DOI: 10.1002/ejoc.200700854

Unusual Magnesium Chloride Catalyzed Non-Evans *anti*-Aldol Reactions of an Enolizable L-Threose Derivative

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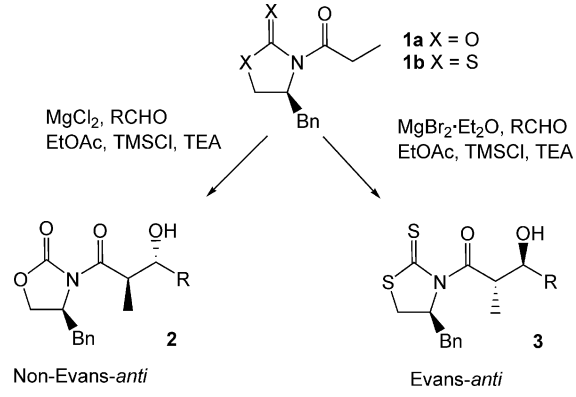
Keywords: Aldol reactions / Synthetic methods / Diastereoselectivity / Natural products

The magnesium chloride catalyzed *anti*-aldol reaction of phenyl acetate derived oxazolidinones proceeds readily with enolizable L-threose derivative **8** to provide *anti*-aldol adducts in high yields and with very high diastereoselectivities. The reaction is also efficient with aromatic aldehydes and provides slightly lower diastereoselectivities. This extension allows access to stereochemically defined fragments applicable to the synthesis of alkaloid and phenylpropanoid derivatives.

Introduction

The directed aldol reaction is widely recognized as one of the most powerful carbon–carbon bond forming reactions available for the regio-, diastereo-, and enantioselective construction of complex intermediates.[1] Despite recent advances in organocatalytic routes to asymmetric aldol reactions,[2] auxiliary-based approaches remain steadfast as a principle means to achieve high yields of aldol adducts with reliably high stereocontrol. Of these, the Evans' oxazolidinones and their sulfur analogs are most reliable in stereocontrolled *syn*-aldol reactions,[3] whereas the Abiko–Masamune norephedrine-based auxiliary is perhaps the most dependable route to *anti*-aldol adducts.[4] In general, *syn*-aldol adducts are readily accessed through a variety of methods, whereas efforts to achieve enantioselective *anti*-aldol reactions are still actively sought.[5]

Most auxiliary-based aldol reactions require the stoichiometric addition of a metal salt (B, Ti, Si, etc.) to form the required enolate derivative.[1] Recently, Evans and coworkers reported the first examples of metal-catalyzed aldol reactions by using both standard[6a] oxazolidinone **1a** and thiazolidine thione[6b] **1b** based auxiliaries. The addition of a magnesium halide (0.1–0.2 equiv.) to a 0.5 M ethyl acetate (EtOAc) solution of the auxiliary (1.0 equiv.) and aldehyde (1.2 equiv.) in the presence of triethylamine (TEA) and trimethylsilyl chloride (TMSCl) yielded non-Evans **2** and Evans *anti*-aldol adducts **3** in high yield and with high selectivity (Scheme 1).[7] This potentially valuable *anti*-aldol route was shown to be restricted to nonenolizable aldehydes under these conditions.



Scheme 1. Magnesium halide catalyzed *anti*-aldol reactions.

We have been engaged in an on-going project to identify and probe the anticancer pharmacophore contained within the pancratistatin series of Amarillidaceae alkaloids exemplified by pancratistatin and its 7-deoxy analog **4** (Scheme 2).[8,9] These compounds initiate apoptosis selectively in various human tumor cell lines through a mechanism currently being elucidated in our laboratories.[8] Recent work[9] has established that the minimum structural requirements for potent anticancer activity consist of a 2,3,4-triol-functionalized ring-C[9a] moderated significantly through inclusion of a β-benzyloxy substituent at position C1,[9b] as depicted in **5** (Scheme 2). In part, we were attracted to an Evans–Ivanoff strategy as a potential means of introducing two key stereocenters that might allow for further elaboration to both **4** and **5**.

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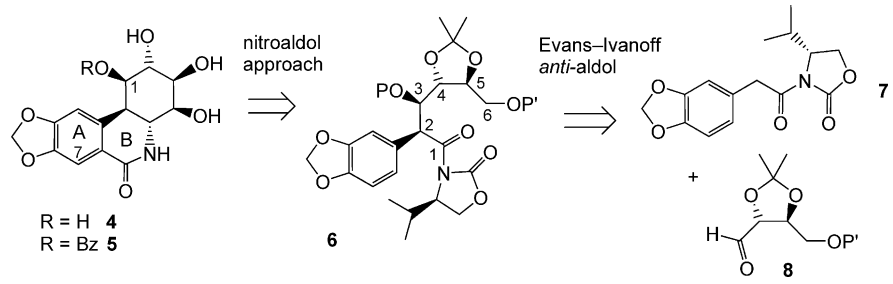
Supporting information for this article is available on the WWW under http://www.eurjoc.org/ or from the author.



Scheme 2. Retrosynthetic analysis of 7-deoxypancratistatin **4**.

The Ivanoff reaction of magnesium carboxylate derived enolates (magnesium ketene acetals) has previously been documented to favor *anti*-aldol reactions through induced stereoselectivity, most likely as a consequence of (*E*)-enolate geometry.[10] Surprisingly, few reports involving the use of phenyl acetate derived auxiliaries have previously been documented in aldol chemistry,[11] despite obvious applicability in the alkaloid field through elaboration of derived chiral β-arylethylamine derivatives. Hence, despite the report that enolizable aldehydes are not general participants in Evans MgX_2-catalyzed crossed-aldol-type processes, the combination of the Ivanoff reactivity in conjunction with these potential applications prompted us to investigate this reaction as a means of accessing stereochemically defined fragments of relevance to both alkaloid and phenylpropanoid[4b] synthesis.

Results and Discussion

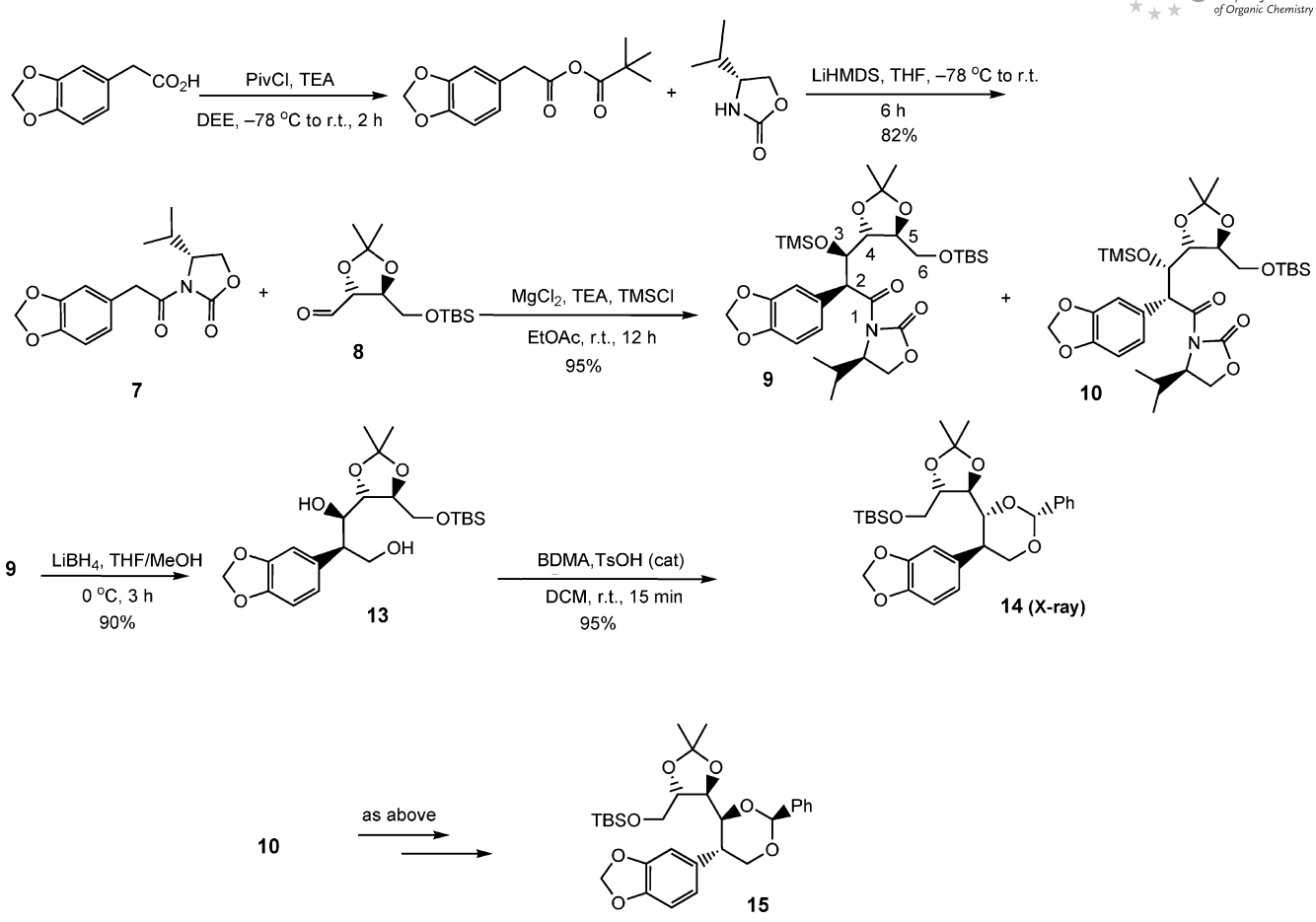
In our retrosynthetic analysis (Scheme 2), a non-Evans *anti*-aldol reaction of methylenedioxy functionalized phenyl acetate derived auxiliary **7** with L-threose chiron **8** (derived from L-tartaric acid) would generate adduct **6**, which is suitably functionalized for elaboration to **4** and **5**. Previous reports on nucleophilic addition to this and related aldehydes indicate that the wrong stereochemistry would be attained through intrinsic diastereoselectivity, and the results explained are in accord with the Felkin–Anh model.[12] In this communication we report the remarkable success of the required *anti*-selective aldol reaction catalyzed by magnesium halides and demonstrate the overriding stereochemical directing effect of the auxiliary.

The overall aldol strategy is outlined in Scheme 3. The necessary phenyl acetate auxiliary **7** was prepared by using standard methods as shown. The aldol addition of **7** to L-tartaric acid derived threose derivative **8** proceeded under Evans' conditions to yield adducts **9** and **10** in a ratio of 95:5 and to our surprise in 98% isolated yield. The reaction was repeated on numerous occasions without incident and was conducted on a 10.0-g scale. The aldol adducts were readily separable by silica gel chromatography. The stereochemistry of adduct **9** was proven to be the expected non-Evans' *anti* diastereomer through reductive removal of the auxiliary to give diol **13**, followed by a subsequent reaction with benzaldehyde/dimethylacetal (BDMA) to yield crystalline benzylidene **14**. X-ray structural determination of **14** confirmed the relative and absolute stereochemistry as shown (Figure 1).

The selective formation (95:5) of stereochemically proven *anti*-aldol adduct **9** is of interest, as it indicates that the facial selectivity of the auxiliary has an over-riding influence on the stereochemical outcome of this reaction and any Felkin–Anh bias on the part of the aldehyde is overcome. Minor adduct **10** from this reaction appeared to be the Evans *anti* adduct through NMR spectroscopic analysis. Reductive removal of the auxiliary from **10** and its reaction with BDMA as above provided diastereomeric benzylidene **15** (Scheme 3).

In order to asses the degree of match/mismatch in the forgoing aldol reaction, the reaction of *ent*-**7** with **8** was investigated under the same conditions. This reaction (Scheme 4) also proceeded efficiently to give non-Evans *anti* adduct **11** as a single stereoisomer in near quantitative yield, and possible *anti*-aldol **12** was not detected in the reaction mixture. Major adduct **11** was treated as before to give diol **16** and then converted into benzylidene **15**, which was identical to that obtained from the minor adduct in the first series. The small mismatch in the former reaction confirms that the auxiliary contributes the over-riding stereodirecting effect on the reaction and that stereoelectronic effects on the part of the aldehyde play only a minor role in diastereoselection.

The most surprising issue in the foregoing aldol reactions is the *efficiency* of the reaction conducted under these conditions with an enolizable aldehyde. We readily confirmed that enolizable aliphatic aldehydes suffer from low conversion as noted by Evans et al.[6a] In fact, acetonide-protected D-glyceraldehyde **17** (Scheme 5) was the only other aldehyde identified that provided reasonable yield of adduct under these conditions.[13] Slow addition of this aldehyde to *ent*-**7** as before provided **18** in 20% yield as the product of the non-Evans *anti*-aldol reaction (90:10 ratio of **18** to Evans *anti* diastereomer). In this reaction, aldehyde **17** was fully consumed and significant portions of imide *ent*-**7** remained, which indicated that enol ether formation or homo-aldol condensation of **17** was an issue.



Scheme 3. Slight mismatched *anti*-aldol reaction.

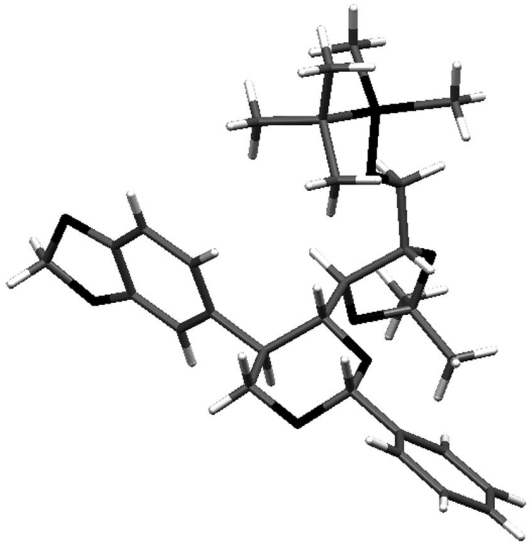
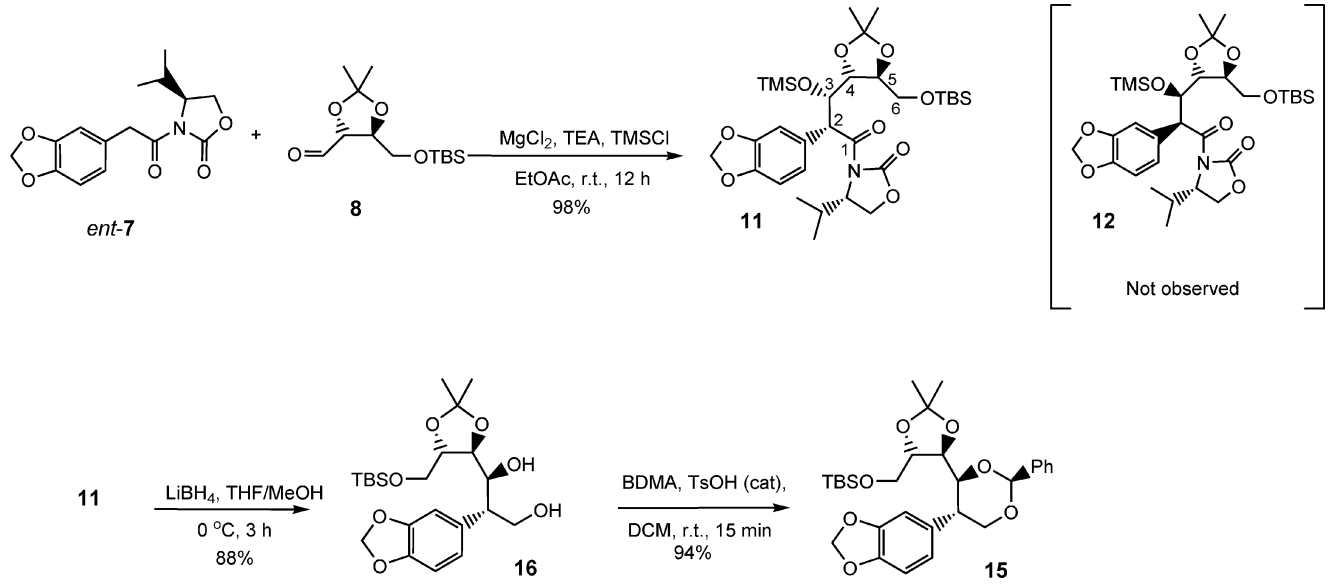


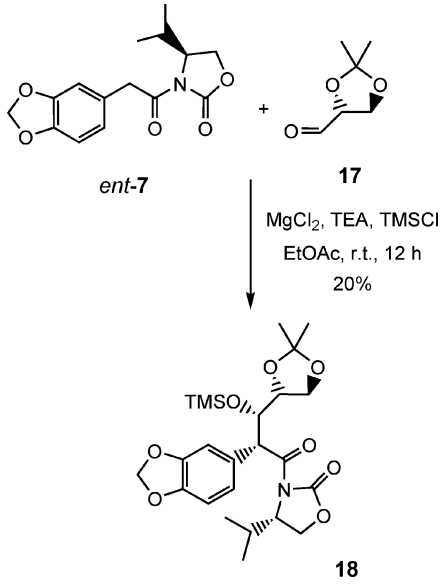
Figure 1. X-ray structure of **14**.

Conformational analysis of the successful aldehyde participants, **8** and **17**, revealed that the enhanced aldol reactivity may be attributed to electronic effects in conjunction with steric crowding around the α-hydrogen, which would be expected to lower the rate of enolization relative to that of aldolization.

The overall results can be explained empirically through changes in the relative rates of these two competitive processes as a result of the contributing conformational and electronic effects. The model shown in Figure 2 depicts aldehyde **8** in its presumed most reactive conformation, incorporating modified Cornforth[14a] (dipole moment minimization on α-alkoxy[14c,14d] aldehydes) and open-chain[14b] (i.e. nonchelation) elements. It is readily apparent that one of the methyl groups of the acetonide is in spatial proximity to the α-hydrogen. This is also the case for aldehyde **17**. Furthermore, in aldehyde **8**, the α-hydrogen is further shielded through an almost *syn*-periplanar relationship to the very bulky C3 to C4 CH_2-OTBS (bold) substituent. Thus, as the expected (*Z*)-magnesium enolate[11d] of **7** or *ent*-**7** approaches the carbonyl in these sterically α-congested aldehydes, aldolization may effectively compete with α-deprotonation in these specific cases. The high yields of aldol product and minor match/mismatch results reported in the reaction of **7** and *ent*-**7** with **8** indicates aldolization to be the preferred mode of reactivity of **8** irrespective of *Si* or *Re* approach of the nucleophile on the aldehyde as controlled by the auxiliary.[6]



Scheme 4. Matched *anti*-aldol reaction.



Scheme 5. *anti*-Aldol reaction of 2,3-acetonide-protected glyceraldehyde.

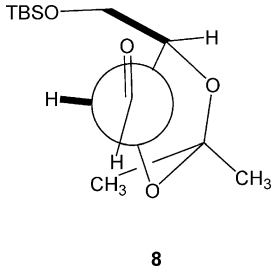
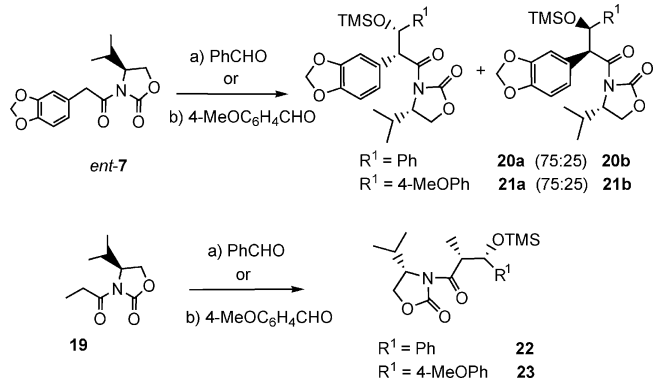


Figure 2. Newman projection of aldehyde **8**.

The successful phenyl acetate derived adducts and derivatives **9**, **11**, **13**, **14**, **15**, and **16** should prove to be of value in natural product synthesis as described in the introduction. In this regard, we were also driven to investigate the use of phenyl acetate derivative *ent*-**7** and propanoyl derivative **19** as a potential asymmetric entry to phenylpropanoids and related derivatives.[4b] As shown in Scheme 6, the reaction of *ent*-**7** with benzaldehyde or anisaldehyde proceeded readily under the standard conditions to give adducts **20a**,**b** and **21a**,**b** in good yields but slightly lower diastereoselectivities. Major adduct **20a** was proven to be non-Evans *anti* though single-crystal X-ray structural determination (Figure 3).[15]



Scheme 6. *anti*-Aldol reactions with aromatic aldehydes.

In contrast, the reactions of aliphatic imide **19** with aromatic aldehydes (benzaldehyde and anisaldehyde, Scheme 6) proceeded in high yields and with high diastereoselectivities, similar to the benzyl oxazolidinones,[6a] to provide *anti*-aldols **22** and **23**. Again, the major product proved to be non-Evans *anti* diastereomer **23** as depicted in Figure 4 (X-ray). These results show that in addition to yield, the diastereoselectivity also depends considerably on both the structure of the aldehyde and the nature of the donor group on the part of the auxiliary.

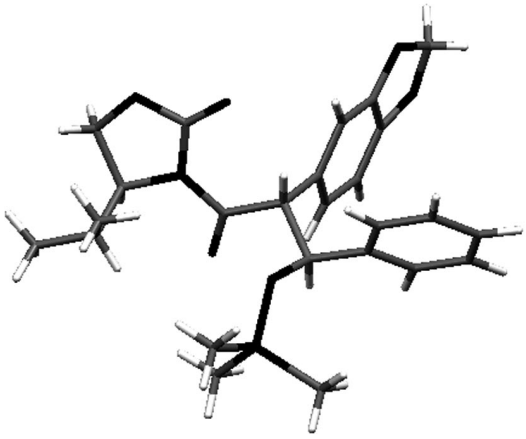


Figure 3. X-ray structure of **20a**.

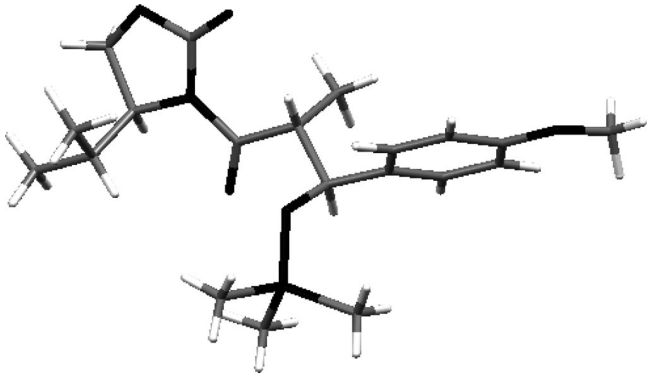


Figure 4. X-ray structure of **23**.

Conclusions

The magnesium halide catalyzed non-Evans *anti*-aldol reaction of phenyl acetate derived oxazolidinones was extended to aromatic aldehydes and conformationally restrained aldehydes having hindered α-hydrogen atoms. Application of this successful *anti*-aldol process towards the synthesis of anticancer alkaloids and phenylpropanoids is now in progress. Further work to explore the reactivity of aldehydes such as **8** in this reaction with achiral enolates under nonchelation conditions is also underway.

Supporting Information (see footnote on the first page of this article): Full procedures and spectroscopic data, selected ORTEP and packing diagrams.

Acknowledgments

We thank NSERC and the Lotte and John Hecht Memorial Foundation for financial support.

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[13] See ref.[6a] footnote 13. A series of aliphatic and α-substituted aldehydes (such as 2-benzyloxyacetaldehyde, Garner aldehyde) did not provide any identifiable crossed-aldol adduct. The use of other solvents (EtOAc, THF, DCM, PhMe), bases, silylating agents TMSCl, TMSOTf, $(TMS)_2O$, etc.], metal salts [$MgCl_2$, $MgBr_2$, MgI_2, $Mg(OTf)_2$, $Yb(OTf)_3$, etc.], modifications to the order of reagent addition or slow addition of aldehyde, and so on also failed to promote the reaction in other cases.
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[15] CCDC-654288 (for **14**), -654286 (for **20a**), and -654287 (for **23**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallography Data Centre via www.ccdc.cam.ac.uk/data_requestcif.html.

Received: September 11, 2007
Published Online: October 16, 2007

