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Synthesis of di- and *cis*-triaryl-3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazoles and their ring-opening reactions

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Abstract—The Δ^3-imidazoline 3-oxides **1** undergo diastereoselective cycloaddition with dimethyl acetylenedicarboxylate **2** to give 3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazoles **3**. Thermally and base induced ring-opening reactions of compounds **3** were demonstrated. *cis*-6-Phenyl substituted adducts **3d**,**e** undergo ring opening with secondary but not with tertiary amines. The same adducts undergo regio- and diastereoselective Michael addition with sodium methoxide to give 2-methoxy-3a,5,6-triphenyl-hexahydro-imidazo[1,5-*b*]isoxazole-2,3-dicarboxylic acid dimethyl esters **6**. © 2001 Elsevier Science Ltd. All rights reserved.

The inter- and intramolecular 1,3-dipolar cycloadditions of nitrones with different dipolarophiles provide valuable routes leading to many heterocyclic compounds. The cycloaddition of nitrones with a variety of alkynes is used in the synthesis of isoxazolines.[1–3] The intramolecular 1,3-dipolar cycloaddition of acetylenic nitrones leading to bicyclic nitrogen heterocycles has been investigated.[4] Intermolecular 1,3-dipolar cycloadditions of acyclic[5–8] and cyclic nitrones[9–12] with DMAD have been reported. Dihydroazet-1-oxide,[9] dihydro-β-carboline *N*-oxide,[10] and 3,4-dihydro-2*H*-pyrrole 1-oxide derivatives[11,12] are the few known heterocyclic nitrones which have been used in 1,3-dipolar cycloaddition reactions with DMAD. The synthesis of the first examples of the 4*H*-imidazo[4,5-*c*]isoxazole ring system was recently reported.[13]

Recently, we have reported our preliminary results on the reaction of imidazoline 3-oxides **1** with DMAD.[14] We report herein, in detail, the diastereoselective synthesis of a new class of 3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazoles by cycloaddition of Δ^3-imidazoline 3-oxides with dimethyl acetylenedicarboxylate as well as their thermal and base induced ring-opening reactions. The *cis* adducts **3d**,**e** were shown to undergo concerted double *cis* elimination with secondary but not with tertiary amines. Bases such as methoxide ion add regio- and diastereoselectively to the carbon–carbon double bond instead of the expected ring opening.

The reaction of the nitrones **1a–e** with dimethyl acetylenedicarboxylate in benzene at reflux gave the corresponding imidazoisoxazolines **3** in almost quantitative yields (Scheme 1, Table 1). Nitrones **1d**,**e** reacted with dimethyl acetylenedicarboxylate with high diastereoselectivity. A tentative *cis* configurational assignment[11,12] for compounds **3d**,**e** was made on the basis of ^{1}H NMR spectroscopic data and NOESY experiments. We have observed the same diastereoselectivity in the reaction of imidazoline oxides **1** with aryl isocyanates and styrene.[15–17]

Thermal treatment of compounds **3a–e** in the condensed phase under vacuum led to the formation of the imidazoles. This was in contrast with the behaviour of the adducts formed from imidazoline 3-oxides and isocyanates or styrene where thermal treatment led to retro 1,3-dipolar cycloaddition.

In the case of *cis*-3a,6-diaryltetrahydroimidazo[1,5-*b*][1,2,4]oxadiazol-2(1*H*)-ones, we have found that secondary amines open the ring producing imidazole, while tertiary amines led to retro 1,3-dipolar cycloaddition giving the starting cyclic nitrone.[18] The adducts obtained from the same imidazoline oxides and styrene did not undergo reaction with secondary and tertiary amines. This reaction would have been useful in distinguishing the diastereomers obtained from the reaction of imidazoline 3-oxides and isocyanates; the *cis* configuration was assigned tentatively on the basis of NOE experiments and the second diastereomer was not available by cycloaddition reaction. The adducts **3** were subjected to the same amine test and showed surprisingly similar behaviour to the imidazooxadiazolones (Scheme 2). Compounds **3a–e** were converted to imidazoles **4a–e** and dimethyl oxaloacetate **5** in refluxing acetonitrile in

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Keywords: Michael addition; cycloaddition; isoxazole.

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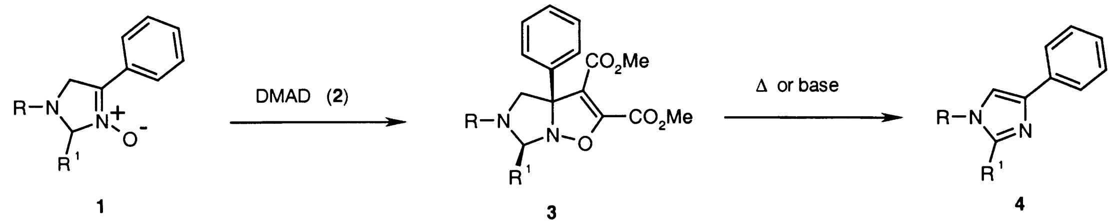
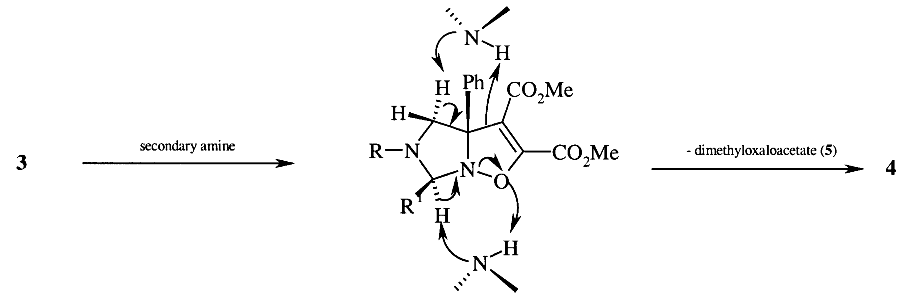


Scheme 1.

Table 1. 3a,4,5,6-Tetrahydroimidazo[1,5-*b*]isoxazoles

Entry	R	R^1	Yield of **3** (%)	Yield of **4** (%)			Mp of **3** (°C)
				Thermal	Piperidine	Triethylamine	
a	4-MeC_6H_4	H	98	85	80	85	134.8
b	4-$MeOC_6H_4$	H	99	72	73	70	116
c	4-ClC_6H_4	H	97	91	85	80	135.5
d	4-MeC_6H_4	Ph	97	68	65	No reaction	129
e	4-$MeOC_6H_4$	Ph	95	67	70	No reaction	104–105.3



Scheme 2.

the presence of an excess of piperidine. Compounds **3d**,**e** were converted to the corresponding imidazoles in the presence of piperidine but remain unchanged in the presence of triethylamine under the same reaction conditions. The easy ring opening of adducts **3** led us to suspect an abnormality in their formation. Such an abnormal adduct would be formed if imidazoline 3-oxides react via their rearranged oxaziridinoimidazole[17] form to give dimethyl 5,6,7,7a-tetrahydroimidazo[5,1-*b*][1,3]oxazole-2,3-dicarboxylates. The IR and ^{1}H NMR spectra were consistent with both structures; therefore, we needed to elucidate this structure by an X-ray diffraction method. The adduct is proved unequivocally to be the *cis* isomer by X-ray crystallographic analysis. A 3D perspective view of the crystal structure of **3e** is shown in Fig. 1. Thus the configuration of adducts **3d**,**e** has to be *cis* for the double *cis* elimination with secondary amines.

The mechanism proposed for the ring opening of adducts **3d**,**e** by bases requires the base to have a proton which is probably involved in the transition state, as shown in Scheme 2. Synchronous abstraction of the *cis* protons at C-4 and C-6, and protonation of the isoxazolidine oxygen and C-3 is possible only in the case of secondary amines. The reaction of *cis* adducts **3d**,**e** with methoxide in refluxing methanol gave the corresponding Michael addition products **6d**,**e** (Scheme 3). This would serve as further evidence for the concerted type of *cis* elimination as depicted in Scheme 2.

On the basis of reported chemical shifts for appropriately substituted isoxazolidine ring hydrogenes,[19,20] we assigned the singlet near 4.25 ppm to the proton at C-3. The C-2 proton of the alternative regioisomer is expected to absorb at δ 5.00–5.20 ppm.[19,20] The presence of characteristic fragments in the mass spectra of the diastereomeric mixtures was evidence for the C-2 methoxy regioisomer.[21]

The stereochemistry of the isoxazolidine ring of compounds **6** was deduced from NOESY experiments made for **6d** (Fig. 2). The ^{1}H NMR spectra of **6d**,**e** have shown that adducts **6**

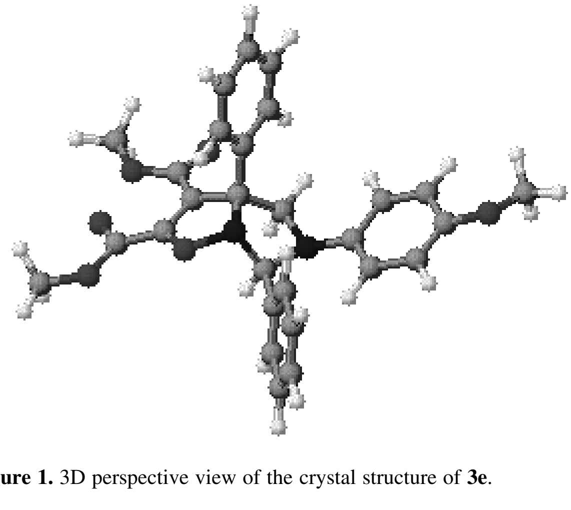
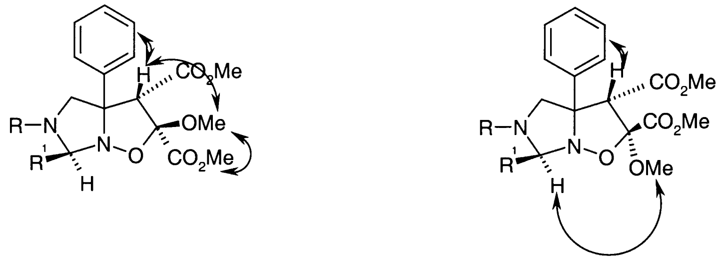
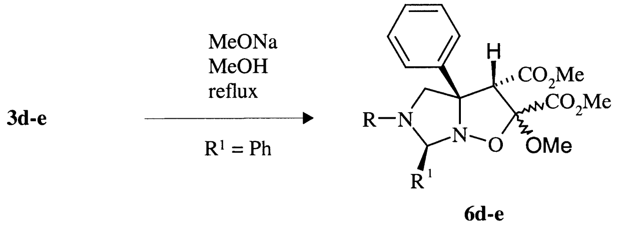


Figure 1. 3D perspective view of the crystal structure of **3e**.



Diastereomer I **Diastereomer II**

Figure 2. Selected NOESY correlations for **6d**.



Scheme 3.

are a mixture of diastereomers due to the difference at the configurations of C-2. The ratio of the diastereomers I and II is approximately 2:1. The major diastereomers of both **6d** and **e** were isolated by preparative TLC. 3D modelling studies show that only in the case of diastereomer II, the proton at C-6 is close enough to the C-2 linked methoxy protons to give cross peaks in the NOESY spectrum. This was the case; cross peaks are observed only for the 6-H and 2-methoxy group of the minor diastereomer II. For both diastereomers, the protons at C-3 gave cross peaks with the *o*-protons of the phenyl at C-3a. The proton at C-3 also gives cross peaks with C-2 methoxy protons which in turn give cross peaks with the methyl protons of the C-2 methoxycarbonyl. This allowed us a tentative *cis*-2,3-dimethoxycarbonyl assignment for the major and *trans* assignment for the minor diastereomer.[22]

1. Experimental

1.1. General

Melting points were taken on an Electrothermal Digital melting point apparatus. Infrared spectra were recorded on a Mattson 1000 FTIR. Proton magnetic resonance spectra were recorded on a Bruker Dpx 400 MHz spectrometer. All spectra were taken in deuteriochloroform. Mass spectra were routinely recorded at 70 eV by electron impact on a Fisons VG Platform II instrument. The X-ray data for **3e** were collected on an Enraf-Nonius CAD-4 automatic diffractometer with graphite-monochromated CuKα radiation (λ=1.5418 Å copper tube) at ambient temperature. The structure was solved by the direct method (SHELXS-97) and was refined by a full-matrix least-square technique. Visualisation was effected with UV light. Freshly prepared imidazoline 3-oxides were used after recrystallisation from either ethanol or acetone.

1.2. Tetrahydroimidazo[1,5-*b*]isoxazolines (3): general procedure

To a solution of imidazoline 3-oxide **1** (3 mmol) in benzene (20 mL) dimethyl acetylenedicarboxylate (12 mmol, 1.704 g) was added. The mixture was refluxed for 1 h. The solvent and the excess of DMAD were removed under vacuum. The product was recrystallised from ether–petroleum ether (2:1).

1.2.1. Dimethyl 3a-phenyl-5-(4-methylphenyl)-3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazole-2,3-dicarboxylate (3a). The compound was obtained according to the general procedure. Yield 98%. The melting point of the colourless crystals after recrystallisation from ether–petroleum ether is 134.8°C. IR (KBr) $\nu_{C=O}$ 1750, 1716; $\nu_{C=C}$ 1665 cm^{-1}; ^{1}H NMR $CDCl_3$ δ 2.27 (3H, s), 3.42 (1H, d, *J*=11 Hz), 3.64 (3H, s), 3.87 (3H, s), 4.19 (1H, d, *J*=11 Hz), 4.65 (1H, d, *J*=11 Hz), 5.05 (1H, d, *J*=11 Hz), 6.71 (2H, d, *J*=8 Hz), 7.08 (2H, d, *J*=8 Hz), 7.28–7.39 (3H, m), 7.60 (2H, d, *J*=8 Hz); ^{13}C NMR $CDCl_3$ δ 20.84; 52.23; 53.60; 57.65; 76.54; 83.06; 111.48; 115.74; 127.34; 128.47; 128.77; 129.60; 130.27; 141.21; 144.24; 152.20; 159.42; 162.87. MS *m/z* 394 (M^{+}). Anal. calcd for $C_{22}H_{22}N_2O_5$ (394.42): C, 66.99; H, 5.62; N, 7.10. Found: C, 67.12; H, 5.69; N, 6.84.

1.2.2. Dimethyl 3a-phenyl-5-(4-methoxyphenyl)-3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazole-2,3-dicarboxylate (3b). Yield 99%. The melting point of the colourless crystals after recrystallisation from ether–petroleum ether is 116°C. IR (KBr) $\nu_{C=O}$ 1750, 1716; $\nu_{C=C}$ 1665 cm^{-1}; ^{1}H NMR $CDCl_3$ δ 3.40 (1H, d, *J*=11 Hz), 3.64 (3H, s), 3.77 (3H, s), 3.88 (3H, s), 4.12 (1H, d, *J*=11 Hz), 4.62 (1H, d, *J*=11 Hz), 5.09 (1H, d, *J*=11 Hz), 6.72 (2H, d, *J*=8 Hz), 6.85 (2H, d, *J*=8 Hz), 7.28–7.39 (3H, m), 7.60 (2H, d, *J*=8 Hz). MS *m/z* 410 (M^{+}). Anal. calcd for $C_{22}H_{22}N_2O_6$ (410.42): C, 64.38; H, 5.40; N, 6.82. Found: C, 64.37; H, 5.47; N, 6.66.

1.2.3. Dimethyl 3a-phenyl-5-(4-chlorophenyl)-3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazole-2,3-dicarboxylate (3c). Yield 97%. The melting point of the colourless crystals after recrystallisation from ether–petroleum ether is 135.5°C. IR (KBr) $\nu_{C=O}$ 1750, 1716; $\nu_{C=C}$ 1665 cm^{-1}; ^{1}H NMR $CDCl_3$ δ 3.44 (1H, d, *J*=11 Hz), 3.65 (3H, s), 3.87 (3H, s), 4.22 (1H, d, *J*=11 Hz), 4.65 (1H, d, *J*=11 Hz), 5.03

(1H, d, J=11 Hz), 6.70 (2H, d, J=8 Hz), 7.22–7.40 (5H, m), 7.60 (2H, d, J=8 Hz). MS *m/z* 413.9 (M^+). Anal. calcd for $C_{21}H_{19}N_2O_5Cl$ (414.84): C, 60.80; H, 4.62; N, 6.75. Found: C, 60.68; H, 4.55; N, 6.64.

1.2.4. Dimethyl 3a,6-diphenyl-5-(4-methylphenyl)-3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazole-2,3-dicarboxylate (3d). Yield 97%. The melting point of the colourless crystals after recrystallisation from ether–petroleum ether is 129°C. IR (KBr) $\nu_{C=O}$ 1750, 1716; $\nu_{C=C}$ 1665 cm^{-1}; ^1H NMR $CDCl_3$ δ 2.23 (3H, s), 3.62 (3H, s), 3.81 (3H, s), 4.13 (1H, d, J=11 Hz), 4.76 (1H, d, J=11 Hz), 5.97 (1H, s), 6.64 (2H, d, J=8 Hz), 7.01 (2H, d, J=8 Hz), 7.21–7.39 (8H, m), 7.57 (2H, d, J=8 Hz); ^{13}C NMR $CDCl_3$ δ 20.79; 52.39; 53.65; 57.72; 81.03; 87.93; 112.27; 115.04; 126.99; 127.94; 128.25; 128.55; 128.72; 128.81; 128.92; 130.17; 137.77; 141.44; 143.97; 151.52; 159.48; 163. 01. MS *m/z* 310 ($M^+-MeO_2CCCCO_2Me-H_2O$). Anal. calcd for $C_{28}H_{26}N_2O_5$ (470.52): C, 71.48; H, 5.57; N, 5.95. Found: C, 72.35; H, 5.47; N, 5.97.

1.2.5. Dimethyl 3a,6-diphenyl-5-(4-methoxyphenyl)-3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazole-2,3-dicarboxylate (3e). Yield 95%. The melting point of the colourless crystals after recrystallisation from ether–petroleum ether is 104–105.3°C. IR (KBr) $\nu_{C=O}$ 1750, 1716; $\nu_{C=C}$ 1665 cm^{-1}; ^1H NMR $CDCl_3$ δ 3.68 (3H, s), 3.70 (3H, s), 3.82 (3H, s), 4.16 (1H, d, J=11 Hz), 4.62 (1H, d, J=11 Hz), 5.82 (1H, s), 6.70 (2H, d, J=8 Hz), 6.77 (2H, d, J=8 Hz), 7.29–7.40 (8H, m), 7.59 (2H, d, J=8 Hz). MS *m/z* 326 ($M^+-MeO_2CCCCO_2Me-H_2O$). Anal. calcd for $C_{28}H_{26}N_2O_6$ (486.52): C, 69.13; H, 5.39; N, 5.76. Found: C, 69.20; H, 5.30; N, 5.78.

2. Ring-opening reactions of compounds 3

2.1. Thermally induced ring opening: general procedure

Compound **3** (0.1 mmol) was placed in a glass sample vial, heated in a vacuum oven at 1.3×10^{-3} mmHg and left to cool at room temperature. The obtained **4** was extracted with warm hexane (3×2 mL). The extract was concentrated and cooled. The formed crystals were collected by filtration. The identity of the obtained imidazoles was determined comparing their melting points as well as their IR spectra with those of the authentic samples.

2.2. Secondary amine induced ring opening: general procedure for imidazoles 4a–e

To a solution of compound **3** (0.33 mmol) in acetonitrile (5 mL), piperidine (1 mL) was added and the reaction mixture was refluxed for 30 min. The solvent was evaporated and the residue extracted with warm hexane (3×5 mL). The combined extracts were filtered and concentrated. The formed crystals were collected by filtration. The compounds were identical in all respects with authentic samples.

2.3. Tertiary amine induced ring opening: general procedure for imidazoles 4a–c

To a solution of compound **3** (1 mmol) in acetonitrile (5 mL), triethylamine (3 mL) was added and the reaction mixture was refluxed for 30 min. The solvent was evaporated and the residue extracted with warm hexane (4×5 mL). The combined extracts were filtered and concentrated. The formed crystals were collected by filtration. The compounds were identical in all respects with authentic samples.

2.4. Reaction of *cis* adducts 3d,e with sodium methoxide

2.4.1. *cis*- and *trans*-2-Methoxy-5-(4-methylphenyl)-3a,6-diphenyl-hexahydro-imidazo[1,5-*b*]isoxazole-2,3-dicarboxylic acid dimethyl ester 6d. To a solution of sodium methoxide (in situ from 0.046 g, 2 mmol sodium) in methanol (10 mL) adduct **3d** (1 mmol) was added and the reaction mixture refluxed for 2 h, then left to cool. The white crystals formed after addition of water (6 mL) were filtered and dried in a vacuum oven. Yield 52%. Mp 98–100°C. IR (KBr) $\nu_{C=O}$ 1750 cm^{-1}; ^1H NMR $CDCl_3$ δ 2.22 (3H, s), 3.29 and 3.62 (3H, two s, C-2 MeO), 3.64 and 3.67 (3H, two s, ester MeO), 3.77 and 3.84 (3H, two s, ester MeO), 3.93 and 4.21 (1H, two s, C-3 H), 4.48 and 4.67 (2H, two AB systems), 5.73 and 6.02 (1H, two s, C-6 H), 6.46 and 6.50 (2H, two d), 7.00–7.05 (9H, m), 7.11 (1H, m), 7.36 and 7.38 (2H, d, C-3a Ph *ortho* H). MS *m/z* 502 (M^+). Anal. calcd for $C_{29}H_{30}N_2O_6$ (502.57): C, 69.31; H, 6.02; N, 5.57. Found: C, 69.43; H, 6.34; N, 5.61.

2.4.2. *cis*-2-Methoxy-5-(4-methylphenyl)-3a,6-diphenyl-hexahydro-imidazo[1,5-*b*]isoxazole-2,3-dicarboxylic acid dimethyl ester 6d. ^1H NMR $CDCl_3$ δ 2.15 (3H, s), 3.62 (3H, s, C-2 MeO), 3.57 and 3.70 (6H, two s, ester MeO), 3.86 (1H, s, C-3 H), 4.43 (2H, AB system, J_{AB}=9.89 Hz), 5.66 (1H, s, C-6 H), 6.42 (2H, d, J=8.23 Hz), 6.91–6.95 (10H, m), 7.30 (2H, d, J=7.29 Hz, C-3a Ph *ortho* H).

2.4.3. 2-Methoxy-5-(4-methoxyphenyl)-3a,6-diphenyl-hexahydro-imidazo[1,5-*b*]isoxazole-2,3-dicarboxylic acid dimethyl ester 6e. Yield 52%. Mp 80–82°C. IR (KBr) $\nu_{C=O}$ 1750 cm^{-1}; ^1H NMR $CDCl_3$ δ 3.31 and 3.62 (3H, two s, C-2 MeO), 3.65 and 3.68 (3H, two s, ester MeO), 3.72 (3H, s), 3.78 and 3.87 (3H, two s, ester MeO), 3.93 and 4.21 (1H, two s, C-3 H), 4.46 and 4.54 (2H, two AB systems), 5.70 and 5.94 (1H, two s, C-6 H), 6.54 and 6.82 (2H, two d), 6.98–7.05 (9H, m), 7.12 (1H, m), 7.37 and 7.45 (2H, d, C-3a Ph *ortho* H). MS *m/z* 518 (M^+). Anal. calcd for $C_{29}H_{30}N_2O_7$ (518.57): C, 67.17; H, 5.83; N, 5.40. Found: C, 67.40; H, 6.00; N, 5.40.

2.4.4. *cis*-2-Methoxy-5-(4-methoxyphenyl)-3a,6-diphenyl-hexahydro-imidazo[1,5-*b*]isoxazole-2,3-dicarboxylic acid dimethyl ester 6e. ^1H NMR $CDCl_3$ δ 3.55 (3H, s, C-2 MeO), 3.58 and 3.65 (6H, two s, ester MeO), 3.71 (3H, s), 3.86 (1H, s, C-3 H), 4.40 (2H, AB system, J_{AB}=9.74 Hz), 5.63 (1H, s, C-6 H), 6.43 and 6.70 (4H, two d, J=8.89 Hz), 6.91–6.98 (8H, m), 7.12 (1H, m), 7.31(2H, d, J=7.06 Hz, C-3a Ph *ortho* H).

Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 149019. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44-(0)1223-336033 or email: deposit@CCDC.cam.ac.uk].

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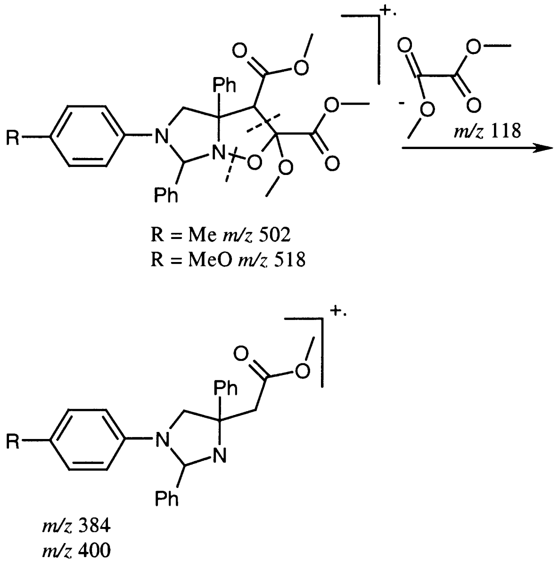
21. The presence of ions at *m/z* 384 and *m/z* 400 in the mass spectra of the diastereomeric mixtures, resulted from the probable fragmentation of adducts **6d**,**e** as shown in the scheme below and the absence of ions at *m/z* 415 and 431 corresponding to the alternative 3-methoxy regioisomers may serve as additional evidence for C-2 methoxy regioisomers. Ion *m/z* 118 is present in both mass spectra but especially intensive in the case of **6d**.



22. The configurations of *cis*-**6d**,**e** were deduced on the basis of NOESY experiment for the pure *cis*-**6d** while the configurations of the *trans*-**6d**,**e** are on the basis of NOESY for the diastereomeric mixture of **6d**.