Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 1033–1038

TETRAHEDRON: *ASYMMETRY*

Synthesis of enantiopure substituted dihydrofurans via the reaction of (*S*)-glyceraldehyde acetonide- or Garner aldehyde acetonide-derived enones with sulfonium ylides

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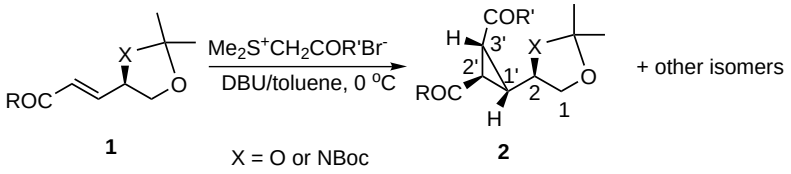
Received 18 March 2002; accepted 2 May 2002

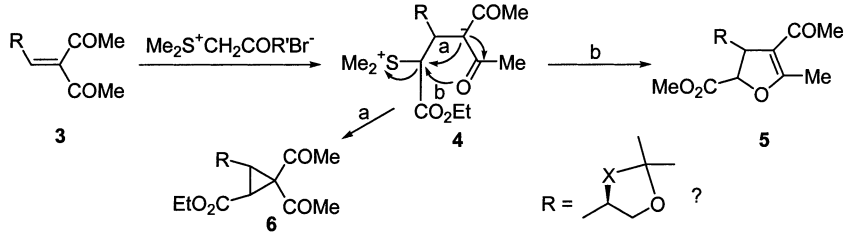
Abstract—The reaction of sulfonium ylides with enones derived from 1,3-diketones or ethyl acetoacetate and (*S*)-glyceraldehyde acetonide or (*S*)-Garner aldehyde acetonide provides enantiopure polysubstituted dihydrofurans in moderate yields.

1. Introduction

Recently, we reported the synthesis of enantiopure 1,2,3-trisubstituted cyclopropanes by the stereochemically controlled cyclopropanation reactions of ethyl dimethylsulfonium acetate bromide with enones derived from (*S*)-glyceraldehyde acetonide and Garner aldehyde (Scheme 1).[1–3] Since it was reported that reaction of ethyl dimethylsulfuranylidene acetate (EDSA) with enones containing two activating groups gave rise to substituted dihydrofurans through the mechanism indicated in Scheme 2,[4] it was an open question as to whether we could use (*S*)-glyceraldehyde acetonide- or Garner aldehyde acetonide-derived enones **3** to run the similar reaction to provide enantiopure dihydrofurans[5] with several interesting functional groups. The studies thus undertook are disclosed herein.



Scheme 1.



Scheme 2.

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0957-4166/02/$ - see front matter
PII: S0957-4166(02)00239-2

2. Results and discussion

Initially, we attempted the reaction using enone **7a** with EDSA generated in situ by treatment of ethyl dimethylsulfonium acetate bromide with DBU in toluene. As summarized in Table 1, we found that this reaction proceeded at 0°C and gave the dihydrofuran product **8a** in 29% yield. However, cyclopropanation still occurred in this case and the side product **10** was isolated in 37% yield (entry 1). The stereochemistry of **8a** was assigned from a combination of its NOESY spectra, in which a *trans*-geometry between the 4- and 5-positions was observed, and the mechanistic analysis described later.

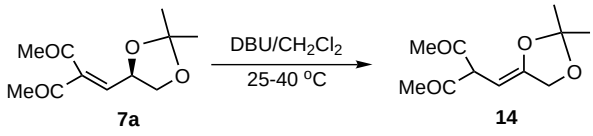
We then completed some experiments aimed at suppressing the cyclopropanation reaction: it was found that increasing the reaction temperature from −78 to 40°C did not give satisfactory results. At higher reaction temperature (25–40°C) isomerization of olefin occurred to provide the β,γ-unsaturated dicarbonyl compound **14** (Scheme 3). However, switching the solvent from toluene to a more polar one such as methylene chloride or acetonitrile favored the formation of **8a**, although the cyclopropanation product was still obtained (compare entries 1–3). In addition, using other sulfur ylides to **7a** provided similar results (entries 4 and 5) and aryl enone **7a** gave low yields for both types of compounds. Although in most cases only *trans*-dihydrofurans **8** were isolated, it is noteworthy that the *cis*-dihydrofuran **9b** was obtained when *tert*-butyl dimethylsulfonium acetate bromide was used. The reason for this difference is not clear at this time.

The above results promoted us to reconsider the mechanisms for the formation of these two types of products. After careful analysis of the mechanism outlined in Scheme 2, we realized that increasing the size of the R group of the enones might disfavor cyclopropanation from the intermediate **4** through route a because of steric hindrance. Thus, we used compound **11a**, derived from (*S*)-Garner aldehyde, as our substrate. As we expected, reaction of **11a** with EDSA in CH_3CN gave **12a** in 53% yield and its isomer **13a** in 20% yield (Table 2, entry 1). Use of chloroform as a solvent for the reaction led to better selectivity (compare entries 1 and 2). The stereochemistry of **12a** was assigned to be (2′*R*,4*R*,5*S*) from its single crystal X-ray analysis as shown in Fig. 1. This result indicates that EDSA attacked the C=C bond from the less hindered *Re* face of **A** and delivered the dihydrofurans through the intermediate **B** as shown in Scheme 4. This stereochemical outcome is quite similar to that of the cyclopropanation reaction of **1** with EDSA or related sulfonium ylides.[1–3]

Using **11a** as a substrate we tested other sulfur ylides. It was found either ketone or *t*-butyl ester derived ylides also worked to provide the corresponding substituted dihydrofuran (Table 2, entries 3 and 4). Moreover, we found **11b**, which was prepared from (*S*)-Garner aldehyde and ethyl acetoacetate, was also a suitable substrate for this reaction to give 3-ethoxycarbonyl dihydrofurans (entries 5–7) in moderate yields.

3. Conclusions

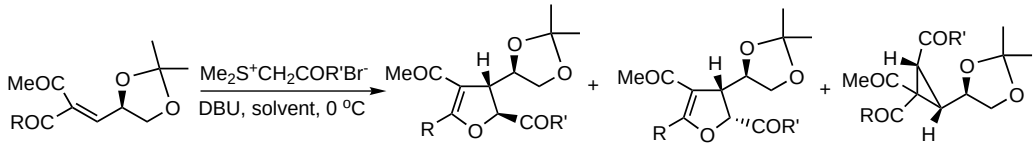
Taking all of these results together, we conclude that the present method will readily allow us to assemble



7a 14

Scheme 3.

Table 1. Reaction of (*S*)-glyceraldehyde acetonide derived enones **7** with EDSA[a]



7
a: R = Me
b: R = Ph

8
a: R = Me, R' = OEt
b: R = Me, R' = OBu-*t*

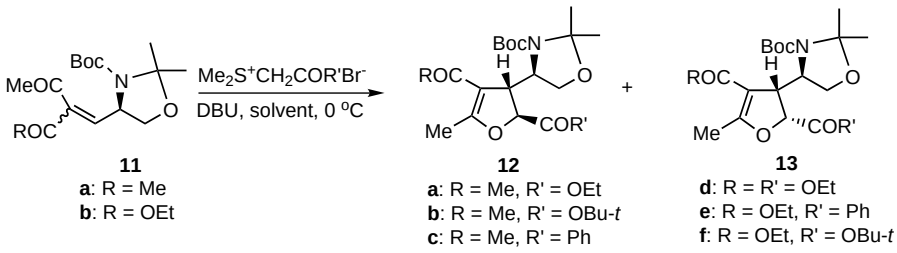
9
c: R = Me, R' = Ph
d: R = Ph, R' = OEt

10

Entry	Substrate	R′	Solvent	Time (h)	Yield (%)[b]		
					8	**9**	**10**
1	**7a**	OEt	Toluene	2	29	–	37
2	**7a**	OEt	CH_2Cl_2	1	47	–	40
3	**7a**	OEt	CH_3CN	1	47	–	43
4	**7a**	OBu-*t*	CH_3CN	1	38	8	44[c]
5	**7a**	Ph	CH_3CN	1	40	–	38
6	**7b**	OEt	Toluene	2	8	–	25

[a] Reaction conditions: enone **7** (1 mmol), sulfonium salt (1.5 mmol), DBU (1.4 mmol) in solvent (10 mL).
[b] Isolated yield.
[c] (3*R*)-Isomer **10b** and (3*S*)-isomer **10b′** were isolated in a ratio of 1/1.

Table 2. Reaction of (*S*)-Garner aldehyde derived enones **11** with EDSA[a]



Entry	Substrate	R′	Solvent	Time (h)	Yield (%)[b]	
					12	**13**
1	**11a**	OEt	CH_3CN	1	53	20
2	**11a**	OEt	$CHCl_3$	1	65	5
3	**11a**	OBu-*t*	$CHCl_3$	1.5	68	0
4	**11a**	Ph	$CHCl_3$	2	57	16
5	**11b**	OEt	CH_3CN	1	56	–
6	**11b**	Ph	CH_3CN	2	53	–
7	**11b**	OBu-*t*	CH_3CN	1.5	50	–

[a] Reaction conditions: enone **11** (1 mmol), sulfonium salt (1.5 mmol), DBU (1.4 mmol) in solvent (10 mL).
[b] Isolated yield.

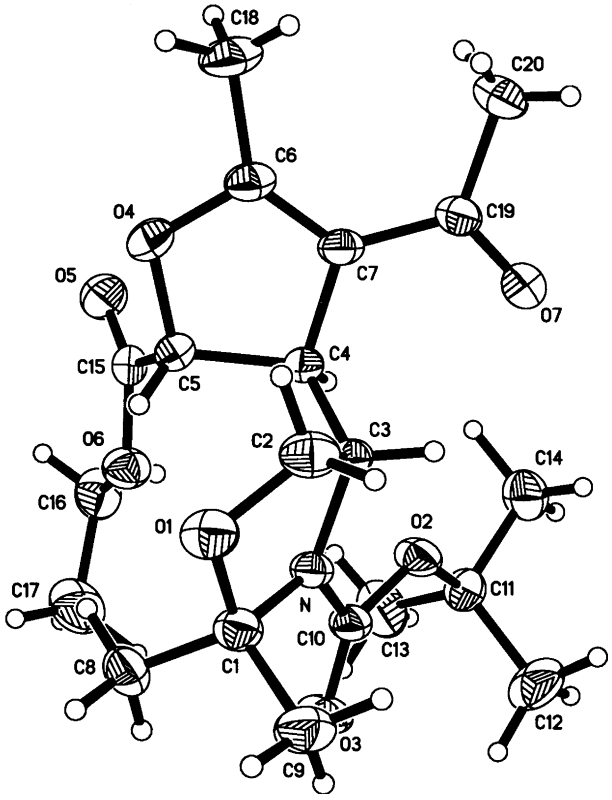
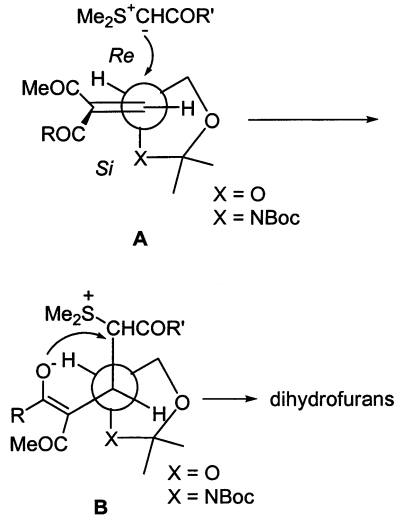


Figure 1. X-Ray structure of **12a**.

structurally diverse substituted dihydrofurans in a stereoselective manner.



Scheme 4.

4. Experimental

4.1. General procedure for synthesis of enones

To a solution of aldehyde (8.0 g, 34.9 mmol) and acetylacetone (4.18 g, 41.8 mmol) in dry CH_2Cl_2 (50 mL) was added HOAc (0.2 mL) at 0°C with stirring. Piperidine (0.35 mL) was added and the mixture was slowly warmed to room temperature and the stirring was maintained overnight. The solvent was evaporated in vacuo and the residue was purified by flash chromatography to give the corresponding enone.

4.1.1. (*R*)-3-(2,2-Dimethyl-1,3-dioxolan-4-ylmethylene)-pentane-2,4-dione 7a. Colorless oil, 50% yield; $[\alpha]_D^{20} =$

+30.7 (*c* 0.9, $CHCl_3$); FT-IR (neat) 2990, 2939, 1701, 1675, 1374 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.70 (d, $J=7.0$ Hz, 1H), 4.77 (m, 1H), 4.31 (dd, $J=7.0$, 8.0 Hz, 1H), 3.71 (m, 1H), 2.41 (s, 3H), 2.38 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H); EIMS *m*/*z* 212 (M^+), 170 ($M^+-C_3H_6$); HRMS found *m*/*z* 212.1039 (M^+), $C_{11}H_{16}O_4$ requires 212.1030.

4.1.2. (*R*)-2-(2,2-Dimethyl-1,3-dioxolan-4-ylmethylene)-1-phenylbutane-1,3-dione 7b. Colorless oil, 70% yield; $[\alpha]_D^{20}=+34.3$ (*c* 1.3, $CHCl_3$); FT-IR (neat) 3064, 2989, 2937, 1723, 1679, 1597, 1581, 1450, 1373 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.85 (m, 2H), 7.60 (m, 1H), 7.48 (m, 2H), 6.9 (d, $J=7.6$ Hz, 1H), 4.57 (m, 1H), 4.11 (dd, $J=6.9$ Hz, 8.5 Hz, 1H), 3.73 (dd, $J=8.5$ Hz, 7.5 Hz, 1H), 2.35 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H); EIMS *m*/*z* 275 (M^++H^+); HRMS found *m*/*z* 274.1222 (M^+), $C_{16}H_{18}O_4$ requires 274.1239.

4.1.3. (*R*)-(2-Acetyl-3-oxo-but-1-enyl)-2,2-dimethyloxazolidine-3-carboxylic acid, *tert*-butyl ester 11a. Pale yellow oil, 86% yield; $[\alpha]_D^{20}=-11.1$ (*c* 0.9, $CHCl_3$); FT-IR (neat) 2985, 2937, 1706, 1683, 1664, 1367 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.7 (m, 1H), 4.59 (m, 1H), 4.30 (m, 1H), 3.87 (dd, $J=3.9$, 8.4 Hz, 1H), 2.4 (m, 6H), 1.71–1.54 (m, 15H); EIMS *m*/*z* 311 (M^+), 255 ($M^+-C_4H_9$); HRMS found *m*/*z* 311.1731 (M^+), $C_{16}H_{25}NO_5$ requires 311.1730.

4.1.4. (*R*)-(2-Ethoxycarbonyl-3-oxobut-1-enyl)-2,2-dimethyloxazolidine-3-carboxylic acid, *tert*-butyl ester 11b. Colorless oil, 80% yield; $[\alpha]_D^{20}=-15.3$ (*c* 1.2, $CHCl_3$); FT-IR (neat) 2983, 2939, 1706, 1368 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.92 (m, 1H), 4.64 (m, 1H), 4.52–4.19 (m, 3H), 3.79 (m, 1H), 2.49–2.42 (m, 3H), 1.68–1.25 (m, 18H); EIMS *m*/*z* 341 (M^+), 285 ($M^+-C_4H_9$); 268 (M^+-CO_2Et); HRMS found *m*/*z* 341.1844 (M^+), $C_{17}H_{27}NO_6$ requires 341.1849.

4.2. General procedure for synthesis of dihydrofuran from the enone 7

To an ice-cold solution of enone **7** (1 mmol) and the corresponding sulfonium ylide (1.5 mmol) in solvent was added DBU (1.4 mmol) with stirring. The mixture was stirred at 0°C until the starting material disappeared monitored by TLC. Water was added to quench the reaction and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over Na_2SO_4. After removal of solvent in vacuo, the residue was purified by flash chromatography to give **8** and **10**.

4.2.1. (2*S*,3*R*)-4-Acetyl-3-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-methyl-2,3-dihydrofuran-2-carboxylic acid, ethyl ester 8a. Pale yellow oil, $[\alpha]_D^{20}=+28.9$ (*c* 0.74, $CHCl_3$); FT-IR (neat) 2987, 2938, 1757, 1627, 1386, 1372 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.02 (d, $J=4.0$ Hz, 1H), 4.52 (m, 1H), 4.24 (q, $J=7.0$ Hz, 2H), 4.09 (dd, $J=8.0$, 7.0 Hz, 1H), 3.89 (dd, $J=8.0$, 5.8 Hz, 1H), 3.48 (m, 1H), 2.35 (s, 3H), 2.33 (s, 3H), 1.44 (s, 3H), 1.32 (s, 3H), 1.29 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 15.6, 25.4, 26.2, 29.3, 47.4, 61.5, 67.5, 74.2, 78.0, 109.2, 114.2, 168.6, 170.6, 193.0; EIMS *m*/*z* 298 (M^+), 283 (M^+-CH_3); HRMS found *m*/*z* 283.1199 (M^+–Me), $C_{14}H_{19}O_6$ requires 283.1182.

4.2.2. (1*R*,3*R*)-2,2-Diacetyl-3-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclopropanecarboxylic acid, ethyl ester 10a. Pale yellow oil, $[\alpha]_D^{20}=-117.7$ (*c* 0.64, $CHCl_3$); FT-IR (neat) 2989, 2938, 2884, 1773, 1710, 1384 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.13 (m, 2H), 4.01 (dd, $J=9.1$, 6.0 Hz, 1H), 3.87 (m, 1H), 3.74 (dd, $J=9.1$, 6.4 Hz, 1H), 2.85 (dd, $J=6.5$, 1.5 Hz, 1H), 2.42 (t, $J=6.5$ Hz, 1H), 2.26 (s, 3H), 2.24 (s, 3H), 1.41 (s, 3H), 1.29 (s, 3H), 1.25 (t, $J=7.0$ Hz, 3H); EIMS *m*/*z* 283 (M^+-CH_3); HRMS found *m*/*z* 283.1173 (M^+–Me), $C_{14}H_{19}O_6$ requires 283.1182.

4.2.3. (2*S*,3*R*)-4-Acetyl-3-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-methyl-2,3-dihydrofuran-2-carboxylic acid, *tert*-butyl ester 8b. Pale yellow oil, $[\alpha]_D^{20}=+38.6$ (*c* 1.5, $CHCl_3$); FT-IR (neat) 2984, 2937, 1751, 1627, 1392 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.91 (d, $J=4.2$ Hz, 1H), 4.54 (m, 1H), 4.09 (m, 1H), 3.89 (dd, $J=8.1$, 5.1 Hz, 1H), 3.42 (m, 1H), 2.34 (s, 6H), 1.49–1.32 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.8, 24.4, 26.2, 27.9, 29.4, 51.2, 67.1, 74.2, 78.1, 82.8, 109.2, 114.2, 168.9, 169.8, 193.2; EIMS *m*/*z* 311 (M^+-CH_3), 268 (M^+-CH_3-COMe); HRMS found *m*/*z* 311.1478 (M^+–Me), $C_{16}H_{23}O_6$ requires 311.1495.

4.2.4. (2*R*,3*R*)-4-Acetyl-3-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-methyl-2,3-dihydrofuran-2-carboxylic acid, *tert*-butyl ester 9b. Colorless oil, $[\alpha]_D^{20}=-35.0$ (*c* 1.0, $CHCl_3$); FT-IR (neat) 2983, 1735, 1617, 1372 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.88 (d, $J=8.7$ Hz, 1H), 4.15 (m, 1H), 3.80 (m, 1H), 3.69 (m, 1H), 3.60 (m, 1H), 2.28 (s, 3H), 2.27 (s, 3H), 1.46–1.41 (m, 15H); EIMS *m*/*z* 311 (M^+-CH_3); HRMS found *m*/*z* 326.1724 (M^+), $C_{17}H_{26}O_6$ requires 326.1718.

4.2.5. (1*R*,3*R*)-2,2-Diacetyl-3-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclopropanecarboxylic acid, *tert*-butyl ester 10b. Pale yellow oil, $[\alpha]_D^{20}=-160.8$ (*c* 0.95, $CHCl_3$); FT-IR (neat) 2985, 2937, 1726, 1702, 1393, 1369 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.06 (dd, $J=7.8$, 6.0 Hz, 1H), 3.94 (m, 1H), 3.80 (dd, $J=7.8$, 6.6 Hz, 1H), 2.87 (d, $J=6.3$ Hz, 1H), 2.45 (t, $J=6.3$ Hz, 1H), 2.31 (s, 3H), 2.30 (s, 3H), 1.49 (s, 12H), 1.37 (s, 3H); EIMS *m*/*z* 311 (M^+-CH_3); HRMS found *m*/*z* 311.1478 (M^+–Me), $C_{16}H_{23}O_6$ requires 311.1495.

4.2.6. (1*R*,3*S*)-2,2-Diacetyl-3-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclopropanecarboxylic acid, *tert*-butyl ester 10b′. Colorless oil, $[\alpha]_D^{20}=+92.1$ (*c* 2.1, $CHCl_3$); FT-IR (neat) 2991, 2939, 1719, 1704, 1382, 1370 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.42 (m, 2H), 3.80 (m, 1H), 2.83 (d, $J=9.6$ Hz, 1H), 2.29 (s, 3H), 2.18 (s, 3H), 1.75 (m, 1H), 1.48 (s, 9H), 1.44 (s, 3H), 1.28 (s, 3H); EIMS *m*/*z* 311 (M^+-CH_3); HRMS found *m*/*z* 311.1478 (M^+–Me), $C_{16}H_{23}O_6$ requires 311.1495.

4.2.7. (4*R*,5*S*)-1-[5-Benzoyl-4-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methyl-4,5-dihydrofuran-3-yl]ethanone 8c. White foam, $[\alpha]_D^{20}=+30.7$ (*c* 0.4, $CHCl_3$); FT-IR (KBr) 2993, 2921, 1695, 1616, 1599, 1450, 1383 cm^{-1}; ^1H

NMR ($CDCl_3$, 300 MHz) δ 8.14 (d, $J=8.1$ Hz, 2H), 7.64 (m, 1H), 7.48 (t, $J=8.1$ Hz, 2H), 5.99 (d, $J=2.7$ Hz, 1H), 4.27 (m, 1H), 3.99 (dd, $J=9.0$, 6.3 Hz, 1H), 3.78 (dd, $J=9.0$, 7.2 Hz, 1H), 3.56 (dd, $J=5.7$, 2.7 Hz, 1H), 2.38 (s, 3H), 2.28 (s, 3H), 1.47 (s, 3H), 1.43 (s, 3H); EIMS m/z 315 (M^+-CH_3), 272 (M^+-CH_3–COMe); HRMS found m/z 315.1261 (M^+–Me), $C_{18}H_{19}O_5$ requires 315.1232.

4.2.8. (1*R*,3*R*)-2,2-Diacetyl-3-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclopropyl phenyl ketone 10c. Colorless oil, $[\alpha]_D^{20}=+74.7$ (c 1.35, $CHCl_3$); FT-IR (neat) 2989, 1701, 1597, 1581, 1450, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.03 (m, 2H), 7.63 (m, 1H), 7.52 (m, 2H), 4.46 (dd, $J=6.3$, 8.7 Hz, 1H), 4.34 (m, 1H), 3.92–3.97 (m, 2H), 2.33 (s, 3H), 2.29 (s, 3H), 2.03 (dd, $J=6.9$, 9.6 Hz, 1H), 1.43 (s, 3H), 1.28 (s, 3H); EIMS m/z 315 (M^+-CH_3); HRMS found m/z 315.1212 (M^+–Me), $C_{18}H_{19}O_5$ requires 315.1232.

4.2.9. (2*S*,3*R*)-4-Acetyl-3-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-phenyl-2,3-dihydrofuran-2-carboxylic acid, ethyl ester 8d. Pale yellow oil, $[\alpha]_D^{20}=-37.2$ (c 0.85, $CHCl_3$); FT-IR (neat) 3065, 2987, 2935, 1723, 1676, 1596, 1581, 1449, 1360 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.63–7.47 (m, 5H), 5.18 (d, $J=3.6$ Hz, 1H), 4.56 (m, 1H), 4.28 (m, 2H), 4.14 (m, 1H), 4.02 (m, 1H), 3.60 (m, 1H), 1.89 (s, 3H), 1.45–1.31 (m, 9H); EIMS m/z 345 (M^+-CH_3); HRMS found m/z 345.1356 (M^+–Me), $C_{19}H_{21}O_6$ requires 345.1338.

4.2.10. (1*R*,3*R*)-2-Acetyl-2-Benzoyl-3-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclopropanecarboxylic acid, ethyl ester 10d. Colorless oil, $[\alpha]_D^{20}=-72.7$ (c 0.95, $CHCl_3$); FT-IR (neat) 2987, 2935, 1710, 1599, 1581, 1450, 1372 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.91 (m, 2H), 7.55 (m, 1H), 7.46 (m, 2H), 3.97 (m, 1H), 3.95–3.77 (m, 4H), 3.29 (d, $J=6.7$ Hz, 1H), 2.61 (dd, $J=6.7$, 8.3 Hz, 1H), 2.10 (s, 3H), 1.44 (s, 3H), 1.32 (s, 3H), 0.91 (t, $J=7.1$ Hz, 3H); EIMS m/z 345 (M^+-CH_3); HRMS found m/z 360.1580 (M^+), $C_{20}H_{24}O_6$ requires: 360.1587.

4.3. General procedure for synthesis of dihydrofuran from the enone 11

To an ice-cold solution of enone **11** (1 mmol) and corresponding sulfonium ylide (3 mmol) in a suitable solvent was added DBU (2.8 mmol) with stirring. The mixture was stirred at 0°C until the starting material disappeared monitored by TLC. Water was added and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over Na_2SO_4. After removal of solvent in vacuo, the residue was purified by flash chromatography to give **12** and **13**.

4.3.1. (*R*)-4-((2*S*,3*R*)-4-Acetyl-2-ethoxycarbonyl-5-methyl-2,3-dihydrofuran-3-yl)-2,2-dimethyloxazolidine-3-carboxylic acid, *tert*-butyl ester 12a. Colorless crystal, mp 116–117°C; $[\alpha]_D^{20}=-4$ (c 0.85, $CHCl_3$); FT-IR (KBr) 2980, 2937, 1757, 1701, 1604, 1389 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.25 (d, $J=4.2$ Hz, 1H), 4.25–4.18 (m, 3H), 4.03–3.9 (m, 2H), 3.71 (m, 1H), 2.40 (s, 3H), 2.37 and 2.34 (s, 3H), 1.70 (s, 3H), 1.66 and 1.63 (s, 3H), 1.45 (s, 9H), 1.28 (t, $J=7.1$ Hz, 3H); EIMS m/z 397 (M^+), 296 (M^+–Boc). Anal. calcd for $C_{20}H_{31}NO_7$: C, 60.44, H, 7.86, N, 3.52. Found: C, 60.46, H, 7.73, N, 3.46%.

4.3.2. (*R*)-4-((2*R*,3*R*)-4-Acetyl-2-ethoxycarbonyl-5-methyl-2,3-dihydrofuran-3-yl)-2,2-dimethyloxazolidine-3-carboxylic acid, *tert*-butyl ester 13a. White foam, $[\alpha]_D^{20}=-15.3$ (c 2.45, $CHCl_3$); FT-IR (KBr) 2984, 2940, 1753, 1703, 1389 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.27 (m, 1H), 4.43 (m, 1H), 4.21 (q, $J=7.2$ Hz, 2H), 4.06 (m, 2H), 3.57 (m, 1H), 2.30 (s, 3H), 2.29 and 2.25 (s, 3H), 1.63 (s, 3H), 1.57 (s, 3H), 1.43 (s, 9H), 1.27 (t, $J=7.2$ Hz, 3H); EIMS m/z 397 (M^+), 296 (M^+–Boc); HRMS found m/z 397.2099 (M^+), $C_{20}H_{31}NO_7$ requires 397.2098.

4.3.3. (*R*)-4-((2*S*,3*R*)-4-Acetyl-2-*tert*-butoxycarbonyl-5-methyl-2,3-dihydrofuran-3-yl)-2,2-dimethyloxazolidine-3-carboxylic acid, *tert*-butyl ester 12b. Solid, $[\alpha]_D^{20}=+79.7$ (c 0.35, $CHCl_3$); FT-IR (KBr) 2981, 2937, 1733, 1701, 1765, 1392 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.17 (m, 1H), 4.30 (m, 1H), 3.94–3.84 (m, 2H), 3.73–3.66 (m, 1H), 2.30–2.24 (m, 6H), 1.72–1.48 (m, 24H); ESIMS m/z 426.3 (M^++H^+). Anal. calcd for $C_{22}H_{35}NO_7$: C, 62.10, H, 8.29, N, 3.29. Found: C, 62.25, H, 7.86, N, 3.18%.

4.3.4. (*R*)-4-((2*S*,3*R*)-4-Acetyl-2-benzoyl-5-methyl-2,3-dihydrofuran-3-yl)-2,2-dimethyloxazolidine-3-carboxylic acid, *tert*-butyl ester 12c. White foam, $[\alpha]_D^{20}=-51.2$ (c 1.56, $CHCl_3$); FT-IR (KBr) 2989, 2937, 1701, 1600, 1454, 1380 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.94 (m, 2H), 7.61 (m, 1H), 7.50 (m, 2H), 6.11 (d, $J=5.1$ Hz, 1H), 4.46 (m, 1H), 4.04–3.68 (m, 3H), 2.28 (s, 6H), 1.68 (s, 6H), 1.31 (s, 9H); EIMS m/z 386 (M^+–COMe); HRMS found m/z 429.2136 (M^+), $C_{24}H_{31}NO_6$ requires 429.2120.

4.3.5. (*R*)-4-((2*R*,3*R*)-4-Acetyl-2-benzoyl-5-methyl-2,3-dihydrofuran-3-yl)-2,2-dimethyloxazolidine-3-carboxylic acid, *tert*-butyl ester 13c. White foam, $[\alpha]_D^{20}=-124.4$ (c 1.55, $CHCl_3$); FT-IR (KBr) 2982, 2933, 1695, 1670, 1598, 1454, 1384, 1367 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.06–7.95 (m, 2H), 7.67–7.64 (m, 1H), 7.61–7.50 (m, 2H), 6.01–5.92 (m, 1H), 4.77–4.45 (m, 1H), 3.94–3.56 (m, 3H), 2.36 (d, $J=7.8$ Hz, 3H), 2.26 (m, 3H), 1.45–1.23 (m, 15H); EIMS m/z 386 (M^+–COMe); HRMS found m/z 429.2131 (M^+), $C_{24}H_{31}NO_6$ requires 429.2111.

4.3.6. (2*S*,3*R*)-3-[(*R*)-3-*tert*-Butoxycabonyl-2,2-dimethyloxazolidine-4-yl]-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid, ethyl ester 12d. White foam, $[\alpha]_D^{20}=+33.8$ (c 0.76, $CHCl_3$); FT-IR (KBr) 2989, 2940, 1755, 1700, 1652, 1393 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.23 (d, $J=4.5$ Hz, 1H), 4.24–4.16 (m, 5H), 3.97–3.92 (m, 2H), 3.79–3.36 (m, 1H), 2.37 (s, 3H), 1.72 and 1.67 (s, 3H), 1.61 (s, 3H), 1.49 (s, 9H), 1.28 (t, $J=7.0$ Hz, 6H); EIMS m/z 354 (M^+–COOEt). Anal. calcd for $C_{21}H_{33}NO_8$: C, 59.00, H, 7.78, N, 3.28. Found: C 59.09, H, 7.67, N, 3.27%.

4.3.7. (*R*)-4-((2*S*,3*R*)-2-Benzoyl-4-ethoxycarbonyl-5-methyl-2,3-dihydrofuran-3-yl)-2,2-dimethyloxazolidine-3-carboxylic acid, *tert*-butyl ester 12e. White foam, $[\alpha]_D^{20} = -35.8$ (*c* 1.23, $CHCl_3$); FT-IR (KBr) 3000, 2978, 2878, 1701, 1646, 1598, 1582, 1455, 1392 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.99 (m, 2H), 7.61 (m, 1H), 7.50 (m, 2H), 6.10 (m, 1H), 4.48–4.12 (m, 3H), 3.99–3.96 (m, 2H), 3.66 (m, 1H), 2.28 (s, 3H), 1.63 (s, 3H), 1.53 (s, 3H), 1.51 (s, 9H), 1.26 (t, $J = 6.9$ Hz, 3H); EIMS m/z 459 (M^+), 416 (M^+–COMe), 354 (M^+–COPh). Anal. calcd for $C_{25}H_{33}NO_7$: C, 65.35, H, 7.24, N, 3.05. Found: C, 65.38, H, 7.22, N, 3.00%.

4.3.8. (2*S*,3*R*)-3-[(*R*)-3-*tert*-Butoxycabonyl-2,2-dimethyloxazolidine-4-yl]-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid, 2-*tert*-butyl ester-4-ethyl ester 12f. White foam, $[\alpha]_D^{20} = +36.7$ (*c* 1.65, $CHCl_3$); FT-IR (KBr) 2988, 2940, 1750, 1699, 1647, 1386 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.10 (d, $J = 4.5$ Hz, 1H), 4.29–4.11 (m, 3H), 3.92–3.68 (m, 3H), 2.27 (s, 3H), 1.67–1.48 (m, 24H), 1.25 (t, $J = 7.0$ Hz, 3H); EIMS m/z 455 (M^+), 354 (M^+–Boc); HRMS found m/z 455.2509 (M^+), $C_{23}H_{37}NO_8$ requires 455.2499.

Acknowledgements

The authors are grateful to the Chinese Academy of Sciences and National Natural Science Foundation of China (grant 20132030) for their financial support.

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