Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 9963–9969

Polymer-supported selenium-induced electrophilic cyclization: solid-phase synthesis of poly-substituted dihydrofurans and tetrahydrofurans

E. Tang,[a] Xian Huang[a,b,*] and Wei-Ming Xu[a]

[a]*Department of Chemistry, Zhejiang University (Xixi Campus), Hangzhou 310028, People's Republic of China*
[b]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, People's Republic of China*

Received 12 May 2004; revised 5 August 2004; accepted 10 August 2004

Available online 11 September 2004

Abstract—Poly-substituted dihydrofurans and tetrahydrofurans have been synthesized through polymer-supported selenium-induced intramolecular electrophilic cyclization, followed by selenoxide *syn*-elimination or novel nucleophilic substitution cleavage of selenium resin with good yields and purities.

1. Introduction

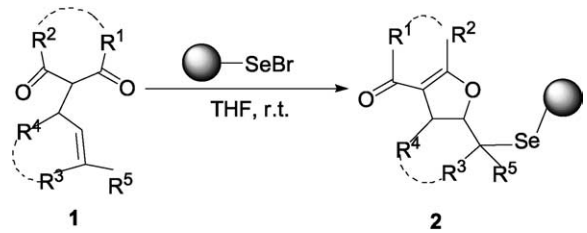
The preparation of diverse libraries of organic compounds is an important fact of modern drug discovery programs. One of the most commonly employed methods in library production is solid phase organic synthesis (SPOS).[1] It has shown that compounds with biological activities are often derived from heterocyclic structures.[2]

Dihydrofurans and tetrahydrofurans are two important classes of heterocycles with widespread occurrence in nature.[3] Possessing a variety of biological activities, they are used as pharmaceutical, flavor, insecticidal, and fish antifeedant agents.[4] Despite having important biological activities there are very few reports dealing with the polymer-supported synthesis of libraries based on functionalized dihydrofurans and tetrahydrofurans.[5] And also, most of the dihydrofurans and tetrahydrofurans prepared by a solid-phase method are mono- or di-substituted.

Since the first organoselenium resin[6] was reported in 1976, several groups have developed organoselenium resins as convenient linkers.[7,8] Recently, our research group has been interested in the application of organic selenium resins in organic synthesis.[9] A simple preparation of polysubstituted dihydrofuran and tetrahydrofuran is reported by polystyrene-supported selenium-induced regioselective intramolecular electrophilic cyclization of allyl substituted 1,3-dicarbonyl compounds. Evident advantages of this reaction are easy operations, odorlessness and good purity of the products. And also the resins can be regenerated and reused.

2. Results and discussion

We began our efforts from polystyrene-supported selenenyl bromide[7] (dark-red resin, Se: 1.02 mmol/g), which was treated with α-allyl substituted 1,3-dicarbonyl compounds **1**, followed by the conditions that Ferraz et al.[10] had devised in solution phase. The rapid decolorization of polystyrene-supported selenenyl bromide occurred when 2.5 equiv of the compound **1** were used (Scheme 1). After stirred at rt for 3 h, the ring-closure reaction on solid-phase completed, which was determined by the elemental analysis of resin **2** (Br was undetectable). The reaction was also monitored by

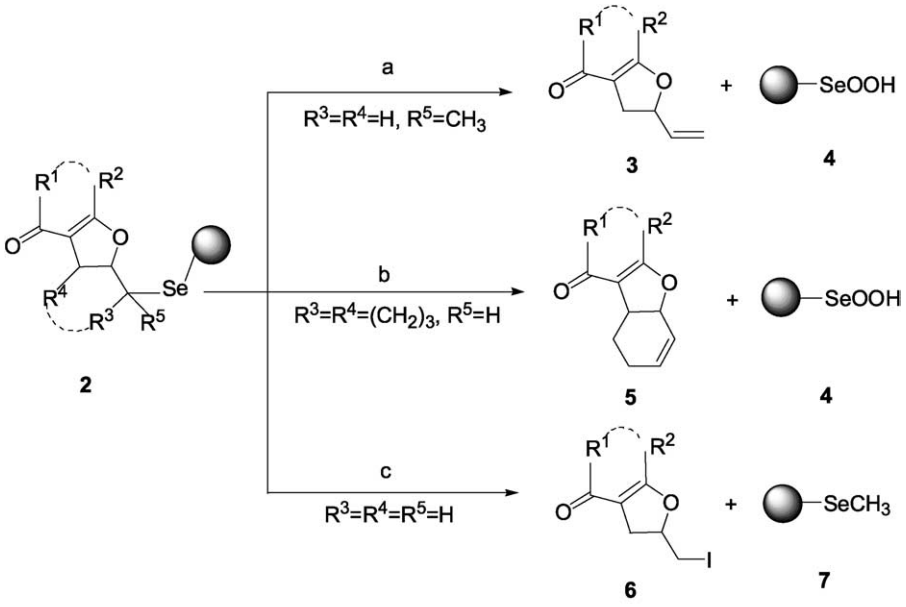


1 2

Scheme 1.

Keywords: Solid phase synthesis; Selenium mediated intramolecular cyclization; Allyl-substituted 1,3-dicarbonyls; Dihydrofurans; Tetrahydrofurans.
* Corresponding author. Tel./fax: +86-571-88807077;
e-mail: huangx@mail.hz.zj.cn

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.08.042



Scheme 2.

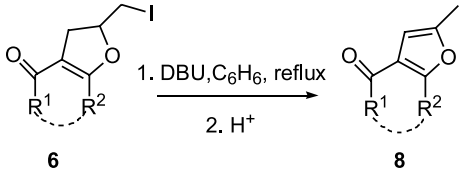
FT-IR, which showed a strong peak of carbonyl absorption between 1680–1730 cm^{-1}.

In our reaction, the cleavage reaction of resins **2** was fully determined by the substituents R^3 and R^5 (Scheme 2). When R^3 or R^5 was not hydrogen, selenoxide *syn*-elimination underwent smoothly to give poly-substituted dihydrofuran **3** and **5** respectively (Scheme 2 step a and b). The generated resin **4** can be recycled and reused.[9a] But when R^3 and R^5 were both hydrogen, selenoxide *syn*-elimination did not occur when we treated resin **2** with H_2O_2 even at 50 °C in THF.

Common cleavage protocols of selenium linkers[11] have been reported using two strategies: selenoxide *syn*-elimination and radical hydride transfer. $^nBu_3SnH$ could be used here as a good radical hydride transfer reagent, but it was too toxic. Herein we report a new cleavage protocol using CH_3I/NaI in DMF under mild conditions that Corey et al.[12] devised in the solution conditions (Scheme 2 step c). Iodomethyl-substituted dihydrofurans **6** were obtained in good yields and purities. The results are listed in Table 1.

A significant feature of this novel nucleophilic substitution cleavage reaction (Scheme 2 step c) was that a new functional group (iodine), with versatile reactivities in organic synthesis, was introduced during the cleavage stage. Iodomethyl dihydrofurans **6** could be dehydrohalogenated to afford the corresponding furans **8** by treated with DBU followed by acid-catalyzed rearrangement (Scheme 3). The results are summarized in Table 2.

In order to expand the diversity of this method, γ-allyl substituted 1,3-dicarbonyl compounds **9** were used to perform the intramolecular electrophilic cyclization with polymer-supported selenenyl bromide (Scheme 4). It was not surprised that resins **10** were obtained almost



Scheme 3.

Table 1. Synthesis of poly-substituted dihydrofurans

Product[a]	R^1	R^2	R^3	R^4	R^5	Yield[b] (%)	Purity[c] (%)
3a[d]	OCH_3	CH_3	H	H	CH_3	85	90
5a[d]	OCH_3	CH_3	$-CH_2CH_2CH_2-$		H	80	87
5b[d]	OC_2H_5	CH_3	$-CH_2CH_2CH_2-$		H	82	82
6a	$-CH_2CH_2CH_2-$		H	H	H	89	89
6b	$-CH_2C(CH_3)_2CH_2-$		H	H	H	88	87
6c	OCH_3	CH_3	H	H	H	80	95
6d	OC_2H_5	CH_3	H	H	H	78	95
6e	C_6H_5	C_6H_5	H	H	H	76	90
6f	CH_3	C_6H_5	H	H	H	79	86
6g	CH_3	CH_3	H	H	H	86	92

[a] NaI, CH_3I, DMF, 75 °C.
[b] Overall yield based on the loading of selenium bromide resin (1.02 mmol/g).
[c] Purity determined by HPLC.
[d] H_2O_2 (30%), 7.0 equiv, THF, 0 °C–rt.

Table 2. Synthesis of poly-substituted furans

Product	R_1	R_2	Yield[a] (%)
8a	$-CH_2CH_2CH_2-$		80
8b	$-CH_2C(CH_3)_2CH_2-$		78
8c	OCH_3	CH_3	74
8d	OC_2H_5	CH_3	71
8e	CH_3	C_6H_5	72
8f	C_6H_5	C_6H_5	79

[a] Isolated yield.

quantitatively. Followed by the deselenenylation reaction with methyl iodide and sodium iodide in DMF at 75 °C, poly-substituted iodomethyl tetrahydrofurans **11**[13] were obtained in good yields and purities. The results are summarized in Table 3.

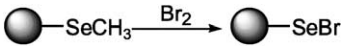
Table 3. Synthesis of poly-substituted tetrahydrofurans

Product	R^1	R^2	R^3	Yield[a] (%)	Purity[b] (%)
11a	CH_3	H	H	85	95
11b	CH_3	H	C_2H_5	80	95
11c	CH_3	H	n-C_4H_9	73	90
11d	CH_3	$CH_2CH{=}CH_2$	H	72	86
11e	CH_3	H	$PhCH_2$	86	88
11f	C_2H_5	H	H	86	95
11g	C_2H_5	CH_3	H	78	93
11h	C_2H_5	C_2H_5	H	82	93
11i	C_2H_5	$PhCH_2$	H	83	87

[a] Overall yield based on the loading of selenium bromide resin (1.02 mmol/g).
[b] Purity determined by HPLC.

It is noteworthy that polystyrene-supported methyl selenide (resin **7**) was generated after the cleavage stage. Resin **7** could be reused as the starting material and recycled in the same reaction for several times without the loss of purities of the products but with a slight decrease in yields. Results are given in Table 4.

Table 4. Circulation of the polymer selenium resin



Substrate	Times	Yield[a] (%)	Purity[b] (%)
6a	1	89	89
6a	2	87	89
6a	3	87	87
6a	4	84	88

[a] Overall yield based on the loading of selenium bromide resin (1.02 mmol/g).
[b] Purity determined by HPLC.

3. Conclusion

In conclusion, a novel preparation of poly-substituted dihydrofurans and tetrahydrofurans has been developed by a polystyrene-supported selenium induced regioselective intramolecular cyclization, followed by the selenoxide *syn*-elimination or a novel nucleophilic substitution cleavage of selenium resin.

4. Experimental

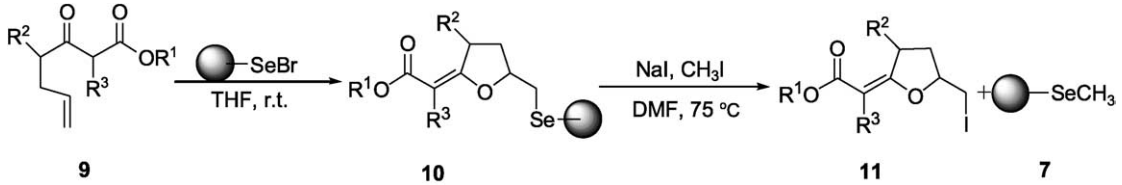
4.1. General

Starting materials were obtained from commercial suppliers and used without further purification. THF was distilled from sodium/benzophenone immediately prior to use. Polystyrene (H 1000, 100–200 mesh, cross-linked with 1% divinylbenzene) for the preparation of selenenyl bromide resin (1.02 mmol Br/g) according to the procedure described by Nicolaou and co-workers[7] was purchased from commercial sources. Allyl substituted 1,3-dicarbonyl compounds **1** and **9** were prepared according to the literature procedures.[14,15] ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance (400 MHz) spectrometer, using $CDCl_3$ as the solvent and TMS as an internal standard. Mass spectra (EI, 70 eV) were recorded on a HP5989B mass spectrometer. Infrared spectra were recorded on a Shimadzu IR-408 spectrometer and measured as thin film or in KBr. Elemental analyses were performed on a Flash EA1112 instrument. HPLC was performed on an Agilernt 1100 High performance liquid chromatograph. The samples were further purified by TLC for ^{13}C NMR and microanalyses.

4.2. General procedure for the preparation of dihydrofurans (3a, 5a, 5b)

To a suspension of the swellen polymer-supported selenium bromide resin (1.0 g, 1.02 mmol/g) in dry THF (15 mL), α-allyl-1, 3-dicarbonyl compounds (2.5 equiv) was added. The suspension was stirred at rt for 3 h. The mixture was filtered and the resin was washed with THF (10 mL×3) and CH_2Cl_2 (10 mL×3) and dried in vacuum at 65 °C to afford dry selenocyclic enol ether resin **2**.

To a suspension of the swellen selenocyclic enol ether resin **2** (1.0 g) in THF (15 mL), 30% H_2O_2 (1.5 mL) was added at 0 °C. The suspension was stirred at 0 °C for 0.5 h and rt for 1.0 h, the mixture was filtered and the resin was washed with CH_2Cl_2 (10 mL×3), the filtrate was washed with saturated $NaHCO_3$, and H_2O, respectively, dried over



Scheme 4.

$MgSO_4$, and evaporated to dryness in vacuum to afford dihydrofurans **3a**, **5a** and **5b**.

4.2.1. 2-Methyl-5-vinyl-4, 5-dihydro-furan-3-carboxylic acid methyl ester (3a). The title compound was obtained as a light yellow oil (85%). ν (neat) 3078, 2975, 1695, 1645, 1226, 990 and 908 cm^{-1}; δ_H 5.95–5.88 (1H, m), 5.30 (1H, d, J=17.2 Hz), 5.20 (1H, d, J=10.4 Hz), 5.08–5.00 (1H, m), 3.70 (3H, s), 3.05 (1H, dd, J=12.4, 14.0 Hz), 2.67 (1H, dd, J=7.6, 14.0 Hz), 2.21 (3H, s); δ_C 168.8, 166.6, 135.6, 115.1, 101.2, 80.0, 50.8, 34.2, 13.4; *m/z* 169 (100%), 168 (M^+, 27), 137 (16), 116 (8). Anal. calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.20; H, 7.08%.

4.2.2. 2-Methyl-3a, 4, 5, 7a-tetrahydro-benzofuran-3-carboxylic acid methyl ester (5a). The title compound was obtained as a light yellow oil (80%). ν (neat) 2978, 1694, 1649, 1444, 1380, 1224, 1084, 964, 758, 615 cm^{-1}; δ_H 6.21–6.17 (1H, m), 5.92 (1H, d, J=10.4 Hz), 4.71 (1H, d, J=8.8 Hz), 3.70 (3H, s), 3.04–2.96 (1H, m), 2.18 (3H, s), 2.13–2.20 (2H, m), 1.92–1.81 (1H, m), 1.28–1.17 (1H, m); δ_C 168.6, 166.6, 134.5, 123.1, 107.6, 78.1, 50.5, 40.0, 24.9, 23.1, 14.5; *m/z* 195 (100%), 194 (M^+, 52), 163 (39), 162 (22), 161 (12), 119 (15), 116 (34), 91 (53), 79 (15), 65 (13), 43 (85). Anal. calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.12; H, 7.35%.

4.2.3. 2-Methyl-3a, 4, 5, 7a-tetrahydro-benzofuran-3-carboxylic acid ethyl ester (5b). The title compound was obtained as a light yellow oil (82%). ν (neat) 2928, 1697, 1636, 1382, 1218, 1099, 1080, 954, 876, 840, 705 cm^{-1}; δ_H 6.13 (1H, dt, J=8.4, 6.8 Hz), 5.92 (1H, d, J=9.6 Hz), 4.71 (1H, d, J=7.6 Hz), 4.13 (2H, t, J=7.2 Hz), 3.02–2.91 (1H, m), 2.15 (3H, s), 2.02 (2H, t, J=12 Hz), 1.93–1.85 (1H, m), 1.24 (3H, t, J=8.0 Hz), 1.28–1.12 (1H, m); δ_C 168.2, 166.2, 134.4, 123.2, 107.8, 77.9, 59.2, 40.1, 24.9, 23.1, 14.4, 14.4; *m/z* 209 (100%), 208 (M^+, 39), 163 (33), 162 (15), 130 (12), 91 (27), 43 (44). Anal. calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.30; H, 7.63%.

4.3. General procedure for the preparation of iodomethyldihydrofurans (6a–6g)

To a suspension of the swellen selenocyclic enol ether resin **2** (1.0 g), in dry DMF (15 mL), NaI (1.5 g) and CH_3I (1.5 mL) were added under nitrogen. The suspension was stirred at 75 °C for 18 h. The mixture was filtered and the resin was washed with CH_2Cl_2 (10 mL×3), the filtrate was washed with saturated $Na_2S_2O_3$ and H_2O respectively and extracted with CH_2Cl_2 (10 mL×3), dried over $MgSO_4$, and evaporated to dryness in vacuum to afford iodomethyldihydrofurans **6a–6g**.

4.3.1. 2-Iodomethyl-3, 5, 6, 7-tetrahydro-2*H*-furan-benzofuran-4-one (6a). The title compound was obtained as a light yellow oil (89%). ν (neat) 2946, 1631, 1402, 1231, 1179, 917, 731 cm^{-1}; δ_H 4.82 (1H, ddt, J=10.4, 6.8, 6.0 Hz); 3.33 (2H, d, J=6.0 Hz); 2.96 (1H, dd, J=14.4, 10.4 Hz); 2.56 (1H, dd, J=14.4, 6.8 Hz); 2.42 (2H, t, J=6.0 Hz); 2.32 (2H, t, J=6.0 Hz); 2.02 (2H, quintet, J=6.0 Hz); δ_C ($CDCl_3$) 195.3, 176.6, 112.9, 83.5, 36.4, 32.5, 23.8, 21.6, 8.1; *m/z* 278 (M^+, 10), 279 (100), 250 (8), 151 (78), 152 (11), 123 (14), 105 (8), 95 (21), 81 (23), 67 (14), 55 (21), 53 (31), 52 (11), 51 (11), 43 (19), 42 (13), 41 (32). Anal. calcd for $C_9H_{11}IO_2$: C, 38.87; H, 3.99; I, 45.63. Found: C, 38.78; H, 4.06; I, 45.58%.

4.3.2. 2-Iodomethyl-6, 6-dimethyl-3, 5, 6, 7-tetrahydro-2*H*-benzofuran-4-one (6b). The title compound was obtained as a light yellow oil (88%). ν (neat) 2957, 1637, 1402, 1218, 1037, 731, 629 cm^{-1}; δ_H 4.86–4.82 (1H, m), 3.31 (2H, d, J=5.2 Hz), 2.92 (1H, dd, J=14.0, 6.8 Hz), 2.53 (1H, dd, J=14.0, 6.8 Hz), 2.24 (2H, s), 2.15 (2H, s), 1.11 (6H, s); δ_C 194.6, 175.6, 111.3, 83.3, 60.8, 37.6, 34.0, 32.4, 28.8, 28.5, 8.9; *m/z* 307 (100%), 306 (M^+, 12), 250 (17), 180 (15), 179 (94) 123 (39), 95 926), 83 (25), 81 (29), 77 (13), 67 (29), 65 (14), 55 (43), 53 (52), 52 (17), 51 (17), 43 (32), 42 (12), 41 (77). Anal. calcd for $C_{11}H_{15}IO_2$: C, 43.16; H, 4.94; I, 41.45. Found: C, 43.22; H, 4.87; I, 41.52%.

4.3.3. 5-Iodomethyl-3-methoxycarbonyl-2-methyl-4, 5-dihydrofuran (6c). The title compound was obtained as a light yellow oil (80%). ν (neat) 2949, 1702, 1650, 1262, 1226, 1086, 981, 761, 613 cm^{-1}; δ_H 4.72–4.67 (1H, m), 3.70 (3H, s), 3.34–3.26 (2H, m); 3.03 (1H, dd, J=13.6, 11.2 Hz), 2.66 (1H, dd, J=14.8, 6.8 Hz), 2.20 (3H, s); δ_C 167.4, 166.1, 101.5, 80.4, 50.9, 36.9, 14.0, 8.8; *m/z* 283 (49%), 282 (M^+, 34), 251 (18), 155 (73), 123 (58), 113 (11), 95 (13), 81 (59), 59 (11), 53 (33), 43 (100), 41 (12). Anal. calcd for $C_8H_{11}IO_3$: C, 34.06; H, 3.93; I, 44.99. Found: C, 33.99; H, 3.85; I, 45.06%.

4.3.4. 3-Ethoxycarbonyl-5-iodomethyl-2-methyl-4, 5-dihydrofuran (6d). The title compound was obtained as a light yellow oil (78%). ν (neat) 2949, 2926, 1702, 1635, 1436, 1382, 1219, 1187, 1099, 994, 875 cm^{-1}; δ_H 4.72–4.64 (1H, m); 4.16 (2H, q, J=7.2 Hz); 3.36–3.24 (2H, m); 3.04 (1H, dd, J=14.4, 11.2 Hz), 2.65 (1H, dd, J=14.4, 6.4 Hz), 2.19 (3H, s); 1.28 (3H, t, J=7.2 Hz); δ_C 167.1, 166.7, 101.7, 80.4, 69.5, 36.9, 14.4, 14.0, 8.8; *m/z* 297 (100%), 296 (M^+, 33), 251 (32), 169 (51), 123 (57), 95 (10), 81 (34), 53 (17), 43 (46). Anal. calcd for $C_9H_{13}IO_3$: C, 36.51; H, 4.43; I, 42.86. Found: C, 36.60; H, 4.37; I, 42.91%.

4.3.5. 3-Benzoyl-5-iodomethyl-2-phenyl-4, 5-dihydrofuran (6e).[16] The title compound was obtained as a light yellow oil (76%). ν (neat) 1620, 1404, 1220, 1033, 734, 628 cm^{-1}; δ_H 7.65–7.51 (2H, m), 7.48–7.41 (2H, m), 7.32–6.98 (6H, m), 5.02 (1H, m), 3.43 (1H, dd, J=9.2, 15.2 Hz), 3.40 (1H, dd, J=5.6, 12.4 Hz), 3.23 (1H, dd, J=7.2, 12.4 Hz), 3.12 (1H, dd, J=7.2, 15.2 Hz); *m/z* 390 (M^+, 11%), 263 (100), 43 (50).

4.3.6. 3-Acetyl-5-iodomethyl-2-phenyl-4, 5-dihydrofuran (6f). The title compound was obtained as a light yellow oil (79%). ν (neat) 2923, 1624, 1592, 1491, 1378, 1243, 1115, 1070, 909, 698 cm^{-1}; δ_H 7.55 (2H, d, J=7.6 Hz), 7.51–7.42 (3H, m), 4.82–4.74 (1H, m), 3.41 (2H, d, J=5.2 Hz), 3.29 (1H, dd, J=10.4, 15.2 Hz), 2.91 (1H, dd, J=6.8, 15.2 Hz), 1.95 (3H, s); δ_C 194.4, 165.4, 130.7, 130.6, 129.1, 129.1, 126.4, 126.4, 114.5, 80.1, 37.7, 26.9, 8.9; *m/z* 328 (M^+, 18%), 327 (25), 201 (15), 115 (12), 105 (100), 77 (60), 51 (23), 43 (95). Anal. calcd for $C_{13}H_{13}IO_2$: C, 47.58; H, 3.99; I, 38.67. Found: C, 47.48; H, 4.07, I, 38.58%.

4.3.7. 3-Acetyl-5-iodomethyl-2-methyl-4, 5-dihydrofuran (6g). The title compound was obtained as a light yellow oil (86%). ν (neat) 2950, 1639, 1404, 1220, 1037, 732, 628 cm^{-1}; δ_H 4.71–4.67 (1H, m); 3.32 (2H, d, $J=6.0$ Hz), 3.10 (1H, dd, $J=14.4$, 10.8 Hz), 2.72 (1H, dd, $J=14.4$, 7.2 Hz), 2.23 (3H, s), 2.22 (3H, s); δ_C 194.2, 166.8, 111.9, 80.4, 36.7, 29.5, 15.0, 8.7; *m/z* 267 (M+1, 100%), 139 (11), 123 (13), 43 (58). Anal. calcd for $C_8H_{11}IO_2$: C, 36.11; H, 4.17; I, 47.69. Found: C, 36.20; H, 4.25; I, 47.62%.

4.4. General procedure for the preparation of alkylidenedihydrofurans (8a–8e)

The mixture of iodomethyldihydrofurans **6a**–**6e** (0.7 mmol) and DBU (2.1 mmol) was stirred under nitrogen for 12 h at 60 °C. The mixture was filtered and the resin was washed with diluted HCl and CH_2Cl_2, the filtrate was extracted with Et_2O (10 mL×3). The organic layer was washed with brine to neutrality, then dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was dissolved in dry Et_2O (0.05 M) and a few drops of H_2SO_4 (10 M) were added. The solution was stirred under nitrogen at rt until the completion of the reaction (TLC monitoring). Then the solution was diluted with Et_2O and washed with brine. After the usual work-up the furan **8a**–**8e** were obtained.

4.4.1. 2-Methyl-6, 7-dihydro-5*H*-benzofuran-4-one (8a). The title compound was obtained as a colorless oil (80%). ν (neat) 1674, 1581, 1434, 1237, 1163, 1010, 913, 732 cm^{-1}; δ_H 6.24 (1H, s), 2.83 (2H, t, $J=6.2$ Hz), 2.46 (2H, t, $J=6.2$ Hz), 2.29 (3H, s), 2.15 (2H, quintet, $J=6.3$ Hz); δ_C 194.6, 166.0, 152.6, 122.0, 101.7, 37.5, 23.3, 22.6, 13.3; *m/z* 150 (M^+, 15%), 122 (59), 94 (90), 79 (11), 53 (13), 52 (11), 51 (26), 50 (22), 43 (100), 42 (16), 41 (14). Anal. calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.90; H, 6.63%.

4.4.2. 2, 6, 6-Trimethyl-6, 7-dihydro-5*H*-benzofuran-4-one (8b). The title compound was obtained as a colorless oil (78%). ν (neat) 1670, 1582, 474, 1252, 1034, 905 cm^{-1}; δ_H 6.23 (1H, s), 2.69 (2H, s), 2.34 (2H, s), 2.29 (3H, s), 1.13 (6H, s); δ_C 194.0, 166.1, 162.8, 120.7, 101.7, 51.9, 37.3, 36.2, 28.5, 28.5, 13.4; *m/z* 178 (M^+, 7%) 122 (100), 94 (97), 51 (11), 43 (81). Anal. calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.08; H, 8.01%.

4.4.3. 2, 5-Dimethyl-3-methoxycarbonyl-furan (8c).[17] The title compound was obtained as a colorless oil (74%). ν (neat) 2953, 1713, 1439, 1207, 1085, 734 cm^{-1}; δ_H 6.21 (1H, s), 3.78 (3H, s), 2.51 (3H, s), 2.22 (3H, s); *m/z* 154 (M^+, 53%), 139 (51), 123 (63), 94 (20), 81 (18), 53 (21), 43 (100).

4.4.4. 2, 5-Dimethyl-3-ethoxycarbonyl-furan (8d).[17] The title compound was obtained as a colorless oil (71%). ν (neat) 2926, 1713,, 1229, 1204, 1075, 988 cm^{-1}; δ_H 6.25 (1H, s), 4.16 (2H, q, $J=7.2$ Hz), 2.52 (3H, s), 2.24 (3H, s), 1.26 (3H, t, $J=7.2$ Hz); *m/z* 168 (M^+, 7), 153 (22), 137 (36), 123 (14), 95 (17), 51 (33), 43 (100).

4.4.5. 3-Acetyl-5-methyl-2-phenyl-furan (8e). The title compound was obtained as a colorless oil (72%). ν (neat) 2926, 1673, 1557, 1234, 908, 733 cm^{-1}; δ_H 7.70–7.72 (2H, m), 7.47–7.36 (3H, m), 6.09 (s, 1H), 2.41 (s, 3H), 2.21 (s, 3H); δ_C 191.8, 158.0, 154.7, 139.3, 131.9, 128.9, 128.9, 128.2, 128.2, 121.1, 107.4, 14.1, 13.2; *m/z* 200 (M^+, 13), 105 (100). Anal. calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.90; H, 6.12%.

4.4.6. 3-Benzoyl-5-methyl-2-phenyl-furan (8f).[18] The title compound was obtained as a colorless oil (79%). ν (neat) 2923, 1618, 1221, 986 cm^{-1}; δ_H 7.9–7.75 (2H, m), 7.75–7.6 (2H, m), 7.6–7.15 (6H, m), 6.25 (s, 1H), 2.35 (s, 3H); *m/z* 262 (M^+, 8), 105 (100).

4.5. General procedure for the preparation of iodomethyltetrahydrofurans (11a–11j)

To a suspension of the swellen selenocyclic enol ether resin **2** (1.0 g), in dry DMF (15 mL), NaI (1.5 g) and CH_3I (1.5 mL) were added under nitrogen. The suspension was stirred at 75 °C for 18 h. The mixture was filtered and the resin was washed with CH_2Cl_2 (10 mL×3), the filtrate was washed with saturated $Na_2S_2O_3$ and H_2O respectively and extracted with CH_2Cl_2 (10 mL×3), dried over $MgSO_4$, and evaporated to dryness in vacuum to afford iodomethyltetrahydrofurans **11a**–**11j**.

4.5.1. (5-Iodomethyl-dihydrofuran-2-ylidene)-acetic acid methyl ester (11a). The title compound was obtained as a light yellow oil (85%). ν (neat) 2951, 1706, 1643, 1436, 1363, 1118 cm^{-1}; δ_H 5.32 (1H, s), 4.50–4.48 (1H, m), 3.66 (3H, s), 3.37–3.24 (3H, m), 3.06–3.01 (1H, m), 2.36–2.30 (1H, m), 1.91–1.86 (1H, m); δ_C 175.6, 168.7, 90.0, 82.3, 50.7, 30.2, 29.7, 6.7; *m/z* 283 (100%), 282 (M^+, 21), 251 (42), 155 (37), 123 (25), 101 (55), 99 (14), 95 (17), 85 (14), 81 (21), 71 (13), 69 (58), 67 (15), 59 (16), 57 (12), 55 (49), 54 (11), 53 (25), 43 (44), 42 (15), 41 (32). Anal. calcd for $C_8H_{11}IO_3$: C, 34.06; H, 3.93; I, 44.99. Found: C, 34.13; H, 3.84; I, 44.90%.

4.5.2. 2-(5-Iodomethyl-dihydrofuran-2-ylidene)-butyric acid methyl ester (11b). The title compound was obtained as a light yellow oil (74%). ν (neat) 2962, 1698, 1635, 1434, 1318, 1255, 1183, 1101, 1027, 780 cm^{-1}; δ_H 4.47–4.44 (1H, m), 3.69 (3H, s), 3.38–3.22 (3H, m), 3.05–2.96 (1H, m), 2.31 (3H, q, $J=7.2$ Hz), 1.90–1.85 (1H, m), 0.99 (3H, t, $J=7.2$ Hz); δ_C 169.3, 169.2, 104.9, 81.4, 50.8, 30.8, 30.0, 19.4, 13.7, 7.6; *m/z* 311 (100%), 310 (M^+, 21) 279 (42), 151 (23), 123 (10), 109 (12), 99 (17), 97 (18), 97 (17), 81 (35), 71 (19), 69 (39), 67 (16), 59 (50), 57 (55), 55 (92), 53 (38), 43 (90), 41 (80). Anal. calcd for $C_{10}H_{15}IO_3$: C, 38.73; H, 4.87; I, 40.92. Found: C, 38.68; H, 4.80; I, 40.86%.

4.5.3. 2-(5-Iodomethyl-dihydrofuran-2-ylidene)-hexanoic acid methyl ester (11c). The title compound was obtained as a light yellow oil (80%). ν (neat) 2954, 2859, 1699, 1634, 1434, 1182, 1113, 733 cm^{-1}; δ_H 4.49–4.42 (1H, m), 3.68 (3H, s), 3.35 (1H, dd, $J=10.0$, 4.8 Hz), 3.31–3.21 (2H, m), 3.07–2.95 (1H, m), 2.30 (3H, t, $J=6.8$ Hz), 1.93–1.80 (1H, m), 1.43–1.23 (4H, m), 0.90 (3H, t, $J=7.2$ Hz); δ_C 169.5, 169.4, 103.5, 81.4, 50.8, 31.3, 30.9, 30.0, 25.6, 22.5, 14.0, 7.5; *m/z* 339 (100%), 338 (M^+, 44), 307 (72), 295 (36), 211 (10), 179 (16), 151 (13), 133 (12), 113 (10), 81 (12), 55

(32), 53 (18), 43 (27), 41 (45). Anal. calcd for $C_{12}H_{19}IO_3$: C, 42.62; H, 5.66; I, 37.53. Found: C, 42.69; H, 5.74; I, 37.60%.

4.5.4. (3-Allyl-5-iodomethyl-dihydrofuran-2-ylidene)-acetic acid methyl ester (11d). The title compound was obtained as a light yellow oil (80%). ν (neat) 2926, 1715, 1650, 1434, 1373, 1277, 1194, 1040, 999, 806 cm^{-1}; δ_H 6.79–6.71 (1H, m), 6.15–5.10 (2H, m), 4.85 (1H, s), 4.57–4.51 (1H, m), 3.68 (3H, s), 3.55 (1H, dd, $J=10.0$, 4.0 Hz), 3.27 (1H, dd, $J=10.0$, 8.8 Hz), 3.08–2.93 (1H, m), 2.57–2.39 (2H, m), 2.27–2.12 (1H, m), 1.53–1.37 (1H, m); δ_C 173.3, 166.0, 134.2, 117.9, 88.1, 82.9, 50.7, 43.4, 36, 35.9, 6.2; *m/z* 322 (M^+, 8%), 195 (12), 163 (40), 135 (30), 122 (14), 121 (35), 119 (16), 117 (27), 113 (10), 109 (33), 107 (27), 101 (72), 95 (66), 81 (97), 69 (100), 55 (77), 43 (80). Anal. calcd for $C_{11}H_{15}IO_3$: C, 41.01; H, 4.69; I, 39.39. Found: C, 40.13; H, 4.59; I, 39.47%.

4.5.5. 2-(5-Iodomethyl-dihydrofuran-2-ylidene)-3-phenyl-propionic acid methyl ester (11e). The title compound was obtained as a light yellow oil (80%). ν (neat) 1705, 1655, 1192, 1047, 913, 734 cm^{-1}; δ_H 7.28–7.22 (2H, m), 7.20–7.11 (3H, m), 4.70–4.65 (1H, m), 3.69 (3H, s), 3.57–3.52 (2H, m), 3.46 (1H, dd, $J=10.0$, 4.5 Hz), 3.26 (1H, dd, $J=5.2$, 4.8 Hz), 2.83 (1H, dd, $J=10.0$, 4.8 Hz), 2.73–2.67 (1H, m), 2.36–2.25 (1H, m),1.78–1.86 (1H, m); δ_C 168.3, 167.3, 140.4, 128.3, 128.3, 127.8, 127.8, 125.9, 99.7, 84.1, 51.2, 34.4, 30.5, 28.8, 6.9; *m/z* 373 (M+1, 100%), 341 (33), 213 (45), 143 (17), 131 (30), 91 (44), 55 (20), 43 (23). Anal. calcd for $C_{15}H_{17}IO_3$: C, 48.41; H, 4.60; I, 34.10. Found: C, 48.47; H, 4.51; I, 34.02%.

4.5.6. (5-Iodomethyl-dihydrofuran-2-ylidene)-acetic acid ethyl ester (11f). The title compound was obtained as a light yellow oil (80%). ν (neat) 2978, 1710, 1653, 1199, 1138, 1044, 804 cm^{-1}; δ_H 4.85 (1H, s), 4.76–4.68 (1H, m), 4.13 (2H, t, $J=6.8$ Hz), 3.50 (1H, dd, $J=10.0$, 3.6 Hz), 3.28 (1H, dd, $J=10.0$, 8.4 Hz), 2.85–2.72 (2H, m), 2.38–2.30 (1H, m), 1.91–1.82 (1H, m), 1.26 (3H, t, $J=6.8$ Hz); δ_C 170.9, 166.6, 88.9, 84.8, 59.3, 31.8, 28.9, 14.4, 6.4; *m/z* 297 (57%), 296 (M^+, 13), 251 (48), 169 (21), 123 (30), 115 (54), 99 (12), 95 (18), 87 (37), 81 (17), 69 (100), 67 (22), 55 (65), 54 (15), 53 (23), 43 (46), 42 (18), 41 (38). Anal. calcd for $C_9H_{13}IO_3$: C, 36.51; H, 4.43; I, 42.86. Found: C, 36.57; H, 4.50; I, 42.78%.

4.5.7. (5-Iodomethyl-3-methyl-dihydrofuran-2-ylidene)-acetic acid ethyl ester (11g). The title compound was obtained as a light yellow oil (80%). ν (neat) 2966, 2873, 1713, 1652, 1372, 1190, 1045, 1003, 806 cm^{-1}; δ_H (two diastereoisomers, ratio 51:49) 4.71 and 4.68 (1H, 2×s), 4.82–4.72 and 4.58–4.47 (1H, 2×m), 4.15 (2H, t, $J=7.2$ Hz), 3.54 and 3.45 (1H, 2×dd, $J=10.0$, 4.4 Hz), 3.29 and 3.23 (1H, 2×t, $J=9.6$ Hz), 3.08–2.96 (1H, m), 2.59–2.53 and 2.22–2.08 (1H, 2×m), 1.99–1.89 and 1.46–1.33 (1H, 2×m), 1.30–1.16 (6H, m); *m/z* 311 (83%), 310 (M^+, 23), 265 (54), 137 (12), 115 (42), 109 (14), 95 (13), 87 (25), 81 (28), 69 (100), 67 (18), 55 (18), 53 (23), 43 (37), 41 (92). Anal. calcd for $C_{10}H_{15}IO_3$: C, 38.73; H, 4.87; I, 40.92. Found: C, 38.65; H, 4.94; I, 40.99%.

4.5.8. (5-Iodomethyl-3-ethyl-dihydrofuran-2-ylidene)-acetic acid ethyl ester (11h). The title compound was obtained as a light yellow oil (80%). ν (neat) 2968, 2873, 1712, 1651, 1459, 1376, 1193, 1045, 1003, 804 cm^{-1}; δ_H (two diastereoisomers, ratio 51:49) 4.80 and 4.77 (1H, 2×s), 4.80–4.73 and 4.57–4.50 (1H, 2×m), 4.19–4.07 (2H, m), 3.46 and 3.54 (1H, 2×dd, $J=10.0$, 4.8 Hz), 3.21 and 3.15 (1H, 2×t, $J=9.6$ Hz), 2.85–2.74 (1H, m), 2.59–2.50 and 2.11–1.99 (1H, 2×m), 2.11–1.99 and 1.89–1.75 (1H, 2×m), 1.75–1.63 and 1.53–1.34 (1H, 2×m), 1.53–1.34 (1H, m), 1.26 (3H, t, $J=7.2$ Hz), 1.00 (3H, t, $J=7.2$ Hz); *m/z* 325 (100%), 324 (M^+, 23), 279 (54), 169 (12), 123 (15), 115 (29), 97 (15), 95 (23), 87 (19), 81 (31), 69 (59), 67 (19), 55 (47), 53 (24), 43 (38), 41 (68). Anal. calcd for $C_{11}H_{17}IO_3$: C, 40.76; H, 5.29; I, 39.15. Found: C, 40.82; H, 5.20; I, 39.22%.

4.5.9. (5-Iodomethyl-3-benzyl-dihydrofuran-2-ylidene)-acetic acid ethyl ester (11i). The title compound was obtained as a light yellow oil (80%). ν (neat) 1708, 1652, 1192, 1045, 911, 732 cm^{-1}; δ_H (two diastereoisomers, ratio 55:45) 7.31 (2H, t, $J=7.2$ Hz), 7.24 (1H, t, $J=7.2$ Hz), 7.20–7.13 (2H, m), 4.92 and 4.83 (1H, 2×s), 4.67–4.60 and 4.48–4.42 (1H, 2×m), 4.19–4.08 (2H, m), 3.46 and 3.40 (1H, 2×dd, $J=10.4$, 4.0 Hz), 3.20 (2H, q, $J=9.6$ Hz), 3.11 and 2.96 (1H, 2×dd, $J=13.6$, 4.4 Hz), 2.67 and 2.60 (1H, 2×dd, $J=13.6$, 9.6 Hz), 2.31–2.22 and 2.10–2.01 (1H, 2×m), 1.93–1.84 and 1.50–1.39 (1H, 2×m), 1.25 (3H, dd, $J=12.0$, 7.2 Hz); *m/z* 386 (M^+, 10%), 341 (6), 145 (19), 115 (47), 91 (100), 69 (25), 41 (21). Anal. calcd for $C_{16}H_{19}IO_3$: C, 49.76; H, 4.96; I, 32.86. Found: C, 49.82; H, 4.89; I, 32.91%.

Acknowledgements

We are grateful to the Natural Science Foundation of China (Project No. 20332060, 20272050) and Zhejiang Province Foundation of Member of Chinese Academy of Science).

References and notes

1. Guilliier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**; 100, 2091–2157. (b) James, I. W. *Tetrahedron* **1999**; 55, 4855–4946. (c) Sammelson, R. E.; Kurth, M. J. *Chem. Rev.* **2001**, 137–202. (d) Czarnik, A. W. *Solid-Phase Organic Synthesis*, Wiley: New York, 2001; Vol. 1. (e) Nicolaou, K. C.; Hanko, R.; Hartwig, W. *Handbook of Combinatorial Chemistry*, Wiley-VCH: Weinheim, 2002.
2. Dolle, R. E. *J. Comb. Chem.* **2003**, *5*, 693–753.
3. Dean, F. M. Advances in Heterocyclic Chemistry; Katritzky, A. R., Ed.; Academic: New York, 1982; Vol. 30, pp 167–283. (b) Dean, F. M., Sargent, M. V. Comprhensive Heterocyclic Chemistry; Bird, C. W., Cheeseman, G. W. H., Eds.; Pergamon: New York, 1984; Vol. 4, Part 3, pp 531–589. (c) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795. (d) Lee, J.; Li, J.-H.; Oya, S.; Snyder, J. K. *J. Org. Chem.* **1992**, *57*, 5301–5312. (e) Jacobi, P. A.; Swlnick, H. G. *J. Org. Chem.* **1990**, *55*, 202–209.
4. Nakanishi, K. Natural Products Chemistry.; Kodansha: Tokyo, 1974. (b) *The Chemistry of Heterocyclic Flavoring and Aroma Compounds*; Vernin, F., Ed.; Ellis Horwood: Chichester, 1982.

(c) Kubo, I.; Lee, Y.W.; Balogh-Nair, V.; Nakanishi, K.; Chapya, A. *J. Chem. Soc., Chem. Commun.*, **1976**, 949–950.
5. Franzen, R. G. *J. Comb. Chem.* **2000**; 2, 195–214. (b) Dowald, F. Z. *Organic Synthesis on Solid Phase*, Wiley-VCH: Weinheim, 2002; Chapter 15.
6. Michels, R.; Kato, M.; Heitz, W. *Makromol. Chem.* **1976**, *177*, 2311–2317.
7. Nicolaou, K. C.; Pastor, J.; Barluenga, S.; Winssinger, N. *Chem. Commun.* **1998**, 1947–1948.
8. Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G. Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939–9953. (b) Ruhland, T.; Andersen, K.; Pedersen, H. *J. Org. Chem.* **1998**, *63*, 9204–9211. (c) Zaragoza, F. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2077–2079. (d) Fujita, K.; Taka, H.; Oishi, A.; Ikeda, Y.; Taguchi, Y.; Fujie, K.; Saeki, T.; Sakuma, M. *Synlett* **2000**, 1509–1511.
9. Huang, X.; Xu, W. M. *Tetrahedron Lett.* **2002**, *43*, 5495–5497. (b) Huang, X.; Xu, W. M. *Org. Lett.* **2003**, *5*, 4649–4652. (c) Qian, H.; Huang, X. *Tetrahedron Lett.* **2002**, *43*, 1059–1061. (d) Huang, X.; Sheng, S. R. *J. Comb. Chem.* **2003**, *5*, 273–277. (e) Qian, H.; Huang, X. *J. Comb. Chem.* **2003**, *5*, 569–576.
10. Ferraz, H. M. C.; Sano, M. K.; Nunes, M. R. S.; Bianco, G. G. *J. Org. Chem.* **2002**, *67*, 4122–4126.
11. Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G. Q.; Kim, S.; Kessabi, J. *Org. Lett.* **1999**, *1*, 807–810.
12. Corey, E. J.; Jautelat, M. *Tetrahedron Lett.* **1968**, *55*, 5787–5788.
13. Stefani, H. A.; Petragnani, N.; Brandt, C. A.; Rando, D. G.; Valduga, C. J. *Synth. Commun.* **1999**, *29*, 3517–3531.
14. Lauer, W. M.; Kilbur, E. I. *J. Am. Chem. Soc.* **1937**, *59*, 2586–2588.
15. Huckin, S. N.; Weiler, J. *J. Am. Chem. Soc.* **1974**, *96*, 1082–1087.
16. Antonioletti, R.; Bonadies, F.; Scettri, A. *Tetrahedron Lett.* **1988**, *29*, 4987–4990.
17. Graziano, M. L.; Iesce, M. R.; Scarpati, R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1955–1958.
18. Tiecco, M.; Testaferri, L.; Tingoli, M.; Marini, F. *J. Org. Chem.* **1993**, *58*, 1349–1354.