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Iodoenolcyclisation of 2-(1,3-disubstituted-1-allyl)-1,3-dicarbonyl compounds: diastereoselective synthesis of tetrasubstituted dihydrofurans

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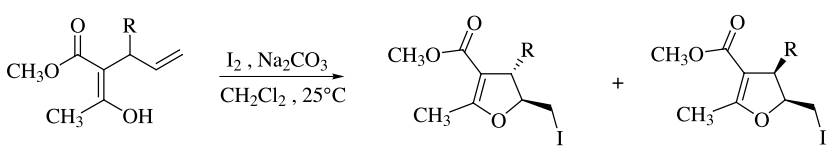
Abstract—The I_2-induced cyclisation of 2-alkenyl-1,3-dicarbonyl compounds with the mono- and di-substituted double bond occurred with good diastereoselectivity. A study of stereochemical aspects for different substituents on the allyl side chain was carried out. When the substituents were alkyl groups, the *trans* isomers formed preferentially, in the case of aromatic substituents the reaction lead instead to *cis* isomers.

In consideration of the increasing attention that the synthesis of dihydrofuran derivatives has attracted in the last years,[1] we have investigated the I_2-induced cyclisation of 2-allyl-1,3-dicarbonyl compounds. As reported, we observed that the reaction leading to dihydrofuran derivatives is regiospecific when the double bond is monosubstituted and regio- and stereospecific when the double bond is a disubstituted one.[2] Compounds with trisubstituted double bonds led to mixtures of dihydrofurans and dihydropyrans.[3] In our previous papers[4] we reported that the 4,5-diastereoselectivity is dependent on the nature of the β-dicarbonyl starting materials and on that of the groups (methyl or phenyl) substituting the allyl side chain. In the same paper the stereochemical assignments were made on the basis of the coupling constant of the prontons on C-4 and C-5 (larger in the *cis* isomers), confirmed by NOE experiments. The same criteria were used to assign the stereochemistry of the products described in the present paper.

Pursuing the matter further we investigated the effect of the substituent borne by the allyl side chain on the 4,5-diastereoselectivity when the double bond is monosubstituted. With this aim we submitted a number of α-allyl-acetoacetic derivatives to the iodoenolcyclisation reaction (Scheme 1), the results of which are presented in Table 1.

When the R substituent in the allylic position was an alkyl group the *trans* isomers formed preferentially, and the larger the bulk of R the higher the diastereoselectivity. Compound **1d** represented an exception due to the strong steric hindrance exerted by the *t*-butyl group which made the approach of an electrophile in conformer A (see Scheme 3 and discussion below) very difficult. When the substituent was an aromatic group, a coordination with the approaching electrophile appears possible thus leading the reaction towards the *cis* isomer.

We then extended our investigation to substrates with disubstituted double bonds and found that the course of the I_2-induced cyclisation was essentially independent of the nature of the β-dicarbonyl moiety giving, in all cases, *trans* tetrasubstituted dihydrofurans with high diastereoselectivities. Table 2 shows the results for both β-keto esters and β-diketones (Scheme 2).



1 **2** **3**

Scheme 1. I_2-induced cyclisation of 2-(1-substituted-1-allyl)acetoacetic esters.

Keywords: iodocyclization; 1,3-dicarbonyl compounds; 2,3-dihydrofurans; furans.

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Table 1. Effect of the substituent on the cyclisation of 2-(1-substituted-1-allyl)acetoacetic esters

Entry	Compound	R	2/3 ratio	Time (h)	Yield (%)
1	**1a**	Me	77:23	4	90
2	**1b**	Pr	78:22	4	85
3	**1c**	*i*-Pr	95:5	6	77
4	**1d**	*t*-Bu	77:23	6	72
5	**1e**	Ph	22:78	6	84
6	**1f**	2-Furyl	3:97	5	20

Table 2. Iodoenolcyclisation of 2-(1,3-dimethyl-1-allyl)-1,3-dicarbonyl compounds at 25°C

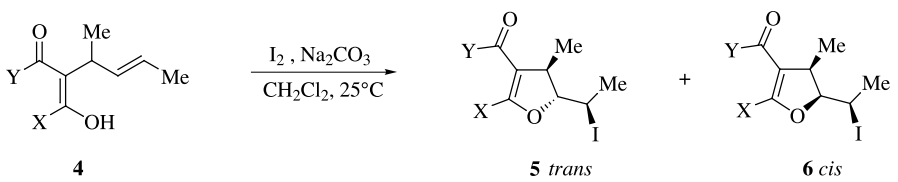
Entry	Compound	X	Y	5/6 ratio	Yield (%)	Time (h)
1	**4a**	Me	MeO	95:5	80	3.5
2	**4b**	*i*-Pr	MeO	91:9	92	3.5
3	**4c**	*t*-Bu	MeO	98:2	91	3
4	**4d**	Ph	MeO	97:3	95	1.5
5	**4e**	Me	EtO	91:9	92	4
6	**4f**	Me	*t*-BuO	–	–	3.5
7	**4g**	Me	Me	60:40	95	1
8	**4h**	Et	Et	97:3	95	1
9	**4i**	*t*-Bu	*t*-Bu	99:1	47	3
10	**4j**	Ph	Ph	97:3	95	1

These findings seem to confirm the mechanism proposed by us for the I_2-induced cyclisation (Scheme 3).[4]

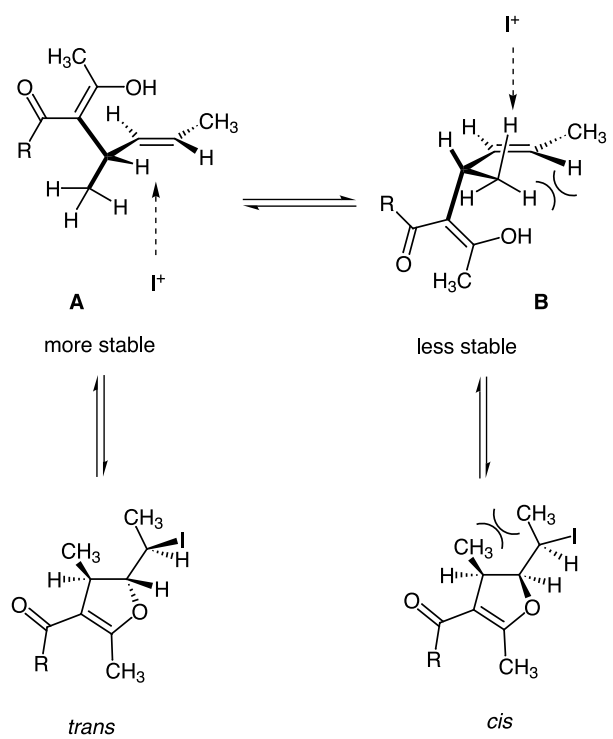
The relative stability and reactivity of the two conformers, A and B, of the substrate should determine the stereochemistry of the products. In this model, the *cis* products derive from the less stable and more reactive conformer B, since the electrophile approaches from the less hindered face, and the intermediate undergoes nucleophilic attack before rearranging to the more stable conformer A.

When the allyl chain is disubstituted the transition state leading to the *cis* compound becomes hindered and conformer B, for this reason, less reactive. In this case, the transition state for the reaction between iodine and conformer A is lower in energy than that resulting from conformer B.

By examining a number of substrates we noted that when a β-keto *t*-butyl ester was used (Table 2, entry 6), the reaction took a different course and a lactonisation product was obtained instead (Scheme 4). The driving force for this process is the loss of a stable *t*-butyl cation, as proposed by Bartlett, who studied its mechanism.[5]



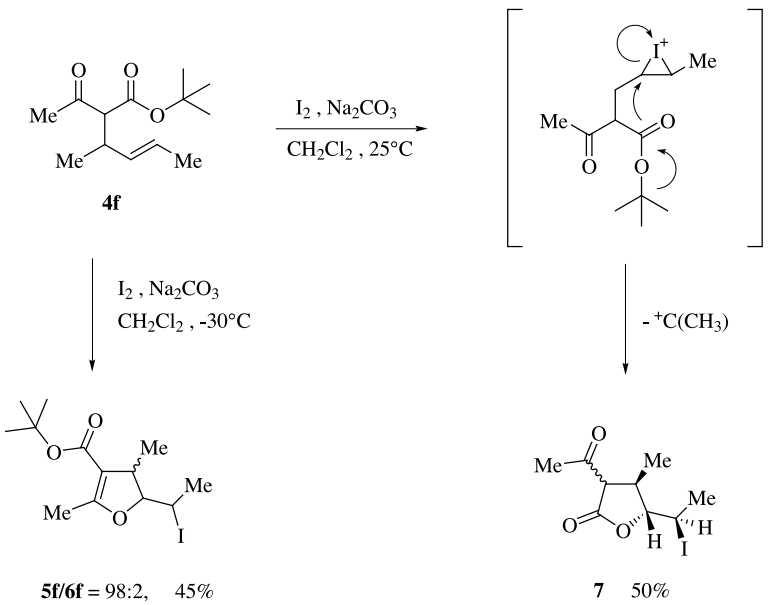
Scheme 2. Iodoenolcyclisation of 2-(1,3-dimethyl-1-allyl)-1,3-dicarbonyl compounds.



Scheme 3. Proposed mechanism for the iodoenolcyclisation.

With the aim of inhibiting this undesired process we performed the reaction at lower temperatures (Table 3, entry 2) and found that at −30°C the correct *trans* dihydrofuran was obtained (although in moderate yield, 45%) together with the lactone (50% yield). It is worth noting that in this case the diastereoselectivity was high whereas, with the other substrates, under the same conditions (−30°C), lower selectivities were observed. These results are in agreement with the proposed mechanism (Scheme 3). The more hindered is the ester moiety, the lower is the reactivity of conformer B and the larger is the amount of the *trans* product. For compound **4f** this is true also at low temperature. For the other compounds, at low temperature the equilibration between the two conformers is slower and some of conformer B reacts to give the *cis* product. For the *t*-butyl ester, instead, conformer B is energetically so disfavoured that it exists only in traces. In the case of 1,3-diketones the trend was the same and *t*-butyl groups made again an exception.

Compund **4i** afforded lower yields of dihydrofuran derivative because a competitive process takes place giving **8**. The driving force for this process is the reduced steric hindrance in **8** which was probably formed upon hydration of the intermediate dihydrofuran by a Michael-like reaction during the work-up. Also in this case, lower temperatures resulted in lower diastereoselectivities (Scheme 5).



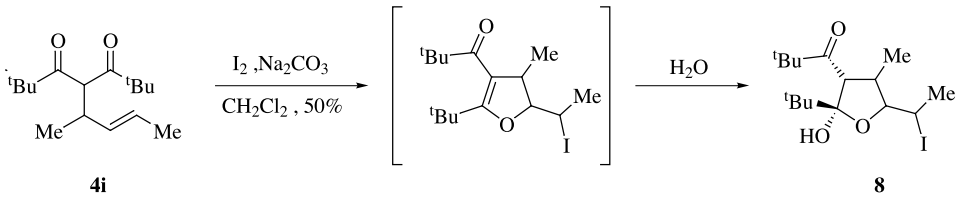
Scheme 4. I_2-induced lactonisation of *t*-butyl esters.

Table 3. Iodoenolcyclisation of 2-(1,3-dimethyl-1-allyl)-1,3-dicarbonyl compounds **4** at −30°C (Scheme 2)[6]

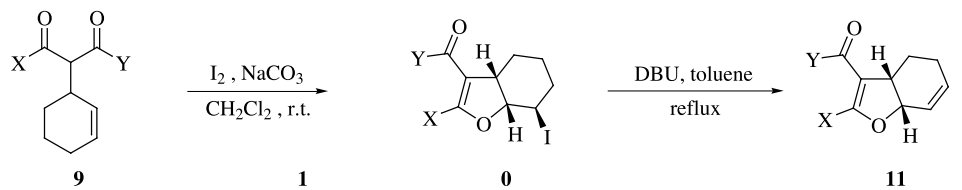
Entry	Compound	X	Y	5/6 ratio[a]	Yield (%)	Time (h)
1	**4a**	Me	MeO	67:33	95	24
2	**4f**	Me	*t*-BuO	98:2	45	2
3	**4b**	*i*-Pr	MeO	75:25	80	3
4	**4g**	Me	Me	25:75	95	4
5	**4i**	*t*-Bu	*t*-Bu	–	–	20
6	**4j**	Ph	Ph	90:10	77	20

[a] Determined by ^{1}H NMR analysis in mixture.

Subsequently we submitted **4g** to the iodoenolcyclisation reaction in the absence of the base. In this case an almost complete formation of the *trans* dihydrofuran derivative was noticed, which strongly supports the correctness of the proposed mechanism. Indeed, in the presence of the base (Na_2CO_3) the iodide anion precipitates as NaI, insoluble in the reaction medium, and the ring closure thus becomes irreversible. The reaction was under kinetic control and the *trans*/*cis* ratio was 60:40. The effect was more evident at −30°C, temperature at which a *trans*/*cis* ratio of 25:75 was obtained.



Scheme 5. Formation of a cyclic hemiketal from **4i**.



Scheme 6. Iodoenolcyclisation of 2-(3-cyclohexenyl)-1,3-dicarbonyl compounds with *Z* configuration.

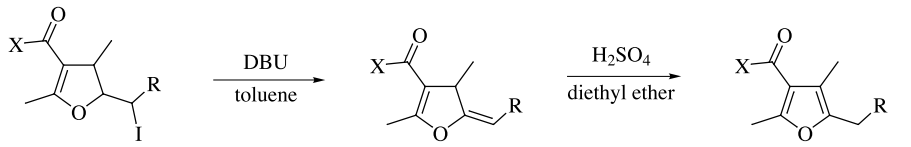
Table 4. Iodoenolcyclisation of 2-(3-cyclohexenyl)-1,3-dicarbonyl compounds with *Z* configuration

Entry	**11**	X	Y	Time (h)	Yield (%)
1	**a**	Me	Me	20	60
3	**b**	Me	OMe	30	75

In the absence of the base, the lack of the counter-ion Na^+ allows the I^- to remain in solution. This anion could capture I^+ from the cyclisation product (**5**, **6**) making the ring closure an equilibrium process. Moreover, the nucleophilic attack of the enol form was slowed down allowing the equilibration between conformers B and A. The reaction was under thermodynamic control and the more stable *trans* isomer was thus produced.

Table 5. Tetrasubstituted furan synthesis from iodoenolcyclisation products

Entry	12	X	R	Solvent	Yield (%)
1	**a**	OMe	H	Benzene	84
2	**b**	Me	H	Benzene	65
3	**c**	OMe	Me	Toluene	80
4	**d**	Me	Me	Toluene	90



2 (3) R=H X=Me, OMe **5 (6)** R=H X=Me, OMe **12** R=H X=Me, OMe

Scheme 7. Tetrasubstituted furan synthesis from iodoenolcyclisation products.

In order to complete our investigation we used another substrate, viz. **9**, in which the allyl group was a 3-cyclohexenyl, with the *Z* configuration of the double bond. The usual reaction led to the bicycle **10** having the ring junction *cis*,[7] the only obtainable upon an *anti*-coplanar attack of the nucleophile (Scheme 6) (Table 4).

To confirm the synthetic pathway leading to tetrasubstituted furans, as previously reported,[8] selected iododihydrofurans were dehydroiodinated by treatment with a non-nucleophilic, sterically hindered amine (DBU) under reflux in benzene or toluene and the obtained products were isomerised to furan derivatives by treatment with sulfuric acid in diethyl ether. All compounds gave good yields of tetrasubstituted furans (Table 5) (Scheme 7).

In conclusion the developed methodology provides an efficient entry to tetrasubstituted 4,5-dihydrofurans, the diastereoselection of the process strictly depending on the substitution degree of the double bond in the starting materials. The obtained iododerivatives can also be employed for the synthesis of tetrasubstituted furans.

1. Experimental

^{1}H NMR 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.

1.1. 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 repeatidly washed with sodium thiosulfate (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 colourless oils.

1.1.1. *trans*-5-Iodomethyl-2-methyl-4-propyl-4,5-dihydro-furan-3-carboxylic acid methyl ester (2b). ^{1}H NMR (δ) 0.90 (t, *J*=7.2 Hz, 3H), 1.1–1.7 (m, 4H), 2.19 (d, *J*=1.2 Hz, 3H), 2.8 (m, 1H), 3.14 (dd, *J*=6.8, 10.2 Hz, part A of an ABX system, 1H), 3.19 (dd, *J*=5.6, 10.2 Hz, part B of an ABX system, 1H), 3.70 (s, 3H), 4.32 (ddd, *J*=3.9, 5.6, 6.8 Hz, 1H). ^{13}C NMR (δ) 7.8, 13.8, 14.1, 18.9, 30.0, 35.4, 47.6, 85.7, 105.7, 166.4, 167.4. MS (*m*/*z*) 324 (12, M^+), 281 (100), 154 (34), 95 (26). IR (cm^{-1}) 2980, 1708, 1385, 1087. Calcd for $C_{11}H_{17}IO_3$ C 40.76, H 5.29; found C 40.5, H 5.1.

1.1.2. *cis*-5-Iodomethyl-2-methyl-4-propyl-4,5-dihydro-furan-3-carboxylic acid methyl ester (3b). ^{1}H NMR (δ) 0.90 (t, *J*=7.2 Hz, 3H), 1.1–1.5 (m, 4H), 2.19 (d, *J*=1.2 Hz, 3H), 2.9 (m, 1H), 3.36 (dd, *J*=6.8, 10.2 Hz, part A of an ABX system, 1H), 3.42 (dd, *J*=7.6, 10.2 Hz, part B of an ABX system, 1H), 3.68 (s, 3H), 4.70 (ddd, *J*=6.8, 6.9, 7.6 Hz, 1H). ^{13}C NMR (δ) 0.5, 13.8, 14.1, 19.9, 29.8, 43.3, 50.6, 86.2, 108.0, 167.3, 168.2. MS (*m*/*z*) 324 (7, M^+), 281 (100), 165 (10), 155 (11), 154 (56), 153 (13), 139 (18), 95 (53), 59 (10). IR (cm^{-1}) 2890, 1650, 1460, 1210. Calcd for $C_{11}H_{17}IO_3$ C 40.76, H 5.29; found C 40.6, H 5.4.

1.1.3. *trans*-5-Iodomethyl-4-isopropyl-2-methyl-4,5-dihydro-furan-3-carboxylic acid methyl ester (2c). ^{1}H NMR (δ) 0.73 (d, *J*=6.9 Hz, 3H), 0.90 (d, *J*=7.0 Hz, 3H), 2.1 (m, 1H), 2.20 (d, *J*=1.3 Hz, 3H), 2.9 (m, 1H), 3.14 (dd, *J*=6.4, 10.3 Hz, part A of an ABX system, 1H), 3.20 (dd, *J*=5.9, 10.3 Hz, part B of an ABX system, 1H), 3.68 (s, 3H), 4.35 (ddd, *J*=3.6, 5.9, 6.4 Hz, 1H). ^{13}C NMR (δ) 8.5, 14.1, 16.3, 19.9, 28.2, 50.7, 53.6, 81.5, 104.5, 166.5, 167.7. MS (*m*/*z*) 324 (5, M^+), 281 (96), 155 (11),154 (98), 153 (32), 139 (24), 95 (100), 59 (15). IR (cm^{-1}) 2890, 1643, 1787, 1210. Calcd for $C_{11}H_{17}IO_3$ C 40.76, H 5.29; found C 40.5, H 5.0.

1.1.4. *trans*-4-*tert*-Butyl-5-iodomethyl-2-methyl-4,5-dihydro-furan-3-carboxylic acid methyl ester (2d). ^{1}H NMR (δ) 0.82 (s, 9H), 2.19 (d, *J*=1.4 Hz, 3H), 2.75 (m, 1H),

3.08 (dd, *J*=7.0, 10.2 Hz, part A of an ABX system, 1H), 3.19 (dd, *J*=6.2, 10.2 Hz, part B of an ABX system, 1H), 3.68 (s, 3H), 4.4 (ddd, *J*=4.2, 6.2, 7.0 Hz, 1H). ^{13}C NMR (δ) 7.3, 14.1, 26.6 (3C), 34.1, 50.6, 56.8, 83.4, 103.9, 167.3, 167.6. MS (*m/z*) 338 (4, M^+), 307 (5), 282 (10), 281 (100), 154 (42), 94 (24). IR (cm^{-1}) 3009, 1699, 1387, 1210. Calcd for $C_{12}H_{19}IO_3$ C 42.62, H 5.66; found C 42.4, H 5.5.

1.1.5. *cis*-4-*tert*-Butyl-5-iodomethyl-2-methyl-4,5-dihydro-furan-3-carboxylic acid methyl ester (3d). ^{1}H NMR (δ) 0.90 (s, 9H), 2.20 (d, *J*=1.3 Hz, 3H), 2.7–2.8 (m, 1H), 3.24 (dd, *J*=6.4, 10.6 Hz, part A of an ABX system, 1H), 3.35 (dd, *J*=5.6, 10.6 Hz, part B of an ABX system, 1H), 3.65 (s, 3H), 5.1–5.2 (m, 1H). ^{13}C NMR (δ) 1.8, 14.1, 27.7 (3C), 29.2, 52.0, 57.1, 79.9, 103.9, 165.0, 166.1. MS (*m/z*) 280 (100), 154 (41), 94 (24). IR (cm^{-1}) 19556, 1640, 1387, 1110. Calcd for $C_{12}H_{19}IO_3$ C 42.62, H 5.66; found C 42.5, H 5.9.

1.1.6. *cis*-2′-Iodomethyl-5′-methyl-2′,3′-dihydro-[2,3′]-bifuranyl-4′-carboxylic acid methyl ester (3f). ^{1}H NMR (δ) 2.29 (d, *J*=1.3 Hz, 3H), 2.95 (dd, *J*=7.6, 10.2 Hz, part A of an ABX system, 1H), 3.00 (dd, *J*=4.5, 10.2 Hz, part B of an ABX system, 1H), 3.59 (s, 3H), 4.45 (bd, *J*=9.0 Hz, 1H), 4.90 (ddd, *J*=4.5, 7.6, 9.0 Hz, 1H), 6.10 (d, *J*=3.3 Hz, 1H), 6.29 (dd, *J*=1.8, 3.3 Hz, 1H), 7.32 (d, *J*=1.8 Hz, 1H). ^{13}C NMR (δ) 1.5, 14.5, 45.1, 51.3, 86.1, 105.2, 108.9, 110.9, 142.7, 151.9, 166.2, 170.1. MS (*m/z*) 219 (63), 104 (32), 95 (30), 92 (100), 67 (80). IR (cm^{-1}) 1645, 1333, 1200. Calcd for $C_{12}H_{13}IO_4$ C 41.40, H 3.76; found C 41.6, H 4.0.

1.1.7. *trans*-5-(1-Iodo-ethyl)-2,4-dimethyl-4,5-dihydro-furan-3-carboxylic acid methyl ester (5a). ^{1}H NMR (δ) 1.23 (d, *J*=6.6 Hz, 3H), 1.87 (d, *J*=7.3 Hz, 3H), 2.19 (d, *J*=0.8 Hz, 3H), 3.03 (ddq, *J*=0.8, 4.8, 6.6 Hz, 1H), 3.68 (s, 3H), 3.95 (dd, *J*=4.8, 7.0 Hz, 1H), 4.11 (dq, *J*=6.6, 7.0 Hz, 1H). ^{13}C NMR (δ) 14.4, 21.3, 23.4, 29.7, 43.0, 50.9, 92.9, 107.2, 166.3, 167.1. MS (*m/z*) 310 (10, M^+), 183 (15),127 (11), 109 (11), 43 (100). IR (cm^{-1}) 2975, 1690, 1648, 1446. Calcd for $C_{10}H_{15}IO_3$ C 38.73, H 4.88; found C 38.9, H 4.6.

1.1.8. *cis*-5-(1-Iodo-ethyl)-2,4-dimethyl-4,5-dihydro-furan-3-carboxylic acid methyl ester (6a). ^{1}H NMR (δ) 1.08 (d, *J*=6.6 Hz, 3H), 2.04 (d, *J*=6.6 Hz, 3H), 2.14 (d, *J*=0.8 Hz, 3H), 3.22 (m, 1H), 3.68 (s, 3H), 4.12 (dq, *J*=6.6, 11.0 Hz, 1H), 4.55 (dd, *J*=7.3, 11.0 Hz, 1H).

1.1.9. *trans*-5-(1-Iodo-ethyl)-2-isopropyl-4-methyl-4,5-dihydro-furan-3-carboxylic acid methyl ester (5b). ^{1}H NMR (δ) 1.10 (d, *J*=7.3 Hz, 6H), 1.22 (d, *J*=7.0 Hz, 3H), 1.89 (d, *J*=7.0 Hz, 3H), 3.03 (dq, *J*=4.4, 7.0 Hz, 1H), 3.57 (ept, *J*=7.3 Hz, 1H), 3.68 (s, 3H), 3.95 (dd, *J*=4.4, 7.4 Hz, 1H), 4.09 (dq, *J*=7.0, 7.4 Hz, 1H). ^{13}C NMR (δ) 19.5, 19.7, 21.2, 23.4, 26.9, 29.6, 42.7, 50.6, 92.4, 104.9, 166.0, 174.6. MS (*m/z*) 338 (10, M^+), 211 (11), 127 (12), 109 (10), 79 (12), 71 (22), 69 (10), 59 (15), 43 (100), 41 (46). IR (cm^{-1}) 3450, 3015, 1732, 1703, 1647, 1470. Calcd for $C_{12}H_{19}IO_3$ C 42.62, H 5.66; found C 42.4, H 5.7.

1.1.10. *cis*-5-(1-Iodo-ethyl)-2-isopropyl-4-methyl-4,5-dihydro-furan-3-carboxylic acid methyl ester (6b). ^{1}H NMR (δ) 1.10 (d, *J*=7.3 Hz, 6H), 1.24 (d, *J*=6.6 Hz, 3H), 2.04 (d, *J*=7.0 Hz, 3H), 3.16 (dq, *J*=6.6, 7.3 Hz, 1H), 3.57 (m, 1H), 3.68 (s, 3H), 4.22 (dq, *J*=7.3, 10.9 Hz, 1H), 4.48 (dd, *J*=7.3, 10.9 Hz, 1H).

1.1.11. *trans*-2-*tert*-Butyl-5-(1-iodo-ethyl)-4-methyl-4,5-dihydro-furan-3-carboxylic acid methyl ester (5c). ^{1}H NMR (δ) 1.22 (d, *J*=6.6 Hz, 3H), 1.29 (s, 9H), 1.90 (d, *J*=6.8 Hz, 3H), 3.09 (dq, *J*=4.0, 6.6 Hz, 1H), 3.62 (s, 3H), 3.85 (dd, *J*=4.0, 7.3 Hz, 1H), 4.10 (dq, *J*=6.8, 7.3 Hz, 1H). ^{13}C NMR (δ) 21.6, 23.5, 27.6 (3C), 29.7, 34.6, 44.5, 50.8, 91.3, 105.3, 165.6, 175.6. MS (*m/z*) 352 (18, M^+), 295 (10), 225 (12), 137 (14), 135 (13), 127 (15), 109 (10), 79 (11), 69 (15), 67 (10), 57 (100). IR (cm^{-1}) 2992, 1720, 1478. Calcd for $C_{13}H_{21}IO_3$ C 44.33, H 6.01; found C 44.2, H 6.3.

1.1.12. *trans*-5-(1-Iodo-ethyl)-4-methyl-2-phenyl-4,5-dihydro-furan-3-carboxylic acid methyl ester (5d). ^{1}H NMR (δ) 1.40 (d, *J*=6.6 Hz, 3H), 2.00 (d, *J*=7.0 Hz, 3H, 3.30 (dq, *J*=4.4, 6.6 Hz, 1H), 4.12 (dd, *J*=4.4, 7.4 Hz, 1H), 4.28 (dq, *J*=7.0, 7.4 Hz, 1H), 7.42 (m, 3H), 7.79 (m, 2H). ^{13}C NMR (δ) 21.3, 23.4, 29.5, 44.3, 50.9, 91.9, 107.4, 127.6 (2C), 129.3 (2C), 128.9, 130.4, 164.3, 165.3. MS (*m/z*) 372 (11, M^+), 245 (10), 171 (11), 105 (100), 77 (46), 51 (11). IR (cm^{-1}) 3015, 2935, 1691, 1651. Calcd for $C_{15}H_{17}IO_3$ C 48.40, H 4.60; found C 48.6, H 4.6.

1.1.13. *trans*-5-(1-Iodo-ethyl)-2,4-dimethyl-4,5-dihydro-furan-3-carboxylic acid ethyl ester (5e). ^{1}H NMR (δ) 1.26 (d, *J*=7.0 Hz, 3H), 1.28 (t, *J*=7.6 Hz, 3H), 1.90 (d, *J*=6.6 Hz, 3H), 2.19 (d, *J*=1.0 Hz, 3H), 3.00–3.10 (m, 1H), 3.98 (dd, *J*=4.2, 7.0 Hz, 1H), 4.05 (q, *J*=7.6 Hz, 2H), 4.24 (dq, *J*=6.6, 7.2 Hz, 1H). ^{13}C NMR (δ) 13.7, 14.4, 21.1, 23.3, 29.5, 42.9, 59.4, 92.7, 107.3, 165.8, 166.8. MS (*m/z*) 324 (16, M^+), 279 (11), 197 (15), 127 (13), 109 (14), 43 (100), 41 (16). IR (cm^{-1}) 3450, 2935, 1691, 1651. Calcd for $C_{11}H_{17}IO_3$ C 40.76, H 5.29; found C 40.9, H 5.1.

1.1.14. *cis*-5-(1-Iodo-ethyl)-2,4-dimethyl-4,5-dihydro-furan-3-carboxylic acid ethyl ester (5e). ^{1}H NMR (δ), representative signals: 1.10 (d, *J*=7.0 Hz, 3H), 1.82 (d, *J*=6.9 Hz, 3H), 2.14 (d, *J*=0.9 Hz, 3H), 4.51 (dd, *J*=7.0, 11.0 Hz, 1H).

1.1.15. *trans*-5-(1-Iodo-ethyl)-2,4-dimethyl-4,5-dihydro-furan-3-carboxylic acid *tert*-butyl ester (5f). ^{1}H NMR (δ) 1.25 (d, *J*=6.6 Hz, 3H), 1.48 (s, 9H), 1.90 (d, *J*=6.6 Hz, 3H), 2.15 (d, *J*=0.7 Hz, 3H), 2.99–3.02 (m, 1H), 3.97 (dd, *J*=4.8, 7.8 Hz, 1H), 4.12 (dq, *J*=6.6, 7.8 Hz, 1H). ^{13}C NMR (δ) 13.3, 20.1, 22.4, 27.4 (3C), 28.8, 42.2, 78.7, 91.6, 107.6, 164.6, 164.7. MS (*m/z*) 352 (21, M^+), 296 (33), 281 (14), 279 (31), 169 (39), 154 (12), 153 (14), 127 (16), 109 (17), 57 (20),43 (100), 41 (29). IR (cm^{-1}) 2980, 1681, 1650, 1460. Calcd for $C_{13}H_{21}IO_3$ C 44.33, H 6.01; found C 44.3, H 6.2.

1.1.16. *trans*-1-[5-(1-Iodo-ethyl)-2,4-dimethyl-4,5-dihydro-furan-3-yl]-ethanone (5g). ^{1}H NMR (δ) 1.11 (d, *J*=7.0 Hz, 3H), 2.06 (d, *J*=7.0 Hz, 3H), 2.19 (d, *J*=0.8 Hz, 3H), 2.25 (s, 3H), 3.12 (m, 1H), 3.95 (dd, *J*=4.4, 7.0 Hz, 1H), 4,12 (dq, *J*=7.0, 7.0 Hz, 1H). ^{13}C NMR (δ) 15.4, 21.4, 21.6, 23.4, 29.4, 43.3, 92.9, 118.2, 166.3, 194.2. MS (*m/z*) 294 (2, M^+), 167 (14), 127 (6), 43 (100). Calcd for $C_{10}H_{15}IO_2$ C 40.83, H 5.14; found C 40.7, H 5.0.

1.1.17. *cis*-1-[5-(1-Iodo-ethyl)-2,4-dimethyl-4,5-dihydro-furan-3-yl]-ethanone (6g). ^{1}H NMR (δ) 1.08 (d, J=6.6 Hz, 3H), 2.04 (d, J=7.0 Hz, 3H), 2.16 (d, J=0.6 Hz, 3H), 2.23 (s, 3H), 3.25 (m, 1H), 4.15 (dq, J=6.6, 11.4 Hz, 1H), 4.52 (dd, J=7.0, 11.4 Hz, 1H). ^{13}C NMR (δ) 12.5, 15.6, 20.9, 25.8, 29.1, 40.2, 90.6, 120.4, 167.3, 194.1. MS (*m*/*z*) 294 (4, M^+), 167 (5), 127 (5), 43 (100). Calcd for $C_{10}H_{15}IO_2$ C 40.83, H 5.14; found C 40.9, H 5.2.

1.1.18. *trans*-1-[2-Ethyl-5-(1-iodo-ethyl)-4-methyl-4,5-dihydro-furan-3-yl]-propan-1-one (5h). ^{1}H NMR (δ) 1.10 (t, J=7.3 Hz, 3H), 1.15 (t, J=7.5 Hz, 3H), 1.25 (d, J=6.7 Hz, 3H), 1.91 (d, J=7.0 Hz, 3H), 2.51 (q, J=7.3 Hz, 2H), 2.60–2.80 (m, 2H), 3.16 (m, 1H), 3.96 (dd, J=4.0, 7.2 Hz, 1H), 4,12 (dq, J=7.0, 7.2 Hz, 1H). ^{13}C NMR (δ) 8.3, 11.3, 21.7, 22.3, 23.5, 29.6, 34.2, 43.2, 92.7, 116.3, 170.4, 197.5. MS (*m*/*z*) 167 (85), 127 (11), 111 (6), 95 (7), 69 (16), 57 (100), 41 (40). IR (cm^{-1}) 3050, 1716, 1684, 1640. Calcd for $C_{12}H_{19}IO_2$ C 44.74, H 5.94; found C 44.5, H 6.1.

1.1.19. *trans*-1-[2-*tert*-Butyl-5-(1-iodo-ethyl)-4-methyl-4,5-dihydro-furan-3-yl]-2,2-dimethyl-propan-1-one (5i). ^{1}H NMR (δ) 1.09 (s, 9H), 1.12 (d, J=6.6 Hz, 3H), 1.21 (s, 9H), 1.95 (d, J=7.3 Hz, 3H), 3.25 (dq, J=4.4, 6.6 Hz, 1H), 3.77 (dd, J=4.4, 7.3 Hz, 1H), 4.20 (dq, J=7.3, 7.3 Hz, 1H). 13C NMR (δ) 21.0, 23.8, 27.9 (3 C), 28.6 (3 C), 31.6, 33.5, 44.8, 47.3, 90.6, 113.4, 161.1, 211.4. MS (*m*/*z*) 269 (3), 255 (5), 167 (5), 127 (12), 85 (9), 69 (7), 57 (100), 41 (27). IR (cm^{-1}) 2992, 1676, 1488. Calcd for $C_{16}H_{27}IO_2$ C 50.80, H 7.19; found C 50.6, H 6.9.

1.1.20. *trans*-[5-(1-Iodo-ethyl)-4-methyl-2-phenyl-4,5-dihydro-furan-3-yl]-phenyl-methanone (5j). ^{1}H NMR (δ) 1.39 (d, J=6.6 Hz, 3H), 1.95 (d, J=7.0 Hz, 3H), 3.51 (dq, J=5.4, 6.6 Hz, 1H), 4.09 (dd, J=5.4, 6.2 Hz, 1H), 4.33 (dq, J=6.6, 7.0 Hz, 1H), 7.4–7.5 (m, 2H), 6.9–7.2 (m, 8H). ^{13}C NMR (δ) 20.9, 23.3, 29.3, 45.7, 92.2, 116.6, 127.6 (2 C), 127.7 (2 C), 128.9 (2 C), 129.1 (2 C), 130.0, 130.1, 131.3, 139.1, 166.5, 193.4. MS (*m*/*z*) 418 (11, M^+), 291 (6), 171 (5), 105 (100), 77 (43), 51 (8). Calcd for $C_{20}H_{19}IO_2$ C 57.43, H 4.58; found C 57.2, H 4.9.

1.1.21. *cis*-[5-(1-Iodo-ethyl)-4-methyl-2-phenyl-4,5-dihydro-furan-3-yl]-phenyl-methanone (6j). ^{1}H NMR (δ) 1.32 (d, J=6.6 Hz, 3H), 2.10 (d, J=6.0 Hz, 3H), 3.62 (dq, J=6.6, 7.3 Hz, 1H), 4.34 (dq, J=6.6, 10.9 Hz, 1H), 4.92 (dd, J=7.3, 10.9 Hz, 1H), 7.0–7.5 (m, 10H). Calcd for $C_{20}H_{19}IO_2$ C 57.43, H 4.58; found C 57.6, H 4.3.

1.1.22. 3-Acetyl-5-(1-iodo-ethyl)-4-methyl-dihydro-furan-2-one (7). Inseparable mixture of two diastereoisomers in 9:1 ratio. Major: ^{1}H NMR (δ) 1.3 (d, J=7.2 Hz, 3H), 2.07 (d, J=6.6 Hz, 3H), 2.4 (s, 3H), 3.2 (ddq, J=1.1, 4.9, 7.2 Hz, 1H), 3.5 (d, J=1.1 Hz, 1H), 3.96 (dq, J=6.6, 11.0 Hz, 1H), 4.66 (dd, J=4.9, 11.0 Hz, 1H); ^{13}C NMR (δ) 12.4, 20.9, 25.7, 29.2, 35.9, 65.0, 86.6, 171.3, 199.1. Minor: ^{1}H NMR (δ) 1.07 (d, J=6.6 Hz, 3H), 2.11 (d, J=6.6 Hz, 3H), 2.42 (s, 3H), 3.0–3.2 (m, 1H), 3.43 (d, J=7.0 Hz, 1H), 3.9–4.1 (m, 1H), 4.45 (dd, J=5.8, 11.0 Hz, 1H); ^{13}C NMR (δ) 13.7, 21.6, 25.8, 30.0, 35.5, 64.9, 86.5, 171.3, 199.1. IR (cm^{-1}) 2880, 1760, 1715, 1160, 1060.

1.1.23. 1-[2-*tert*-Butyl-2-hydroxy-5-(1-iodo-ethyl)-4-methyl-tetrahydro-furan-3-yl]-2,2-dimethyl-propan-1-one (8). It was obtained as one diastereoisomer of which we did not determine the stereochemistry. ^{1}H NMR (δ) 0.95 (s, 9H), 1.04 (d, J=7.0 Hz, 3H), 1.22 (s, 9H), 1.88 (d, J=6.6 Hz, 3H), 2.48 (ddq, J=3.6, 7.0, 9.5 Hz, 1H), 3.22 (dd, J=3.6, 3.6 Hz, 1H), 3.66 (d, J=9.5 Hz, 1H), 4.39 (dq, J=3.6, 6.6 Hz, 1H). ^{13}C NMR (δ) 18.9, 24.3, 25.7, 26.5, 34.0, 38.0, 42.4, 45.6, 48.4, 88.0, 111.2, 219.9. IR (cm^{-1}) 3250, 2955, 1710, 1067. Calcd for $C_{16}H_{29}IO_3$ C 48.49, H 7.38; found C 48.6, H 7.1.

Compounds **2a**, **3a**, **2e**, **3e**,[4] **10a**,**b**,[2] **11a**,**b**,[9] **12a**,[10] **12b**,[11] **12c**,**d**,[12] are already known and physical data were identical to that reported in literature.

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