



Synthesis of multifunctionalized building blocks via vinylogous addition of Chan's diene to carbonyl and carbonyl-related electrophiles, mediated by molecular iodine

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ABSTRACT

The synthesis of multifunctionalized β -ketoesters has been achieved by using molecular iodine as a catalyst under very mild conditions. The vinylogous addition of Chan's diene **1** to carbonyl and carbonyl-related compounds (aldehydes, ketones, imines and acetals) occurred with high efficiencies and with complete γ -selectivity, giving a useful method for the synthesis of interesting libraries of different δ -functionalized β -ketoesters.

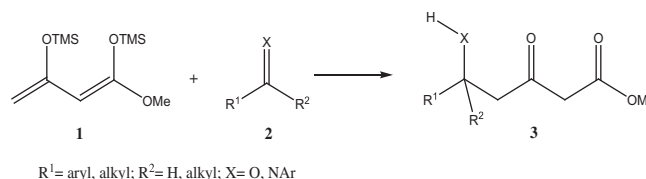
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1. Introduction

The vinylogous aldol addition of Chan's diene **1** is one of the most elegant and powerful methods for the synthesis of δ -hydroxy- β -ketoesters,² molecules containing a C-5 highly functionalized fragment (**3** with $R^2=H$ and $X=O$, Scheme 1), which are useful key-intermediates in the synthesis of many complex natural products.³ Consequently, the development of more efficient and competitive methodologies for their synthesis is of great importance.⁴

On the other hand, the number of known protocols of the reaction that can be extended from aldehydes to other carbonyl and carbonyl-related electrophiles with good results is very limited,^{1c,2c,5} so the development of more efficient and general conditions for the synthesis of libraries of compounds **3**, with different R^1 , R^2 and X (Scheme 1), is an extremely interesting research area.

Lewis acids, such as $TiCl_4$ or BF_3OEt_2 were often used as promoters in the vinylogous aldol addition but these methods always require harsh and strictly controlled reaction conditions (dry solvents and reagents, inert atmosphere, stoichiometric amounts of Lewis acids, very low temperatures).² Moreover, poor results were



Scheme 1. Synthesis of libraries of δ -functionalized β -ketoesters by vinylogous addition of Chan's diene **1**.

often obtained by using these activators in the presence of electrophiles other than aldehydes.

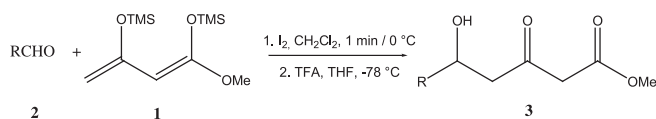
Recently, molecular iodine has been used in many organic transformations⁶ and, even though its catalytic action has not been completely investigated from a mechanistic point of view,⁷ its mild Lewis acidity makes this system compatible with a lot of different substrates. In a recent paper,⁸ iodine was proposed as a very efficient catalyst for Mukaiyama aldol addition of 2-(trimethylsilyloxy)furan to several aromatic and aliphatic aldehydes. Compared to other catalysts, iodine presents many advantages including that it is very inexpensive, has low toxicity and is readily available; moreover, short reaction times and operative simplicity (no special precautions in order to exclude air and moisture from the system are required) make iodine-mediated procedures particularly convenient.

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Here we report an efficient approach for the addition of Chan's diene to aldehydes by using molecular iodine as catalyst, under very mild reaction conditions. The same reaction conditions, optimized for aldehydes, were applied to other carbonyl and carbonyl-related electrophiles with the production of a library of interesting scaffolds.

2. Results and discussion

In a model study, benzaldehyde **2a** and Chan's diene **1** in CH_2Cl_2 solution were stirred at 0°C in the presence of a catalytic amount of molecular iodine (10%) (Scheme 2). Quantitative conversion was observed after only 1 min and, more importantly, after the desilylation procedure the vinylogous aldol **3a** was isolated in 95% yield (Table 1, entry 1), indicating that the process occurs with complete γ -selectivity in spite of the presence of two reactive nucleophilic sites.⁹ No improvements were observed in the reaction outcome by using increased catalyst loading (up to 25%) or more prolonged reaction times (up to 3 h).



Scheme 2. Vinylogous addition of Chan's diene **1** to aldehydes **2**.

Table 1
Vinylogous addition to aldehydes via Scheme 2

Entry ^a	Aldehyde	2	Product	Yield 3 % ^b
1	PhCHO	2a	3a	95
2	<i>p</i> MeO–C ₆ H ₄ CHO	2b	3b	99
3	<i>p</i> NO ₂ –C ₆ H ₄ CHO	2c	3c	90
4	<i>o</i> NO ₂ –C ₆ H ₄ CHO	2d	3d	95
5	<i>p</i> CF ₃ –C ₆ H ₄ CHO	2e	3e	89
6 ^c	<i>p</i> F–C ₆ H ₄ CHO	2f	3f	41
7	<i>p</i> F–C ₆ H ₄ CHO	2f	3f	99
8	2-FuCHO	2g	3g	79
9	PhCH=CHCHO	2h	3h	97
10	CH ₃ (CH ₂) ₉ CH ₂ CHO	2i	3i	70

^a In all entries 1/2/0.1 aldehyde/diene/iodine ratio was used.

^b All the yields refer to isolated chromatographically pure compounds, whose structures were assigned by analytical and spectroscopic data.

^c In this entry 1/1.5 aldehyde/diene ratio was used.

In order to demonstrate the generality of these reaction conditions, a variety of aldehydes were reacted with Chan's diene under the optimized experimental conditions (Table 1, entries 2–10). It is notable that high yields and no side products were obtained with different classes of aldehydes. In fact, as shown in Table 1, variously substituted aromatic aldehydes (entries 1–7) as well as hetero-aromatic (entry 8) and α,β -unsaturated substrates (entry 9) could react with Chan's diene to give, after the desilylation procedure, δ -hydroxy- β -ketoesters of type **3** in good to excellent yields. Furthermore, the result reported in entry 10 is particularly intriguing since the addition of masked acetoacetic esters to aliphatic aldehydes, according to known procedures, often takes place with low

efficiency. Moreover, a 1/2 aldehyde/Chan's diene ratio seemed to be the key for high efficiency (compare entries 6 and 7, Table 1).

These results are particularly interesting also because, in the absence of electrophiles and under the typical reaction conditions (CH_2Cl_2 , 0°C , 1 min), molecular iodine caused the complete decomposition of Chan's diene leading to a very complex mixture of products, confirming that the addition to electrophiles is much faster than other competing processes.

The versatility of this methodology was demonstrated by evaluating the reactivity of N-containing electrophiles, particularly imines, under the same reaction conditions, leading to the achievement of a new protocol for the vinylogous Mannich addition of Chan's diene.^{10,11}

In the initial phase, a one-pot approach was attempted by using imines synthesized in situ according to a known procedure¹⁰ (Scheme 3, Table 2, entries 1 and 3). Therefore, aldehydes **2a** and **2b**, chosen as representative substrates, were submitted to reaction with aniline **5** for 1 h at room temperature in the presence of silica gel and anhydrous 3 Å molecular sieves (MS). Then, in the same vessel the resulting imines were directly reacted with Chan's diene **1** under the usual conditions, as reported in Scheme 3 and Table 2. Notably, the formation of the expected adducts **6a,b** was found to take place albeit in moderate yields. However a control experiment, carried out on **2a** by omitting the addition of Chan's diene **1**, indicated the occurrence of significant decomposition of the imine to the corresponding aldehyde, so that, after 1 min at 0°C a mixture 45/55 aldehyde/imine was recovered. Therefore, bearing in mind that both the catalytic properties of I_2 and the stability of Chan's diene **1** could be negatively influenced by the presence of molecular sieves/silica gel system, the experiments of entries 1 and 3 (Table 2) were repeated, first removing the solid phase by rapid filtration, and then adding **1** and I_2 . This simple modification of the original protocol allowed the attainment of the corresponding products **6a,b** in significantly higher yields (entries 2 and 4). The procedure proved to be successful with other aromatic and α,β -unsaturated aldehydes (entries 5,6) while the aliphatic derivative **2i** was completely unreactive (entry 7).

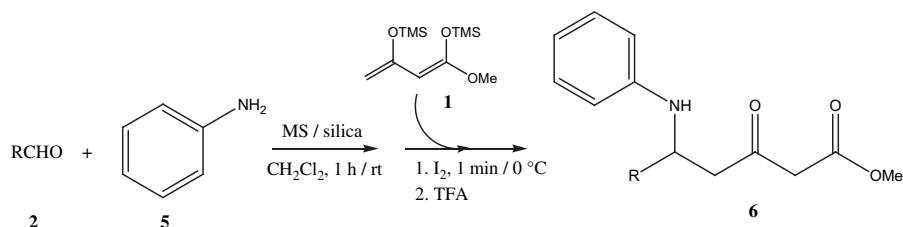
Table 2
Vinylogous addition to imines via Scheme 3

Entry	R-CHO	2	Product	Yield 6 % ^a
1	Ph	2a	6a	59
2 ^b	Ph	2a	6a	80
3	<i>p</i> MeO–C ₆ H ₄	2b	6b	66
4 ^b	<i>p</i> MeO–C ₆ H ₄	2b	6b	84
5 ^b	<i>p</i> NO ₂ –C ₆ H ₄	2c	6c	90
6 ^b	PhCH=CH	2h	6h	96
7 ^b	CH ₃ (CH ₂) ₉ CH ₂	2i	6i	ND

^a All the yields refer to isolated chromatographically pure compounds, whose structures were assigned by analytical and spectroscopic data.

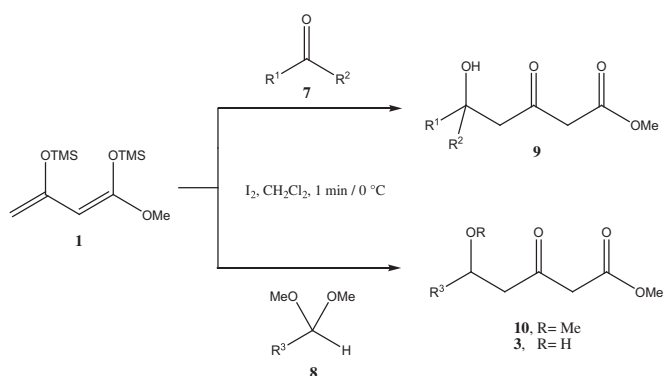
^b In this entry molecular sieves and silica were removed before adding I_2 and Chan's diene.

In our opinion, these results are of particular synthetic value because we have realized a very efficient methodology for the direct synthesis of a series of δ -amino- β -ketoesters, by using a one-pot approach, which is particularly appropriate for the diversity-oriented synthesis.



Scheme 3. Vinylogous addition of Chan's diene **1** to imines synthesized in situ according to a known procedure.¹⁰

Encouraged by these findings, we examined the behaviour of other two classes of milder electrophiles, that is, ketones and acetals, which have often proven to be unreactive under the conditions suitable for aldehydic substrates (Scheme 4).



Scheme 4. Vinylogous addition of Chan's diene **1** to ketones **7** and acetals **8**.

As summarized in Fig. 1, both ketones and acetals exhibited high reactivity under the typical conditions, resulting in the very efficient and exclusive formation of γ -vinylogous aldol-type products and confirming the significant catalytic versatility of molecular iodine.

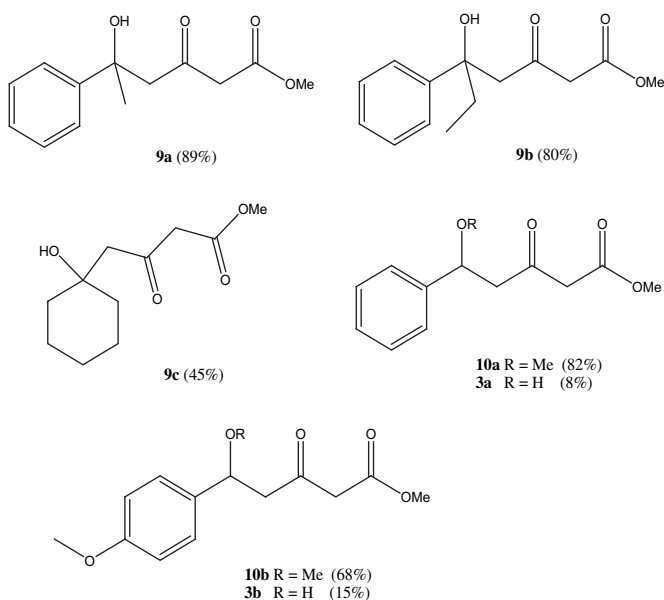


Fig. 1. Synthesis of products **9** and **10** by vinylogous addition of Chan's diene **1** to ketones and acetals. All the yields in parentheses refer to isolated chromatographically pure compounds.

In particular, ketones seemed to be particularly intriguing electrophiles for the possibility to introduce a quaternary carbon in the scaffold (**9a–c**, Fig. 1). It has to be noted that, in the case of employment of cyclohexanone as starting material of type **7**, the modest yield (45%) can be attributed to a partial decomposition of aldol **9c** on silica gel via retro-aldol reaction.

Furthermore, as regards acetals **8**, the usual protocol proved to be appropriate to circumvent the main difficulty represented by the well-known instability of acetals in the presence of iodine.¹² In fact, a control experiment, carried out on *p*-methoxy-benzaldehyde dimethyl acetal **8b** in the absence of Chan's diene, (CH_2Cl_2 solution, 0°C , I_2) indicated the fast and quantitative regeneration of the aldehydic functionality after 1 min. Nevertheless, under the typical

conditions, the vinylogous addition of **1** to acetals **8** proved to be much faster than other competing processes, allowing a very efficient approach to δ -alkoxy- β -ketoesters, while aldehydes **2a,b**, generated by the I_2 -mediated decomposition of the starting materials **8a,b**, could afford the corresponding vinylogous aldols **3a,b** in rather poor yields.

These latter results were particularly interesting; in fact, a careful screening in the literature highlighted how the availability of efficient methodologies for the vinylogous addition of dienoxysilanes to acetals was very limited and usually very strong Lewis acids (as TiCl_4 , SnCl_4 or ZnCl_2) and very controlled experimental conditions were necessary in order to have good yields.^{2,13} In this context, only a few examples concerned the employment of Chan's diene but generally the acetalic function was in a more complex structure (α -haloacetals, 2,5-dimethoxytetrahydrofuran, etc.), so that, after the preliminary γ -addition of the diene, a rapid in situ evolution of intermediates (usually by involving α -position of **1**) was observed.^{1c,14}

3. Conclusion

In conclusion, molecular iodine was found to be an efficient catalyst for the vinylogous addition of Chan's diene to several carbonyl and carbonyl-related electrophiles, under very mild conditions and without side-products formation. This methodology is very competitive because it is simple, fast, quite cheap and very efficient and the reagents used have low toxicity. Moreover, thanks to iodine properties, no particular operational precautions are necessary.

Finally, the generality of this method and the possibility to extend the experimental conditions from aldehydes to other carbonyl-related electrophiles (ketones, imines and acetals) make this strategy potentially useful in order to access to a library of structurally diversified compounds, which could be appropriate for drug discovery.

4. Experimental section

4.1. General

All reactions were performed in oven-dried (140°C) vials. Thin-layer chromatography was performed on Merck Kiesegel 60 F₂₅₄ plates eluting with the solvents indicated, visualized by a 254 nm UV lamp and aqueous ceric sulfate solution. Column chromatographic purification of products was carried out using silica gel 60 (70–230 mesh, Merck). All reagents (Aldrich and Fluka) were used without further purification. Infrared spectra were recorded on a Bruker 22 series FT-IR spectrometer. NMR spectra were recorded on a Varian 400 (400.135 MHz for ^1H and 100.03 MHz for ^{13}C) spectrometer. ESI-mass spectra are reported in the form of m/z .

4.2. Typical procedure for the iodine-catalyzed vinylogous addition to aldehydes

To a solution of iodine (10 mol %, 0.025 mmol) in CH_2Cl_2 (1 mL), aldehyde **2** (0.25 mmol) was added. The mixture was cooled at 0°C and diene **1** (2 equiv, 0.50 mmol) was added. The mixture was stirred at this temperature for 1 min, then the reaction was quenched with aqueous sodium thiosulfate solution to remove iodine and extracted with CH_2Cl_2 . Evaporation of the solvent, followed by desilylation according to Carreira's protocol^{4k} and purification on silica gel (ethyl acetate/hexane) afforded pure δ -hydroxy- β -ketoesters **3**. The spectroscopic data of aldols **3a**,^{4f} **3b**,^{4f} **3c**,^{4f} **3d**,^{4c} **3e**,¹⁵ **3f**,^{4e} **3g**^{4e} and **3h**^{4f} matched the ones reported in the literature.

4.2.1. Methyl 5-hydroxy-3-oxohexadecanoate (**3i**). Pale yellow oil. R_f 0.5 ($\text{Et}_2\text{O}/\text{CHCl}_3$ 1/9); HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{33}\text{O}_4$ [$\text{M}+\text{H}$]⁺:

301.2379, found: 301.2368; ν_{\max} (liquid film) 1740, 1616, 1514, 1378, 1106 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.09–4.03 (m, 1H), 3.75 (s, 3H), 3.49 (s, 2H), 2.73 (dd, 1H, $J=3.3$, 17.4 Hz), 2.64 (dd, 1H, $J=8.8$, 17.4 Hz), 1.51–1.25 (m, 20H), 0.88 (t, 3H, $J=6.8$ Hz). ^{13}C NMR δ 203.6, 167.4, 67.5, 52.4, 49.6, 36.5, 31.9, 29.62, 29.59, 29.55, 29.53, 29.47, 29.3, 25.4, 22.6, 14.1.

4.3. Typical procedure for the iodine-catalyzed vinylogous addition to imines

In a dry vial silica gel (90 mg), 3 Å molecular sieves (89 mg, activated by heating under the atmosphere at 120 °C for at least 48 h), CH_2Cl_2 (0.2 mL), aldehyde **2** (1 equiv, 0.125 mmol) and aniline (1 equiv, 0.125 mmol) were added. The resulting mixture was stirred for 1 h at room temperature, then it was cooled at 0 °C and after few minutes a solution of iodine (10 mol %, 0.012 mmol) in CH_2Cl_2 (0.8 mL) and Chan's diene **1** (2 equiv, 0.25 mmol) were added.

The resulting mixture was stirred for 1 min at 0 °C, then it was quenched by the addition of aqueous sodium thiosulfate solution.

The reaction mixture was extracted with CH_2Cl_2 and the combined organic phase was dried (MgSO_4) and concentrated.

The desilylation of the residue according to Carreira's protocol^{4k} followed by purification on silica gel (petroleum ether/AcOEt 9/1) gave the products **6** (entries 1 and 3 in Table 2). For entries 2, 4, 5, 6 and 7 (Table 2) a variation of this procedure was realized. In particular, after the synthesis of the imine, molecular sieves and silica gel were removed by filtration (by using a Pasteur pipette plugged with a bit of cotton wool) before cooling at 0 °C and before adding iodine solution and **1**, but no isolation of the imine was required. The spectroscopic data of imino-aldols **6** matched the ones reported in the literature.¹⁰

4.4. Typical procedure for the iodine-catalyzed vinylogous addition to ketones or acetals

To a solution of iodine (10 mol %, 0.012 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C, ketone **7** (or acetal **8**, 0.125 mmol) was added followed by the addition of diene **1** (2 equiv, 0.25 mmol). The mixture was stirred at this temperature for 1 min, then the reaction was quenched with aqueous sodium thiosulfate solution and extracted with CH_2Cl_2 . Evaporation of the solvent, followed by desilylation procedure according to Carreira's protocol^{4k} and purification on silica gel (ethyl acetate/hexane) afforded pure products **9** (or **10**). The spectroscopic data of aldols **9a** and **9c** matched the ones reported in the literature.¹⁶

4.4.1. Methyl 5-hydroxy-3-oxo-5-phenylhexanoate (9a). Pale yellow oil. R_f 0.2 (petroleum ether/AcOEt 9/1); ^1H NMR (400 MHz, CDCl_3) δ 7.44–7.40 (m, 2H), 7.36–7.31 (m, 2H), 7.25–7.21 (m, 1H), 3.69 (s, 3H), 3.36 (s, 2H), 3.30 (d, $J=16.8$ Hz, 1H), 2.97 (d, $J=16.8$ Hz, 1H), 1.55 (s, 3H). ^{13}C NMR δ 203.9, 167.0, 146.8, 128.3, 126.9, 124.2, 73.3, 53.8, 52.4, 50.3, 30.5 (NMR data in the literature¹⁶ were recorded in CCl_4).

4.4.2. Methyl 5-hydroxy-3-oxo-5-phenylheptanoate (9b). Pale yellow oil. R_f 0.2 (petroleum ether/AcOEt 9/1); HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{19}\text{O}_4$ $[\text{M}+\text{H}]^+$: 251.1283, found: 251.1291; ν_{\max} (liquid film) 2560, 1740, 1700 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.39–7.30 (m, 4H), 7.25–7.20 (m, 1H), 3.69 (s, 3H), 3.33 (s, 2H), 3.32 (d, $J=16.8$, 1H), 2.96 (d, $J=16.8$, 1H), 1.89–1.73 (m, 2H), 0.74 (t, $J=7.6$ Hz, 3H). ^{13}C NMR δ 204.2, 167.0, 145.0, 128.2, 126.8, 124.9, 75.8, 52.5, 52.4, 50.5, 35.8, 7.6.

4.4.3. Methyl 4-(1-hydroxycyclohexyl)-3-oxobutanoate (9c). Pale yellow oil. R_f 0.2 (petroleum ether/AcOEt 9/1); ^1H NMR (400 MHz, CDCl_3) δ 3.74 (s, 3H), 3.49 (s, 2H), 2.70 (s, 2H), 1.68–1.25 (m, 10H).

^{13}C NMR δ 204.2, 167.3, 70.9, 52.8, 52.4, 50.6, 37.5, 25.6, 21.9 (NMR data matched the ones reported in the literature).¹⁶

4.4.4. Methyl 5-methoxy-3-oxo-5-phenylpentanoate (10a). Slightly yellowish oil. R_f 0.5 (petroleum ether/AcOEt 8/2); HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{17}\text{O}_4$ $[\text{M}+\text{H}]^+$: 237.1127, found: 237.1115; ν_{\max} (liquid film) 3032, 2951, 1745, 1716, 1330 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.38–7.28 (m, 5H), 4.64 (dd, $J=4.0$, 9.4 Hz, 1H), 3.72 (s, 3H), 3.49 (s, 2H), 3.20 (s, 3H), 3.05 (dd, $J=9.4$, 16.0 Hz, 1H), 2.70 (dd, $J=4.0$, 16.0 Hz, 1H). ^{13}C NMR δ 200.7, 167.4, 140.5, 128.6, 128.0, 126.5, 79.5, 56.8, 52.3, 51.2, 50.0.

4.4.5. Methyl 5-methoxy-5-(4-methoxyphenyl)-3-oxopentanoate (10b). Yellow oil. R_f 0.5 (petroleum ether/AcOEt 8/2); HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{19}\text{O}_5$ $[\text{M}+\text{H}]^+$: 267.1232, found: 267.1239; ν_{\max} (liquid film) 3033, 2945, 1740, 1708, 1330 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.23 (d, $J=8.4$ Hz, 2H), 6.88 (d, $J=8.4$ Hz, 2H), 4.57 (dd, $J=4.0$, 9.0 Hz, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.48 (br s, 2H), 3.16 (s, 3H), 3.04 (dd, $J=9.0$, 15.6 Hz, 1H), 2.68 (dd, $J=4.0$, 15.6 Hz, 1H). ^{13}C NMR δ 200.8, 167.4, 159.4, 132.4, 127.8, 114.0, 79.1, 56.5, 55.2, 52.3, 51.2, 50.0.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.02.036.

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