Ketolactone **20** contains the functionality to cyclize the E ring with the addition of the angular methoxy group, but the lactone moiety is vulnerable to the harshly acidic conditions of the cyclization reaction.

The key departure in our new approach was the presentation of the F ring as a vinylogous butenolide **24** (Scheme 6). Given the instability of ketolactone **20**, it was hoped that the stable, structurally simpler vinylogous butenolide could function as a more durable surrogate. Moreover, since decarboxylation was a serious problem in reaching the lactone, the vinylogous butenolide would prove to be more amenable to a straightforward construction of the F ring. The hope was that methanol-induced cyclization would lead to **25**. Conversion of **25** into **2** should be straightforward, even though the oxidation state would require adjustment.



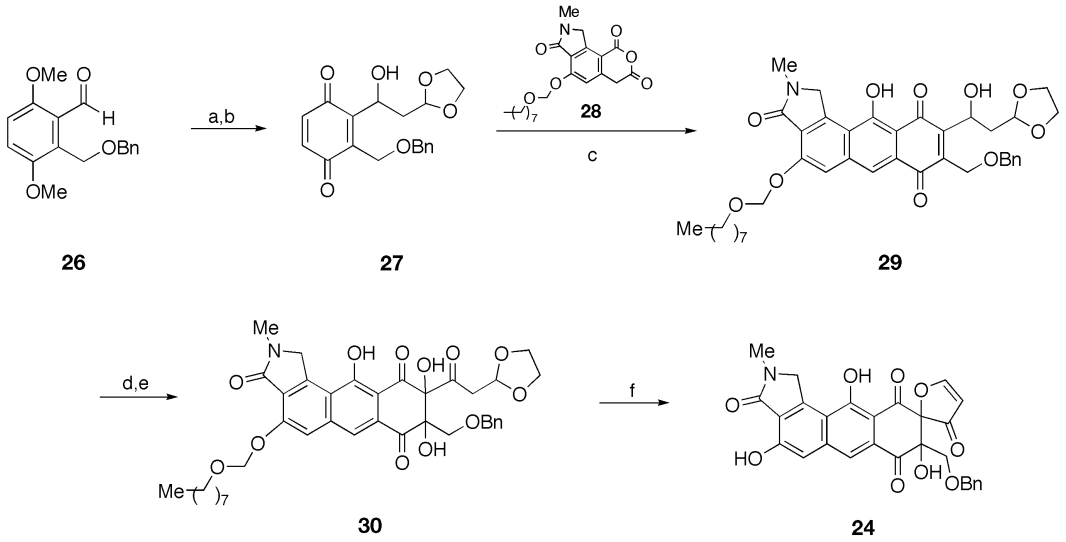
Scheme 6. Proposed new strategy to form the E and F rings.

Our campaign commenced with the addition of (1,3-dioxolan-2-ylmethyl)magnesium bromide[10] to aldehyde **26**[1] followed by oxidation to produce quinone **27** in 55% yield over two steps (Scheme 7). As described earlier, the strategic alcohol function at the future C3′ in **27** directed the Tamura reaction with the previously described homophthalic anhydride **28**,[1] thereby affording **29** in 42% yield. Subsequent oxidation followed by dihydroxylation afforded **30** (89%, two steps). With diol **30** in hand, treatment with aqueous HCl (3N) led to deprotection of the octyloxymethyl ether with concomitant intramolecular attack of the tertiary alcohol at the proximal acetal to afford butenolide **24** in 82% yield.

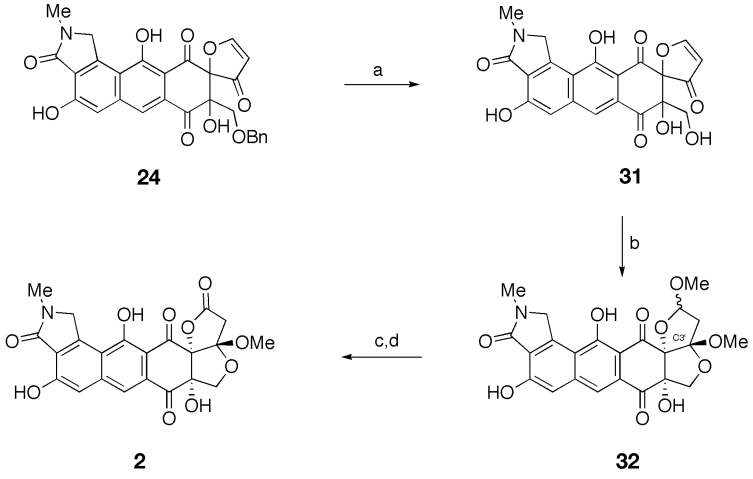
Deprotection of the benzyloxy ether produced the pivotal intermediate **31** (Scheme 8). Gratifyingly, when this compound was heated at reflux with HCl/dioxane/methanol, acetal **32** was obtained in 51% yield (over two steps, based on recovered starting material). Hydrolysis of **32** gave rise to an anomeric mixture of lactols in quantitative yield, with the C3′ methoxy group intact.

During the planning stages of the new strategy, the task of oxidizing a lactol to a lactone seemed straightforward. Unfortunately, what had initially been anticipated to be an uneventful oxidation turned out to be anything but routine. After a systematic survey of many oxidants, it was discovered that only TEMPO[11]-mediated oxidation was able to complete the transformation to lactonamycinone (**2**) (58% yield). The ^{1}H and ^{13}C NMR spectra of the synthetic aglycone of lactonamycin were similar to those of the natural product, lactonamycin, which bears the carbohydrate attachment.[12] Conclusive comparison data came from the identical NMR spectra of synthetic peracetylated lactonamycinone **33** and naturally derived peracetylated lactonamycinone, kindly provided by Tekeuchi and co-workers.

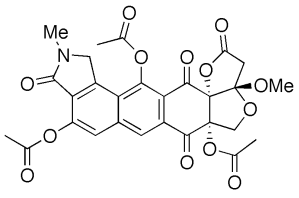
In the total synthesis of lactonamycinone, it was found that there was considerable kinetic resistance to fashioning a



Scheme 7. Reagents and conditions. a) (1,3-dioxolan-2-ylmethyl)-magnesium bromide, LiBr, THF, reflux, 69%; b) CAN, 0°C, CH_3CN/H_2O (1:1), 80%; c) NaH, **28**,[1] THF, 42%; d) Dess–Martin periodinane, CH_2Cl_2, quantitative; e) 1) OsO_4, TMEDA, CH_2Cl_2, 2) HCl (1 N), $NaHSO_3$, THF, 89%; f) HCl (3 N), acetone/THF, reflux, 82% (based on recovered starting material).



Scheme 8. Reagents and conditions. a) BBr_3, CH_2Cl_2, −78°C, b) HCl (4.0 N), dioxane/MeOH, 65°C, 51% (two steps, based on recovered starting material); c) HCl (1 N)/THF, quantitative yield; d) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, 58%.
TEMPO = 2,2,6,6 tetramethyl-1-piperidinyloxy free radical.



full hexacyclic system by closure of the tetrahydrofuran E ring at C3′ in a reversible reaction. A dihydrofuranone was used to overcome this problem. This allowed us to craft a setting for closure, by which concurrent methanolysis at C3′ caps the reaction in the "forward" sense (see formation of compound **32**). Clearly, there is much still to be learnt about the origins of the resistance to formation of this hexacyclic array at the ring F lactone level of oxidation.

It is tempting to conjecture that, with such understanding, could come valuable insight into the role of this novel ring system in the biological function of the antibiotic itself. Although some yield issues must be overcome,[1] and a scheme for an enantiocontrolled synthesis implemented, the conciseness of the present synthesis will be of great advantage in dealing with these problems.

As we address these challenges, we also plan to generalize the concept of using proximal intramolecular catalytic devices to differentiate closely balanced functional groups.[1] The ability to distinguish between cognate functions in a multifunctional setting is surely one of the continuing challenges of organic synthesis.

Received: August 7, 2003 [Z52592]

Keywords: antibiotics · Diels–Alder reaction · natural products · quinones · total synthesis

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[4] CCDC-216742 (**8**) 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 Cam-

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