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Diastereoselective synthesis of 4,5-dihydrofurans by iodoenolcyclisation of 2-allyl-1,3-dicarbonyl compounds

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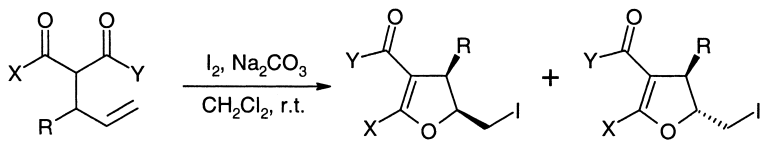
Abstract—A study of the stereochemical aspects of I_2-induced cyclisation of 2-alkenyl-1,3-dicarbonyl compounds reveals that the iodoenolcyclisation is strictly dependent on the dicarbonyl species and the substituents in the allylic position.

Owing to the importance of dihydrofuran derivatives as chemical units present in a large variety of naturally occurring substances,[1] their synthesis has attracted increasing attention, and a whole series of new synthetic methods have recently been reported.[2] In previous papers[3] we reported preliminary results for a general route to substituted dihydrofurans and dihydropyrans from 2-alkenyl-1,3-dicarbonyl compounds by I_2-induced cyclisation.

In the course of our studies on the iodocyclisation reaction with the aim of preparing tetrasubstituted furans,[4] we observed that the reaction was regioselective.[5] 2-Allyl-1,3-dicarbonyl compounds carrying an allylic substituent, such as **1** (R=Ph or Me) lead to *cis*- and *trans*-5-iodomethyl-4,5-dihydrofurans (**2** and **3**, respectively) in different ratios. Table 1 shows the effects that the active methylene compounds and the allylic substituents have on the stereochemical course of the process. Performing the iodoenolcyclisation reaction on substrates **1a**–**d**[6] [iodine (2 equiv.) and anhydrous Na_2CO_3 (2 equiv.) in CH_2Cl_2, 0.1 M] we observed that β-diketones (**1c** and **1d**) gave *cis* isomers **2** as main products, while β-keto esters (**1a** and **1b**) gave products with diastereoselectivities depending on R.

These results prompted us to better investigate the effects controlling the stereochemistry of iodoenolcyclisation reactions, also in the light of literature reports[7] on iodolactonisations and iodoetherifications. Initially we had to fully characterise reaction products since data reported in the literature are few and uncertain.[8] To this end, **1c** was submitted to iodoenocyclisation to give **2c** and **3c** as a mixture of two diastereoisomers of which we determined the ratio (82:18) by ^{1}H NMR spectroscopy. The chemical shift of the proton on C-5 was 4.68 ppm for the most

Table 1. Iodoenolcyclisation of 1,3-dicarbonyl compounds



1 **2** **3**

Entry	Compound	X	Y	R	%	Time (h)	*cis*/*trans*
1	**1a**	Me	OMe	Me	90	4	23:77
2	**1b**	Me	OMe	Ph	84	6	78:22
3	**1c**	Me	Me	Me	86	0.6	82:18
4	**1d**	Me	Me	Ph	70	1	80:20

Keywords: cyclisation; furans; enols and derivatives.

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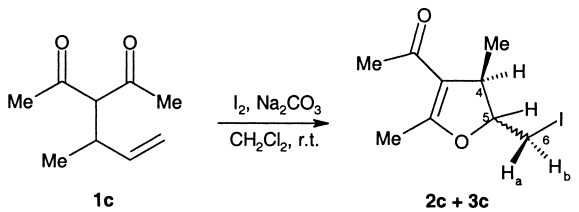
Table 2. Differential NMR characteristics of diastereoisomers resulting from the cyclisation reaction



1c 2c + 3c

H–C	Major isomer	Minor isomer
H-4	δ=3.22, dq, *J*=6.9, 7.0 Hz	δ=3.04, dq, *J*=4.2, 6.0 Hz
H-5	δ=4.68, ddd, *J*=7.0, 7.0, 7.8 Hz	δ=4.19, ddd, *J*=4.2, 5.4, 7.1 Hz
H_a-6	δ=3.29, dd, *J*=7.8, 10.1 Hz	δ=3.19, dd, *J*=7.1, 10.0 Hz
H_b-6	δ=3.38, dd, *J*=7.0, 10.1 Hz	δ=3.21, dd, *J*=5.4, 10.0 Hz

abundant isomer, and at 4.19 ppm for the minor one. By decoupling techniques we gauged the chemical shifts and the coupling constants for both isomers and their values are reported in Table 2.

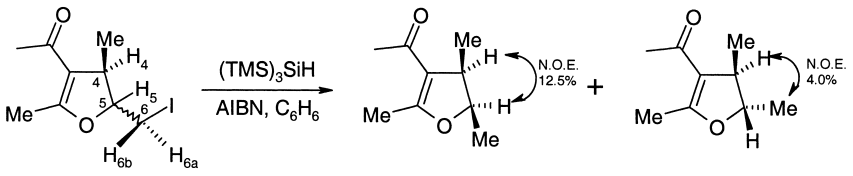
The two protons on C-6 (CH_aH_bI) are diastereotopic and appeared as the AB portion of an ABX spin system. In the major isomer the lines were well separated while in the minor one the signals collapsed to an apparent doublet. By modelling examination, dihedral angles between H-4 and H-5 resulted ϑ_{cis}=10° and ϑ_{trans}=110°, respectively, the larger coupling constant being assigned to the *cis* isomer.[9] Moreover, full characterisation was made by NOE measurement between the protons on C-4 and C-5. To simplify these experiments the mixture of isomers **2c**+**3c** was reductively dehalogenated, by means of $(Me_3Si)_3SiH$, to the two 4,5-dihydrofurans **4** and **5**, respectively (Scheme 1). Results were in agreement with the preceding observation. Indeed, upon irradiating proton H-5, **4** showed an NOE effect of 12.5% for the proton H-4 and no effects for methyl group on C-5. In contrast, **5** showed an NOE effect of 4% for the methyl group on C-5 and no effect for the proton H-4. The coupling constant J_{cis} (8–9 Hz) is thus larger than J_{trans} (4–6 Hz).[2a,i]

We also noticed a significant solvent effect on the stereochemical course of the reaction; indeed, performing the reaction on **1a** in non polar solvents (CH_2Cl_2 and CCl_4) *trans*-selectivity was observed, while in polar or aromatic solvents ($CHCl_3$, ethers, acetone, benzene) *cis*-selectivity was obtained. For our studies we chose CH_2Cl_2 as the solvent because in it the highest diastereoselectivity and the best chemical yields were obtained: indeed, from **1a**, in CH_2Cl_2 solvent, **2**+**3** formed in 90% yield with 54% de relative to the *trans* isomer.[10]

Our experiments showed that the course of the iodocyclisation reaction is strongly affected also by the nature of the 1,3-dicarbonyl compound. Under identical experimental conditions, 1,3-diketones gave products having mainly *cis* stereochemistry (Table 3), while with 1,3-keto esters *trans* stereoselectivity was prevalent (Table 4).

Moreover, 1,3-keto esters bearing a phenyl group as the allylic substituent led to lower stereoselectivities and, in some cases, to an opposite one (Table 4, entries 5 and 6). To rationalise these results we referred to models used for iodolactonisations[11] and iodoetherifications.[12] The resulting stereochemistry of the reaction is due to the diastereotopic faces of the double bond and the presence of the substituent R in the allylic position. The model of Chamberlain indicates that the stereochemistry is dependent on the relative stability of the different conformers.[13]

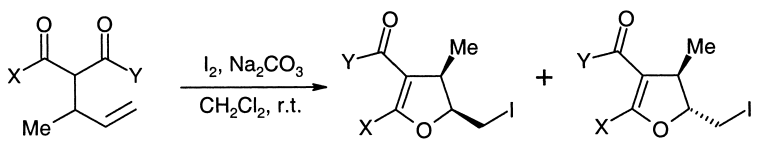
In the iodocyclisation the electrophile (I^+) and the nucleophile (enolic –OH) must attack from opposite faces of the double bond and the rate-determining step of the



2c + 3c 4 5

Scheme 1. NOE studies on diastereoisomers obtained from the cyclisation reaction.

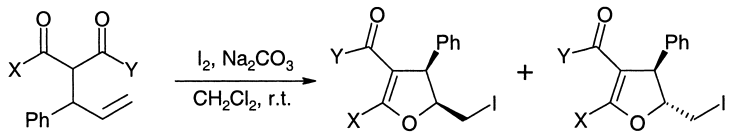
Table 3. Cyclisation of compounds **1** with R=Me



1 2 3

Entry	Compound	X	Y	Time	%	**2/3**
1	**1c**	Me	Me	10 min	86	82:18
2	**1e**	Et	Et	80 min	82	82:18
3	**1a**	Me	OMe	4 h	90	23:77
4	**1f**	Ph	OEt	18 h	90	3:97
5	**1g**	*i*Pr	OEt	2 h	78	15:85
6	**1h**	*n*Pr	OEt	4 h	91	12:88

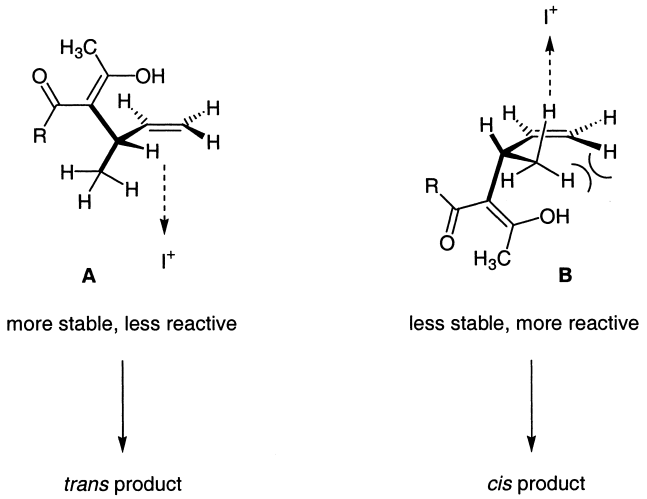
Table 4. Cyclisation of compounds **1** with R=Ph



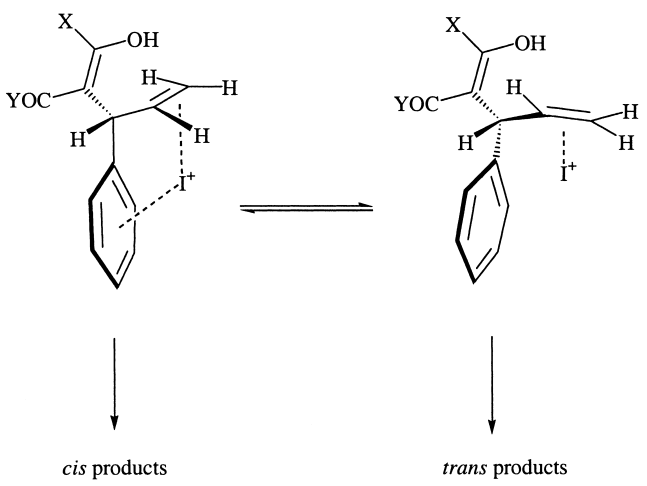
1 **2** **3**

Entry	Compound	X	Y	Time (h)	%	**2/3**
1	**1d**	Me	Me	1	70	80:20
2	**1i**	Et	Et	3	79	83:17
3	**1l**	Ph	Ph	1	88	62:38
4	**1b**	Me	OMe	6	84	78:22
5	**1m**	Ph	OEt	24	95	42:58
6	**1n**	*i*Pr	OEt	48	91	36:64
7	**1o**	*n*Pr	OEt	48	81	60:40

reaction is the formation of a π-complex between the iodonium ion and the olefinic system, which immediately undergoes intramolecular nucleophilic attack.[14] The substrate is present in two conformers: **A** and **B** (Scheme 2). In conformer **A** the allylic proton is in the plane of the double bond and R is out of plane, while in conformer **B** the allylic group (R) is in the plane. When R=Me, conformer **B** is the less stable one because of the steric interaction between the methyl group and the olefinic H, but the approach of the electrophile is easier because the attack is on the free face. Conversely, in conformer **A** there are no steric interactions, but the approach of the electrophile is partially hindered by the presence of the methyl group.



Scheme 2. Proposed mechanism for the I_2-induced cyclisation when R=Me.



Scheme 3. Proposed mechanism for the I_2-induced cyclisation when R=Ph.

Thus the *cis* stereochemistry observed for β-diketones can be explained on the basis of their high reactivity; I^+ approaching from the less hindered face of conformer **B** and the intermediate undergoing nucleophilic attack before rearranging to the more stable conformer **A**. In the case of the less reactive β-keto esters the two conformers have time to equilibrate and the attack of the enol occurs on the more stable one, leading to *trans* products.

When a phenyl group is present in the allylic position it is able instead to anchimerically assist the attack of the electrophile thus allowing preferential formation of the *cis* product (Table 4, Scheme 3).

Data presented in this work show that the iodoenolcyclisation is strictly dependent on the dicarbonyl species and on the substituents in the allylic position. Our main project is to further investigate this reaction and to exploit the method for the synthesis of biologically interesting natural compounds.

1. Experimental

1.1. General procedures

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with either Varian XL-300 or Varian 'Gemini' 200-MHz instruments, while IR spectra were recorded in CCl_4 and $CHCl_3$ with a Shimadzu IR-740 instrument. MS spectra were recorded by an HP5971A/MS detector coupled with an HP5890 gas chromatograph. The stereoselective ratios were determined on HP 5880 and HP 5890 gas chromatographs equipped with capillary columns. CH_2Cl_2 was dried by distillation on CaH_2 and stored on molecular sieves. Column chromatography, unless otherwise stated, was carried out on Kieselgel Merck (70–230 mesh and 230–400 mesh). All

reactions were carried out in amber-glass flasks under an argon atmosphere.

1.2. General procedure for cyclisation

A solution of the α-allyl-β-dicarbonyl compound (2 mmol) in dry CH_2Cl_2 (4 ml) was added to a mixture of anhydrous Na_2CO_3 (4 mmol) and iodine (4 mmol) in dry CH_2Cl_2 (40 ml). The mixture was stirred at rt until the substrate disappeared (TLC and GC monitoring). Et_2O was added and the organic phase was repeatedly washed with sodium thiosulphate (2 M) and brine and finally dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude products were purified by flash chromatography. Elution with hexane/EtOAc mixtures afforded pure 5-iodoalkyl-4,5-dihydrofurans, as oils.

1.2.1. *cis*-5-Iodomethyl-3-methoxycarbonyl-2,4-dimethyl-4,5-dihydrofuran (2a). ^{1}H NMR (δ) 1.04 (d, J=6.9 Hz, 3H), 2.15 (d, J=1.2 Hz, 3H), 2.97 (m, 1H), 3.30 (dd, J=7.3, 10.2 Hz, part A of an ABX system, 1H), 3.32 (dd, J=7.7, 10.2 Hz, part B of an ABX system, 1H), 3.70 (s, 3H), 4.70 (ddd, J=7.3, 7.7, 7.8 Hz, 1H). ^{13}C NMR (δ) 1.3, 11.7, 21.1, 43.0, 52.9, 80.4, 107.6, 166.5, 171.4. MS (*m*/*z*) 296 (21, M^+), 281 (18), 265 (10), 169 (35), 154 (41), 139 (15), 137 (31), 127 (33), 95 (100), 67 (26), 59 (30). IR (cm^{-1}) 1180, 1420, 1366, 1118, 921. Calcd for $C_9H_{13}IO_3$ C 36.51, H 4.43; found C 36.2, H 4.6.

1.2.2. *trans*-5-Iodomethyl-3-methoxycarbonyl-2,4-dimethyl-4,5-dihydrofuran (3a). ^{1}H NMR (δ) 1.21 (d, J=6.7 Hz, 3H), 2.18 (d, J=1.2 Hz, 3H), 2.95 (m, 1H), 3.15 (dd, J=7.2, 10.0 Hz, part A of an ABX system, 1H), 3.23 (dd, J=5.2, 10.0 Hz, part B of an ABX system, 1H), 3.69 (s, 3H), 4.20 (ddd, J=4.7, 5.2, 7.2 Hz, 1H). ^{13}C NMR (δ) 7.2, 11.7, 21.2, 39.1, 52.9, 79.8, 105.7, 166.3, 170.5. MS (*m*/*z*) 296 (95, M^+), 281 (100), 265 (27), 154 (57), 137 (34), 127 (24), 95 (60), 59 (12). IR (cm^{-1}) 1601, 1385, 1320, 1080. Calcd for $C_9H_{13}IO_3$ C 36.51, H 4.43; found C 36.5, H 4.9.

1.2.3. *cis*-5-Iodomethyl-3-methoxycarbonyl-2-methyl-4-phenyl-4,5-dihydrofuran (2b). ^{1}H NMR (δ) 2.35 (d, J=1.1 Hz, 3H), 2.74 (dd, J=6.3, 10.6 Hz, part A of an ABX system, 1H), 2.92 (dd, J=8.0, 10.6 Hz, part B of an ABX system, 1H), 3.52 (s, 3H), 4.30 (bd, J=8.9 Hz, 1H), 5.00 (ddd, J=6.3, 8.0, 8.9 Hz, 1H), 7.1–7.4 (m, 5H). ^{13}C NMR (δ) 1.9, 13.9, 50.9, 54.1, 86.1, 108.2, 127.2, 128.4 (2C), 128.7 (2C), 136.9, 165.9, 169.0. MS (*m*/*z*) 358 (40, M^+), 199 (96), 157 (84), 128 (90), 91 (100). IR (cm^{-1}) 1645, 1333, 1200, 1094, 984. Calcd for $C_{14}H_{15}IO_3$ C 46.95, H 4.22; found C 47.0, H 4.1.

1.2.4. *trans*-5-Iodomethyl-3-methoxycarbonyl-2-methyl-4-phenyl-4,5-dihydrofuran (3b). ^{1}H NMR (δ) 2.34 (d, J=1.1 Hz, 3H), 3.28 (dd, J=5.6, 10.4 Hz, part A of an ABX system, 1H), 3.35 (dd, J=6.6, 10.4 Hz, part B of an ABX system, 1H), 3.53 (s, 3H), 4.14 (bd, J=4.6 Hz, 1H), 4.43 (ddd, J=4.6, 5.6, 6.6 Hz, 1H), 7.1–7.4 (m, 5H). ^{13}C NMR (δ) 7.4, 14.1, 50.7, 54.1, 88.6, 106.4, 127.1, 127.6 (2C), 128.7 (2C), 142.8, 166.0, 168.2. MS (*m*/*z*) 358 (50, M^+), 199 (100), 157 (88), 128 (76), 91 (46). IR (cm^{-1}) 1645, 1445, 1216, 1129, 984. Calcd for $C_{14}H_{15}IO_3$ C 46.95, H 4.22; found C 46.7, H 4.4.

1.2.5. *cis*-3-Acetyl-5-iodomethyl-2,4-dimethyl-4,5-dihydrofuran (2c). ^{1}H NMR (δ) 1.03 (d, J=6.9 Hz, 3H), 2.18 (d, J=1.0 Hz, 3H), 2.22 (s, 3H), 3.22 (dq, J=6.9, 7.0 Hz, 1H), 3.29 (dd, J=7.8, 10.1 Hz, part A of an ABX system, 1H), 3.38 (dd, J=7.0, 10.1 Hz, part B of an ABX system, 1H), 4.68 (ddd, J=6.9, 7.0, 7.8 Hz, 1H). ^{13}C NMR (δ) 1.9, 12.1, 21.6, 26.0, 38.9, 80.9, 108.5, 176.9, 199.5. MS (*m*/*z*) 280 (100, M^+), 265 (35), 153 (65), 138 (93), 127 (20), 11 (90), 95 (74). IR (cm^{-1}) 1690, 1532, 1129, 947. Calcd for $C_9H_{13}IO_2$ C 38.59, H 4.68; found C 38.4, H 4.9.

1.2.6. *trans*-3-Acetyl-5-iodomethyl-2,4-dimethyl-4,5-dihydrofuran (3c). ^{1}H NMR (δ) 1.22 (d, J=6.8 Hz, 3H), 2.20 (d, J=1.2 Hz, 3H), 2.23 (s, 3H), 3.04 (dq, J=6.8, 4.2 Hz, 1H), 3.19 (dd, J=7.1, 10.0 Hz, part A of an ABX system, 1H), 3.21 (dd, J=5.4, 10.0 Hz, part B of an ABX system, 1H), 4.19 (ddd, J=4.2, 5.4, 7.1 Hz, 1H). ^{13}C NMR (δ) 12.0, 14.2, 19.1, 26.9, 40.2, 89.0; 110.6; 176.4; 199.5. MS (*m*/*z*) 280 (24, M^+), 265 (19), 153 (22), 138 (100), 123 (19), 111 (98), 95 (76), 67 (21). IR (cm^{-1}) 3004, 1687, 1560, 1452, 1470, 923. Calcd for $C_9H_{13}IO_2$ C 38.59, H 4.68; found C 38.7, H 4.6.

1.2.7. *cis*-3-Acetyl-5-iodomethyl-2-methyl-4-phenyl-4,5-dihydrofuran (2d). ^{1}H NMR (δ) 1.87 (s, 3H); 2.37 (d, J=1.5 Hz, 3H); 2.74 (dd, J=6.3 and 10.6 Hz, 1H, part A of an ABX system), 2.92 (dd, J=8.0 and 10.6 Hz, 1H, part B of an ABX system) 4.36 (bd, J=8.9 Hz, 1H), 5.00 (ddd, J=6.3, 8.0, 8.9 Hz, 1H); 7.1–7.3 (m, 5H). ^{13}C NMR (δ) 1.7, 14.8, 29.2, 51.7, 86.1, 117.5, 128.0, 128.9 (2C), 129.1 (2C), 136.7, 169.1, 195.3. MS (*m*/*z*) 342 (18, M^+), 215 (100), 173 (40), 150 (38), 128 (48), 91 (51). IR (cm^{-1}) 1640, 1596, 1392, 1219, 938. Calcd for $C_{14}H_{15}IO_2$ C 49.14, H 4.42; found C 48.9, H 4.7.

1.2.8. *trans*-3-Acetyl-5-iodomethyl-2-methyl-4-phenyl-4,5-dihydrofuran (3d). ^{1}H NMR (δ) 1.90 (s, 3H), 2.37 (d, J=1.5 Hz, 3H), 3.35 (bd, J=5.6 Hz, 2H), 4.14 (bd, J=4.6 Hz, 1H), 4.43 (dt, J=4.6, 5.6 Hz, 1H), 7.1–7.4 (m, 5H). ^{13}C NMR (δ) 7.6, 14.8, 29.5, 55.0, 88.7, 117.1, 127.6, 128.7 (2C), 129.2 (2C), 136.5, 168.6, 195.5. MS (*m*/*z*) 342 (19, M^+), 215 (100), 200 (20), 173 (38), 150 (32), 128 (52), 91 (60). IR (cm^{-1}) 1597, 1450, 1200, 940. Calcd for $C_{14}H_{15}IO_2$ C 49.14, H 4.42; found C 48.9, H 4.4.

1.2.9. *cis*-2-Ethyl-5-iodomethyl-4-methyl-3-propionyl-4,5-dihydrofuran (2e). ^{1}H NMR (δ) 1.0–1.2 (m, 9H), 2.4–2.7 (m, 4H), 3.2 (m, 1H), 3.21 (dd, J=6.6, 10.0 Hz, part A of an ABX system, 1H), 3.33 (dd, J=8.1, 10.0 Hz, part B of an ABX system, 1H), 4.63 (ddd, J=6.6, 8.1, 8.3 Hz, 1H). ^{13}C NMR (δ) 0.5, 7.9, 10.9, 12.6, 22.1, 33.6, 38.9, 85.3, 118.5, 171.6, 197.4. MS (*m*/*z*) 308 (14, M^+), 279 (27), 151 (17), 95 (15), 57 (100). IR (cm^{-1}) 1686, 1561, 1389, 1268, 900. Calcd for $C_{11}H_{17}IO_2$ C 42.87, H 5.56; found C 42.6, H 5.4.

1.2.10. *trans*-2-Ethyl-5-iodomethyl-4-methyl-3-propionyl-4,5-dihydrofuran (3e). ^{1}H NMR (δ) 1.0–1.2 (m, 9H), 2.4–2.7 (m, 4H), 3.0 (m, 1H), 3.10 (dd, J=4.5, 10.0 Hz, part A of an ABX system, 1H), 3.19 (dd, J=5.3, 10.0 Hz, part B of an ABX system, 1H), 4.18 (ddd, J=4.5, 5.3, 7.6 Hz, 1H). ^{13}C NMR (δ) 7.1, 7.9, 10.9, 12.6, 22.0, 33.8, 43.0, 87.5, 125.2, 171.6, 199.5. MS (*m*/*z*) 308 (42, M^+), 279 (100), 223

(12), 166 (18), 151 (20), 95 (18), 57 (74). IR (cm^{-1}) 1698, 1571, 1409, 1380, 900. Calcd for $C_{11}H_{17}IO_2$ C 42.87, H 5.56; found C 42.8, H 5.8.

1.2.11. *trans*-5-Iodomethyl-3-ethoxycarbonyl-4-methyl-2-phenyl-4,5-dihydrofuran (3f). ^1H NMR (δ) 1.19 (t, J=7.0 Hz, 3H), 1.34 (d, J=6.6 Hz, 3H), 3.20 (dq, J=4.6, 6.6 Hz, 1H), 3.28 (dd, J=7.4, 10.2 Hz, part A of an ABX system, 1H), 3.32 (dd, J=5.5, 10.2 Hz, part B of an ABX system, 1H), 4.12 (d, J=7.0 Hz, 2H), 4.33 (ddd, J=4.6, 5.5, 7.4 Hz, 1H), 7.3–7.5 (m, 3H), 7.6–7.8 (m, 2H). ^{13}C NMR (δ) 7.7, 14.4, 21.0, 44.9, 60.1, 87.4, 108.1, 128.1 (2C), 130.1 (2C); 130.4; 131.0, 164.6, 165.6. MS (*m/z*) 372 (17, M^+), 199 (10), 157 (29), 128 (11), 105 (100), 77 (38). IR (cm^{-1}) 1700, 1611, 1325, 1210, 1034, 980. Calcd for $C_{15}H_{17}IO_3$ C 48.40, H 4.60; found C 48.2, H 4.4.

1.2.12. *cis*-3-Ethoxycarbonyl-5-iodomethyl-2-isopropyl-4-methyl-4,5-dihydrofuran (2g). ^1H NMR (δ) 1.06 (d, J=7.1 Hz, 6H), 1.21 (t, J=7.1 Hz, 3H), 1.28 (d, J=7.0 Hz, 3H), 2.87 (dq, J=7.0, 8.4 Hz, 1H), 3.28 (dd, J=8.0, 9.9 Hz, part A of an ABX system, 1H), 3.34 (dd, J=6.3, 9.9 Hz, part B of an ABX system, 1H), 3.51 (heptet, J=7.1 Hz, 1H), 4.16 (q, J=7.1 Hz, 2H), 4.68 (ddd, J=6.3, 8.0, 8.4 Hz, 1H). ^{13}C NMR (δ) 0.5, 12.3, 13.9, 18.1, 20.5, 29.5, 47.1, 61.5, 84.5, 107.3, 165.7, 175.8. MS (*m/z*) 338 (100, M^+). IR (cm^{-1}) 1620, 1460, 1325, 1024, 910. Calcd for $C_{12}H_{19}IO_3$ C 42.62, H 5.66; found C 42.5, H 5.4.

1.2.13. *trans*-3-Ethoxycarbonyl-5-iodomethyl-2-isopropyl-4-methyl-4,5-dihydrofuran (3g). ^1H NMR (δ) 1.08 (d, J=7.0 Hz, 6H), 1.21 (d, J=6.7 Hz, 3H), 1. 25 (t, J=7.1 Hz, 3H), 2.95 (dq, J=4.1, 6.7 Hz, 1H), 3.13 (dd, J=7.3, 10.1 Hz, part A of an ABX system, 1H), 3.21 (dd, J=5.2, 10.1 Hz, part B of an ABX system, 1H), 3.55 (heptet, J=7.0 Hz, 1H), 4.14 (q, J=7.1 Hz, 2H), 4.16 (ddd, J=4.1, 5.2, 7.3, Hz, 1H). ^{13}C NMR (δ) 7.3, 14.1, 19.1, 19.5, 20.5, 26.7, 42.8, 59.3, 87.3, 105.1, 165.9, 174.8. MS (*m/z*) 338 (100, M^+), 323 (93), 295 (25), 293 (41), 196 (23), 167 (22), 165 (31), 123, (50), 95 (20), 71 (35). IR (cm^{-1}) 1620, 1460, 1325, 1024, 910. Calcd for $C_{12}H_{19}IO_3$ C 42.62, H 5.66; found C 42.8, H 5.6.

1.2.14. *cis*-3-Ethoxycarbonyl-5-iodomethyl-4-methyl-2-propyl-4,5-dihydrofuran (2h). ^1H NMR (δ) 0.91 (t, J=7.5 Hz, 3H), 1.05 (d, J=7.4 Hz, 3H), 1.18 (t, J=7.1 Hz, 3H), 1.5–1.7 (m, 2H), 2.4–2.7 (m, 3H), 3.26 (dd, J=6.9, 10.4 Hz, part A of an ABX system, 1H), 3.37 (dd, J=7.3, 10.4 Hz, part B of an ABX system, 1H), 4.15 (q, J=7.1 Hz, 2H), 4.67 (ddd, J=6.9, 7.3, 8.1 Hz, 1H). ^{13}C NMR (δ) 0.3, 12.8, 13.9, 14.5, 20.4, 29.9, 43.3, 59.7, 85.6, 109.7, 166.3, 171.6. MS (*m/z*) 338 (15, M^+), 323 (12), 196 (16), 165 (32), 123 (65), 95 (22), 71 (100). IR (cm^{-1}) 2990, 1702, 1501, 1381, 1111, 910. Calcd for $C_{12}H_{19}IO_3$ C 42.62, H 5.66; found C 42.9, H 5.9.

1.2.15. *trans*-3-Ethoxycarbonyl-5-iodomethyl-4-methyl-2-propyl-4,5-dihydrofuran (3h). ^1H NMR (δ) 0.92 (t, J=7.2 Hz, 3H), 1.22 (d, J=6.6 Hz, 3H), 1.26 (t, J=7.1 Hz, 3H), 1.5–1.7 (m, 2H), 2.4–2.7 (m, 2H), 2.97 (dq, J=4.4, 6.6 Hz, 1H), 3.14 (dd, J=7.4, 10.1 Hz, part A of an ABX system, 1H), 3.23 (dd, J=5.5, 10.1 Hz, part B of an ABX system, 1H), 4.14 (q, J=7.2 Hz, 2H), 4.16 (ddd, J=4.4, 5.5, 7.4, Hz, 1H). ^{13}C NMR (δ) 7.7, 12.9, 13.0, 14.5, 20.9, 30.1, 39.2, 59.9, 88.0, 107.5, 166.1, 171.0. MS (*m/z*) 338 (100, M^+), 323 (90), 295 (22), 293 (47), 196 (23), 165 (34), 123 (55) 71 (42). IR (cm^{-1}) 2986, 1600, 1369, 1309, 1120, 910. Calcd for $C_{12}H_{19}IO_3$ C 42.62, H 5.66; found C 42.6, H 5.6.

1.2.16. *cis*-2-Ethyl-5-iodomethyl-4-phenyl-3-propionyl-4,5-dihydrofuran (2i). ^1H NMR (δ) 0.82 (t, J=7.2 Hz, 3H); 1.20 (t, J=7.5 Hz, 3H); 1.90 (dq, J=7.2, 17.7 Hz, 1H); 2.30 (dq, J=7.2, 17.7 Hz, 1H); 2.71 (dd, J=6.7, 10.4 Hz, part A of an ABX system, 1H); 2.81 (bq, J=7.5 Hz, 2H); 2.95 (dd, J=7.5 and 10.4 Hz, part B of an ABX system, 1H); 4.34 (bd, J=8.8 Hz, 1H); 4.97 (ddd, J=6.7, 7.5, 8.8 Hz, 1H); 7.4–7.1 (m, 5H). ^{13}C NMR (δ) 1.7, 7.4, 11.0, 21.8, 34.1, 51.3, 86.1, 115.9, 127.4, 128.0 (2C), 128.8 (2C), 136.8, 173.5, 198.1. MS (*m/z*) 370 (10, M^+), 293 (75), 236 (51), 152 (100), 129 (43), 90 (33), 77 (79); IR (cm^{-1}) 1656, 1520, 1407, 1298, 900. Calcd for $C_{16}H_{19}IO_2$ C 51.91, H 5.17; found C 51.8, H 5.3.

1.2.17. *trans*-2-Ethyl-5-iodomethyl-4-phenyl-3-propionyl-4,5-dihydrofuran (3i). ^1H NMR (δ) 0.86 (t, J=7.2 Hz, 3H); 1.22 (t, J=7.5 Hz, 3H); 1.95 (dq, J=7.2, 17.7 Hz, 1H); 2.30 (dq, J=7.2, 17.7 Hz, 1H); 2.80 (bq, J=7.5 Hz, 2H); 3.31 (ddd, J=5.4, 6.4, 10.2 Hz, 2H); 4.12 (bd, J=4.3 Hz, 1H); 4.36 (ddd, J=4.3, 5.4, 6.4 Hz, 1H); 7.1–7.4 (m, 5H). ^{13}C NMR (δ) 1.6, 7.8, 11.1, 21.8, 34.5, 54.6, 88.4, 113.6, 128.0, 128.9 (2C), 129.0 (2C), 142.8; 173.1; 198.2. MS (*m/z*) 370 (12, M^+), 293 (81), 236 (28), 152 (100), 129 (45), 90 (23), 77 (87). IR (cm^{-1}) 1670, 1587, 1467, 1390, 910. Calcd for $C_{16}H_{19}IO_2$ C 51.91, H 5.17; found C 51.7, H 5.2.

1.2.18. *cis*-3-Benzoyl-5-iodomethyl-2,4-diphenyl-4,5-dihydrofuran (2l). ^1H NMR (δ) 2.88 (dd, J=6.3, 10.5 Hz, part A of an ABX system, 1H), 3.15 (dd, J=7.9, 10.5 Hz, part B of an ABX system, 1H), 4.71 (d, J=8.7 Hz, 1H), 5.25 (ddd, J=6.3, 7.9, 8.7 Hz, 1H), 7.0–7.5 (m, 15H). ^{13}C NMR (δ) 1.8, 54.3, 85.8, 116.9, 127.8 (2C), 128.0 (4C), 128.8 (2C), 129.1 (2C), 129.5, 129.8 (2C), 130.7, 131.5, 136.7, 138.9, 166.1, 192.7. MS (*m/z*) 235 (36), 105 (100), 77 (82), 51 (18). IR (cm^{-1}) 1723, 1685, 1478, 1378. Calcd for $C_{24}H_{19}IO_2$ C 61.82, H 4.11; found C 61.6, H 3.9.

1.2.19. *trans*-3-Benzoyl-5-iodomethyl-2,4-diphenyl-4,5-dihydrofuran (3l). ^1H NMR (δ) 3.49 (dd, J=5.3, 10.5 Hz, part A of an ABX system, 1H), 3.56 (dd, J=5.7 and 10.5 Hz, part B of an ABX system, 1H), 4.57 (d, J=6.0 Hz, 1H), 4.68 (ddd, J=5.3, 5.7, 6.0 Hz, 1H), 7.0–8.0 (m, 15H). ^{13}C NMR (δ) 7.4, 57.6, 88.0, 115.8, 127.6 (2C), 127.8 (4C), 128.5, 128.6, 128.9, 129.0 (4C), 130.4, 136.0, 131.5, 140.0, 142.0, 164.5, 196.1. MS (*m/z*) 235 (57), 105 (100), 77 (60), 51 (16). IR (cm^{-1}) 1623, 1600, 1500, 1360, 1210, 1123. Calcd for $C_{24}H_{19}IO_2$ C 61.82, H 4.11; found C 61.6, H 4.0.

1.2.20. *cis*-3-Ethoxycarbonyl-5-iodomethyl-2,4-diphenyl-4,5-dihydrofuran (2m). ^1H NMR (δ) 0.98 (t, J=7.0 Hz, 3H), 2.84 (dd, J=6.8, 10.4 Hz, part A of an ABX system, 1H), 3.10 (dd, J=7.5, 10.4 Hz, part B of an ABX system, 1H), 3.95 (q, J=7.0 Hz, 2H), 4.52 (d, J=8.9 Hz, 1H), 5.15 (ddd, J=6.8, 7.5, 8.9 Hz, 1H), 7.1–7.4 (m, 10H). ^{13}C NMR (δ) 1.5, 13.6, 55.7, 59.7, 85.4, 106.9, 127.2 (2C), 127.6, 127.8 (2C), 128.7 (2C), 128.9 (2C), 131.0, 137.0,

142.9, 164.7, 165.6. MS (*m*/*z*) 434 (4, M^+), 261 (15), 105 (100), 77 (19). IR (cm^{-1}) 1685, 1512, 1380, 1210, 1086. Calcd for $C_{20}H_{19}IO_3$ C 56.31, H 4.41; found C 56.5, H 4.6.

1.2.21. *trans*-3-Ethoxycarbonyl-5-iodomethyl-2,4-diphenyl-4,5-dihydrofuran (3m). ^1H NMR (δ) 0.98 (t, J=7.0 Hz, 3H), 3.45 (d, J=6.0 Hz, 2H), 3.95 (q, J=7.0 Hz, 2H), 4.28 (d, J=4.5 Hz, 1H), 4.60 (dt, J=4.5, 6.0 Hz, 1H), 7.2–7.5 (m, 8H), 7.8–8.0 (m, 2H). ^{13}C NMR (δ) 7.5, 13.6, 52.5, 59.7, 87.5, 106.9, 127.5 (2C), 127.8 (2C), 128.5 (2C), 128.8, 129.7 (2C), 130.9, 137.0, 142.9, 164.8, 165.6. MS (*m*/z) 434 (8, M^+), 261 (14), 105 (100), 77 (19). IR (cm^{-1}) 1615, 1467, 1310. Calcd for $C_{20}H_{19}IO_3$ C 56.31, H 4.41; found C 56.3, H 4.5.

1.2.22. *cis*-2-Isopropyl-3-ethoxycarbonyl-4-phenyl-5-iodomethyl-4,5-dihydrofuran (2n). ^1H NMR (δ) 0.99 (t, J=7.0 Hz, 3H), 1.16 (d, J=6.0 Hz, 3H), 1.23 (d, J=5.8 Hz, 3H), 2.74 (dd, J=7.0, 10.3 Hz, part A of ABX system, 1H), 3.01 (dd, J=7.3, 10.3 Hz, part B of ABX system, 1H), 3.7 (m, 1H), 3.97 (q, J=7.0 Hz, 2H), 4.30 (d, J=8.9 Hz, 1H), 4.93 (ddd, J=7.0, 7.3, 8.9 Hz, 1H), 7.17.4 (m, 5H). ^{13}C NMR (δ) 1.8, 13.8, 19.4 (2C), 26.9, 50.9, 59.3, 85.8, 106.6, 127.3 (2C), 128.4 (2C), 128.8, 137.4, 165.4, 176.6. MS (*m*/*z*) 400 (4, M^+), 274 (21), 233 (91), 204 (37), 203 (42), 189 (30), 185 (65), 159 (100), 134 (46), 131 (60), 117 (79), 115 (56), 91 (51), 77 (18), 71 (40). IR (cm^{-1}) 1687, 1467, 1347, 1101. Calcd for $C_{17}H_{21}IO_3$ C 51.01, H 5.29; found C 50.9, H 5.3.

1.2.23. *trans*-2-Isopropyl-3-ethoxycarbonyl-5-iodomethyl-4-phenyl-4,5-dihydrofuran (3n). ^1H NMR (δ) 1.01 (t, J=7.2 Hz, 3H), 1.16 (d, J=4.9 Hz, 3H), 1.21 (d, J=5.5 Hz, 3H), 3.27 (dd, J=6.4, 10.0 Hz, part A of an ABX system, 1H), 3.32 (dd, J=5.6, 10.0 Hz, part B of an ABX system, 1H), 3.7 (m, 1H), 3.95 (q, J=7.2 Hz, 2H), 4.02 (d, J=4.0 Hz, 1H), 4.46 (ddd, J=4.0, 5.6, 6.4 Hz, 1H); 7.1–7.4 (m, 5H). ^{13}C NMR (δ) 7.6, 13.8, 19.6 (2C), 26.8, 54.1, 59.3, 88.0, 104.6, 127.1, 127.5 (2C), 128.7 (2C), 143.3, 165.5, 175.7. MS (*m*/*z*) 400 (7, M^+), 274 (63), 226 (35), 210 (21), 185 (100), 159 (15), 129 (22), 117 (18), 115 (15), 91 (18), 77 (10). IR (cm^{-1}) 1623, 1577, 1322, 1023. Calcd for $C_{17}H_{21}IO_3$ C 51.01, H 5.29; found C 50.9, H 5.6.

1.2.24. *cis*-3-Ethoxycarbonyl-5-iodomethyl-4-phenyl-2-propyl-4,5-dihydrofuran (2o). ^1H NMR (δ) 1.01 (t, J=7.2 Hz, 3H), 1.03 (t, J=7.3 Hz, 3H), 1.6–1.8 (m, 2H), 2.6–2.8 (m, 2H), 2.75 (dd, J=6.4, 10.6 Hz, part A of an ABX system, 1H), 2.97 (dd, J=7.8, 10.6 Hz, part B of an ABX system, 1H), 3.98 (q, J=7.2 Hz, 2H), 4.31 (d, J=9.2 Hz, 1H), 4.96 (ddd, J=6.4, 7.8, 9.2 Hz, 1H), 7.1–7.4 (m, 5H). ^{13}C NMR (δ) 2.0, 13.8 (2C), 20.3, 29.6, 51.1, 59.3, 85.8, 106.4, 128.4 (2C), 128.7 (2C), 128.8, 137.3, 165.4, 172.4. MS (*m*/*z*) 400 (16, M^+), 227 (37), 157 (100), 129 (46), 91 (86), 71 (68). IR (cm^{-1}) 1690, 1381, 1208, 1100. Calcd for $C_{17}H_{21}IO_3$ C 51.01, H 5.29; found C 51.0, H 5.4.

1.2.25. *trans*-3-Ethoxycarbonyl-5-iodomethyl-4-phenyl-2-propyl-4,5-dihydrofuran (3o). ^1H NMR (δ) 0.97 (t, J=7.0 Hz, 3H), 1.04 (t, J=7.2 Hz, 3H), 1.6–1.8 (m, 2H), 2.6–2.8 (m, 2H), 3.25 (dd, J=5.6, 10.2 Hz, part A of an ABX system, 1H), 3.31 (dd, J=7.1, 10.2 Hz, part B of an ABX system, 1H), 3.92 (q, J=7.2 Hz, 2H), 4.06 (d, J=4.2 Hz, 1H), 4.46 (ddd, J=4.2, 5.6, 7.1 Hz, 1H), 7.1–7.4 (m, 5H). ^{13}C NMR (δ) 7.5, 13.7, 13.8, 20.3, 30.1, 54.3, 59.3, 88.3, 108.3, 127.0, 127.5 (2C), 128.5 (2C), 143.1, 165.5, 171.5. MS (*m*/*z*) 400 (25, M^+), 227 (45), 157 (100), 129 (35), 91 (32), 71 (50). IR (cm^{-1}) 1640, 1325, 1200, 1117. Calcd for $C_{17}H_{21}IO_3$ C 51.01, H 5.29; found C 51.3, H 5.3.

1.3. Dehalogenation of 3-acetyl-5-iodomethyl-2,4-dimethyl-4,5-dihydrofuran

1.1 mmol of tris(trimethylsilyl)silane and AIBN (0.1 mmol) were added to a solution of iododihydrofuran **2c**+**3c** in benzene (10 ml). The solution was refluxed (80°C) for 1 h until all substrate was used up (TLC).Then the solvent was evaporated and the crude was purified by chromatography on silica gel, eluting with hexane/diethyl ether 9:1, in order to obtain dihydrofurans **4** and **5**.

1.3.1. *cis*-3-Acetyl-2,4,5-trimethyl-4,5-dihydrofuran (4). ^1H NMR (δ) 0.98 (d, J=6.9 Hz, 3H), 1.31 (d, J=6.6 Hz, 3H), 2.17 (d, J=1.5 Hz, 3H), 2.20 (s, 3H), 3.02 (ddq, J=1.5, 6.9, 8.3 Hz, 1H), 4.60 (dq, J=6.6, 8.3 Hz, 1H). ^{13}C NMR(δ) 16.1, 25.2, 26.45, 26.8, 43.1, 89.2, 102.3, 176.7, 194.5. Calcd for $C_9H_{14}O_2$ C 70.10, H 9.15; found C 69.9, H 9.1.

1.3.2. *trans*-3-Acetyl-2,4,5-trimethyl-4,5-dihydrofuran (5). ^1H NMR (δ) 1.13 (d, J=6.6 Hz, 3H), 1.25 (d, J=6.2 Hz, 3H), 2.15 (d, J=1.5 Hz, 3H), 2.25 (s, 3H), 2.75 (ddq, J=1.5, 4.8, 6.6 Hz, 1H), 4.19 (dq, J=4.8, 6.2 Hz, 1H). ^{13}C NMR (δ) 16.3, 26.3, 27.0, 27.5, 47.2, 95.2, 109.5, 176.3, 196.6. Calcd for $C_9H_{14}O_2$ C 70.10, H 9.15; found C 69.8, H 9.4.

References

1. (a) Westley, J. W. *Polyether Antibiotics*, Marcel Dekker: New York, 1982; Vols. 1,2. (b) Nakanishi, K. *Natural Products Chemistry*. Academic: New York, 1974. (c) Vernin, G. *The Chemistry of Heterocyclic Flavoring and Aroma Compounds*. Ellis Horwood: Chichester, 1982. (d) Harding, K. E.; Tiner, H. T. *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 4, p 363. (e) Sargent, M. V.; Cresp, T. M. *Comprehensive Organic Chemistry*, Barton, D. H. R., Ollis, D. W., Eds.; Pergamon: New York, 1979; Vol. 4, p 693. (f) Bird, C. W.; Cheesman, G. H. W. *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R., Rees, C. W., Eds.; Pergamon: New York, 1984; Vol. 4, Part 3, p 3. (g) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795.
2. (a) Ferraz, H. M. C.; Sano, M. K.; Nunes, M. R. S.; Bianco, G. G. *J. Org. Chem.* **2002**, *67*, 4122. and references herein. (b) Garrido, J. L.; Alonso, I.; Carretero, J. C. *J. Org. Chem.* **1998**, *63*, 9406. and references cited therein. (c) Stefani, H. A.; Brandt, C. A. *Tetrahedron Lett.* **1997**, *38*, 4977. (d) Lee, Y. R.; Kim, B. S. *Tetrahedron Lett.* **1997**, *38*, 2095. (e) Hayashi, T.; Yamane, M.; Ohno, A. *J. Org. Chem.* **1997**, *62*, 204. (f) Jones, A. D.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **1996**, 915. (g) Nair, V.; Mathew, J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 187. (h) Lee, C. W.; Hong, J. E.; Oh, D. W. *J. Org. Chem.* **1995**, *60*, 7027. (i) Ferraz, H. M. C.; de Oliveira, E. O.; Payret-Arrau, M. E.; Brandt, C. A. *J. Org. Chem.* **1995**, *60*,

7357. (j) Jung, J. H.; Lee, J. W.; Oh, D. Y. *Tetrahedron Lett.* **1995**, *36*, 923. (k) Tiecco, M.; Testaferri, L.; Tingoli, M.; Marini, F. *Synlett* **1994**, 373. (l) Barluenga, J.; Tomàs, M.; Suàrez-Sobrino, A. *Synlett* **1990**, 673.

3. (a) Antonioletti, R.; Bonadies, F.; Scettri, A. *Tetrahedron Lett.* **1988**, *29*, 4987. (b) Antonioletti, R.; Magnanti, S.; Scettri, A. *Tetrahedron Lett.* **1994**, *35*, 4987. (c) Antonioletti, R.; D'Onofrio, F.; Rossi, B. *Synth. Commun.* **2001**, *31*, 911.
4. Antonioletti, R.; Cecchini, C.; Ciani, B.; Magnanti, S. *Tetrahedron Lett.* **1995**, *36*, 9019.
5. (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Johnson, C. D. *Acc. Chem. Res.* **1993**, *26*, 476.
6. Antonioletti, R.; Bovicelli, P.; Malacona, S. *Tetrahedron* **2002**, *58*, 589.
7. (a) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, 171. (b) Staninets, V. I.; Shilov, E. A. *Russ. Chem. Rev. (Eng. Transl.)* **1971**, *40*, 272. (c) Bartlett, P. A. *Asymmetric Synthesis*, Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, p 411. (d) Cardillo, G.; Orena, M. *Tetrahedron Lett.* **1990**, *46*, 3321.
8. (a) Hudlicky, T. *J. Org. Chem.* **1991**, *56*, 4598. (b) Engler, T. A. *J. Org. Chem.* **1995**, *60*, 3700. (c) Boyd, D. R. *J. Chem. Soc., Chem. Commun.* **1996**, 2361. (d) Shibya, S. *Terahedron Lett.* **1992**, 6999.
9. (a) Thomas, W. A. *J. Chem. Soc., Chem. Commun.* **1965**, 431. (b) Stevens, J. D. *J. Org. Chem.* **1968**, *33*, 1799.
10. In non-polar solvents the stereoselectivity is high probably because in the transition state the reactive species (polar or polarised) interact less with the solvent and can better arrange themselves in the energetically most favorable conformation. The following *cis*/*trans* ratios (yield) were obtained for **1a** in different solvents: CH_2Cl_2 23:77 (90%), CCl_4 18:82 (76%), hexane 35:65 (38%), $CHCl_3$ 70:30 (43%), DME 69:31 (81%), Et_2O 72:28 (40%), acetone 58:42 (35%), benzene 57:43 (78%). Other electrophiles were also tried to promote the heterocyclisation but the best results were obtained by using I_2 in the presence of Na_2CO_3. For example, in the cyclisation of **1a**, the used electrophiles afforded the following *cis*/*trans* ratios: NIS 20:80 (70%), NBS 35:65 (66%), PhSeCl 33:67 (53%), DMD 40:60 (69%). Other electrophiles, such as $HgCl_2$, $Hg(OAc)_2$, *m*CPBA, and *p*TsOH, did not gave reaction at all.
11. (a) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2. (b) Bartlett, P. A.; Richardson, D. P.; Mayerson, J. *Tetrahedron* **1984**, *40*, 2317.
12. Bartlett, P. A.; Rychnovsky, *J. Am. Chem. Soc.* **1981**, *103*, 3963.
13. (a) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMillis, M. *J. Am. Chem. Soc.* **1983**, *105*, 5819. (b) Chamberlin, A. R.; Mulholland, R. L. *Tetrahedron* **1984**, *40*, 2297. (c) Chamberlin, A. R.; Mulholland, R. L.; Kahn, S. D.; Hehre, W. *J. Am. Chem. Soc.* **1987**, *109*, 672.
14. Evans, R. D.; Mogee, J. W.; Schamble, J. H. *Synthesis* **1988**, 862.