Approach to novel isotetronic acid derivatives: DBU-Et$_3$N-mediated aldol/lactonization/O-protection sequence of 2-oxocarboxylic esters

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Abstract
An efficient synthesis of novel O-protected isotetronic acids is described. The method relies on DBU (1,8-diazabicyclo[5.4.0]-undec-7-ene) and triethylamine triggered homo-aldol reactions of 2-oxocarboxylic esters, followed by successful ring closure via lactonization and O-protection with various electrophiles. The unprotected isotetronic acids were also achieved with moderate to high yields if the free-OH group were pre-capped by the silylation agent TMSCl. All the three reaction steps were conducted in a sequential manner, without isolation of any intermediates.

Keywords: Pyruvate, aldol reaction, lactonization, isotetronic acids

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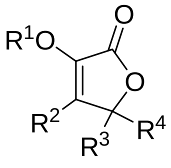
Introduction

Isotetronic acids, having the general structure **I** of a central 3-hydroxy-2(5*H*)-furanone unit (Figure 1), constitute a significant subclass of α-hydroxybutenolides.[1,2] This kind of compounds have been isolated from a variety of natural sources,[1,2] and their properties leading to use as flavoring agents,[3] perfumes[4] and anti-depressants[5] have been evaluated, and analgesic[6] and antifungal[7] activities have been documented.

Many strategies have been developed to access these butenolides.[8-14] Based on retrosynthetic analysis, homoaldol condensation of 2-oxocarboxylic esters and subsequent lactonization of the adduct would be a straightforward way to isotetronic acids. García-Tellado and coworker has devised a novel ABB' three-component reaction system based on triethylamine catalyzed homoaldol reaction of α-ketoesters in the presence of terminal conjugated alkynoates.[15] This method allows the easy construction of 3-alkenoxy substituted isotetronic acid derivatives. Quite recently, Vincent's group reported a very concise enantioselective route to isotetronic acids by using a benzoimidazolepyrrolidine as an organocatalyst to promote the aldol reaction between 2-oxocarboxylic acids and aldehydes with generally good enantioselectivities.[16]

Working on this line, other authors have already found that triethylamine and related simple amines[15] as well as *L*-proline are not the appropriate catalyst to promote the homoaldolic reactions of 2-oxocarboxylic esters like ethyl pyruvate.[14] Thus, there still remains much room for improvement in terms of reaction strategy and operation simplicity.

At the onset of a program toward the synthesis of isotetronic acid derivatives, we have recently shown that O-protected isotetronic acid derivatives can be achieved via a base couple DBU/Et_3N (equivalent ratio 0.20:0.85) mediated sequential homoaldol-lactonization-alkylation reactions of ethyl pyruvate with electrophiles like alkyl halides.[17] The protocol carried several notable advantages such as the wide substrates, simple operation, exceedingly mild condition and no use of any expensive reagents.[18]



I

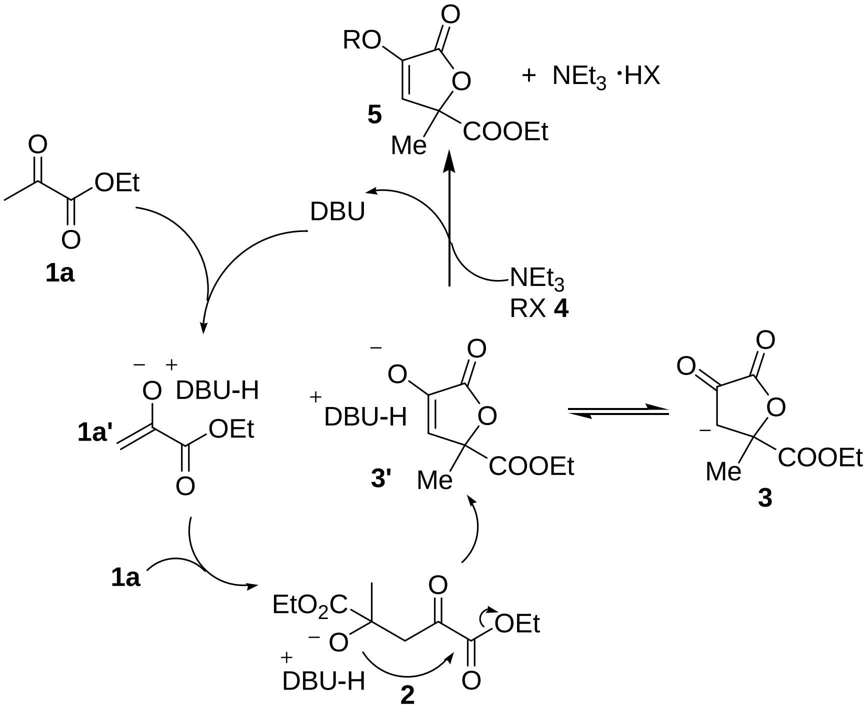
Figure 1. General structure of isotetronic acid derivatives.

Results and Discussion

A plausible reaction pathway is depicted in Scheme 1. Although a clear-cut determination of the role of the two bases can not be made, it is reasonable that the reaction begins with generation of the ammonium enolate **1a′** by action of ethyl pyruvate **1a** with DBU, which behaves as a carbonyl donor to attack another molecule of **1a**, whereby providing the aldol adduct **2**. Intermediate **2** undergoes further lactonization to afford the isotetronic acid anion **3**. Compound **3** occurs in equilibrium with its enolate form **3′**. Under basic conditions, **3′** proceeds functional group manipulation with an electrophile **4** assisted by Et_3N to afford the isolated O-substituted isotetronic acid **5** and regenerate DBU (Scheme 1).

According to this hypothesis, we decided to probe the efficiency and scope of the method in terms of types of 2-oxocarboxylic esters and electrophiles. In this paper, we wish to report that the combination use of DBU and Et_3N can trigger both the homo-aldol and cross-aldol reactions of a range of 2-oxocarboxylic esters, and the intermediate aldol products can undergo further ring closure and O-protection with diverse electrophiles such as acid chlorides, sulfonates, sulfonyl halides, whereupon leading to the formation of a series of novel highly functionalized isotetronic acid derivatives.

Reaction with **1a** using various sulfonates as the O-alkylation agents were firstly examined. As shown in Table 1, the sequential homoaldol-lactonization-alkylation reaction was applicable to diverse sulfonates to provide the O-alkylation isotetronic acid products **5** in moderate to good yields. Both primary tosylates (Table 1, entries 1-3) and methanesulfonates (Table 1, entries 4-6) worked satisfactorily to afford the products **5** in higher than 54% yields, except 3-phenylallyl tosylate **4b** which provided a lower yield of **5b**. Under the similar conditions, the secondary alkyl tosylates **4g** and **4h** could also be used as the electrophiles, however, only afforded lower yields of the products. This is obviously attributable to the higher steric hindrance in the secondary substrates. For the similar reasons, the reaction with more bulky tertiary sulfonates was totally unsuccessful under our conditions (Table 1, entry 9).

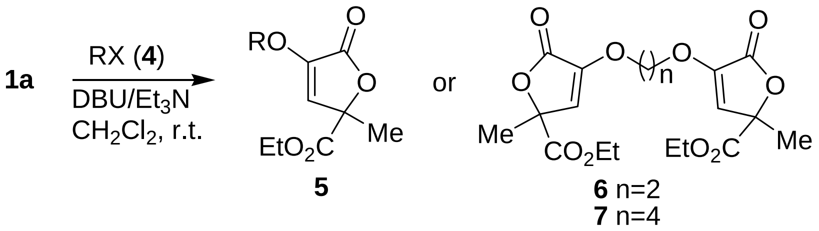


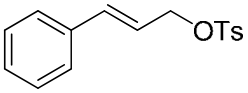
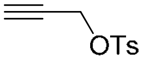
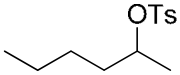
Scheme 1. Rationalization of the homoaldol-lactonization-alkylation reactions of ethyl pyruvate.

We also studied the reaction with 2-chloroethyl tosylate **4j** as the electrophile. Not surprisingly, only the more reactive tosyl group was displaced while the chloride atom remained untouched under the standard conditions, thus affording 45% yield of the isotetronic acid **5j** (Table 1, entry 10). This verified that primary alkyl tosylate behaves better than that the respective chloride as electrophile partners.

We next took the di-tosylate compounds **4k** and **4l** as the electrophiles, however, half molar equivalent amount as compared to the other usual mono-tosylates was employed. Under the compared reaction conditions, the corresponding bis-isotetronic acid derivatives **6** and respectively **7** could be obtained in moderate yields, albeit somewhat longer reaction time was required for a maximal conversion (Table 1, entries 11 and 12). To our surprise, a 35% yield of the two-carbon-linkage product **6** has been achieved. This was a significant improvement in comparison to the result by using the dibromoalkane counterparts, which gave only a low-yielding mixture of the mono and bis-isotetronic acids.[17]

Table 1. One-pot synthesis of O-alkylated isotetronic acids from ethyl pyruvate **1a** and sulfonates[a]



Entry	RX	Product	Yield (%)[b]
1	EtOTs **4a**	**5a**	54
2	 **4b**	**5b**	31
3	 **4c**	**5c**	68
4	*n*BuOMs **4d**	**5d**	63
5	Ph(CH$_2$)$_3$OMs **4e**	**5e**	59
6	BnOMs **4f**	**5f**	56
7	*s*BuOTs **4g**	**5g**	44
8	 **4h**	**5h**	22
9	*t*BuOTs **4i**	**5i**	0
10	ClCH$_2$CH$_2$OTs **4j**	**5j**	45[c]
11	TsO(CH$_2$)$_2$OTs **4k**	**6**	35[c]
12	TsO(CH$_2$)$_4$OTs **4l**	**7**	42[c]

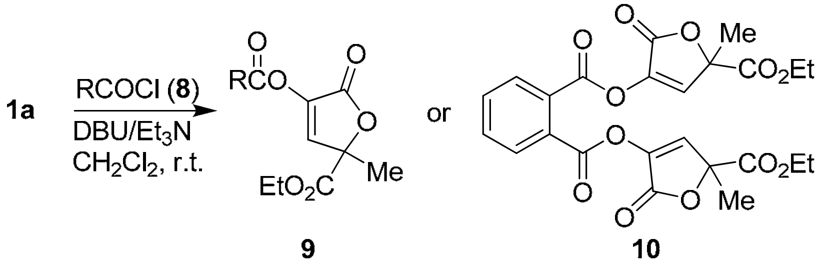
[a] Ethyl pyruvate **1a** (2.33 g, 20.0 mmol), DBU (0.30 g, 2.0 mmol), Et$_3$N (0.86 g, 8.5 mmol), CH$_2$Cl$_2$ (50 mL), r. t., 0.5 h; then sulfonate **4** (10.5 mmol) in CH$_2$Cl$_2$ (20 mL) was added at r. t. and stirred for 15 h.

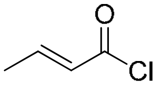
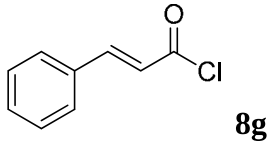
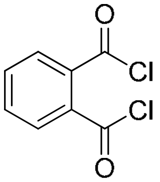
[b] Isolated yield by column chromatography.

[c] 5.5 mmol of sulfonate were used. The reaction time was prolonged to 24-36 h until no further conversion.

In place of sulfonates, a set of acid chlorides **8** were applied in our sequential homoaldo-lactonization-substitution reactions with ethyl pyruvate **1a**. As can be seen from Table 2, both aliphatic (Table 2, entries 1-7) and aromatic acyl chlorides (Table 2, entries 8-10) could efficiently intercept the enolate intermediate **3'** to furnish the 3-O-acylated products **9** in satisfactory yields. It was found that acyl chlorides were generally superior as a 3-OH capping agent to both alkyl halides and sulfonates. For the α,β-unsaturated acid chlorides **8f** and **8g**, none of the plausible Micheal adduct by the enolate **3'** could be detected from the reaction mixture (Table 2, entries 6 and 7). When 4-methoxybenzoyl chloride **8i** was used as the electrophile, the yield of the isotetronic acid **9i** reached 89%.

Table 2. One-pot synthesis of O-acylated isotetronic acids using ethyl pyruvate **1a** and acid chlorides **8**[a]



Entry	RCOCl	Product	Yield (%)[b]
1	CH_3COCl **8a**	**9a**	55
2	*t*BuCOCl **8b**	**9b**	74
3	$PhCH_2COCl$ **8c**	**9c**	54
4	$EtO_2C(CH_2)_2COCl$ **8d**	**9d**	48
5	$EtO_2C(CH_2)_4COCl$ **8e**	**9e**	39
6	 **8f**	**9f**	79
7	 **8g**	**9g**	50
8	4-ClC_6H_4COCl **8h**	**9h**	58
9	4-$MeOC_6H_4COCl$ **8i**	**9i**	89
10	 **8j**	**10**	49[c]
11	TsCl **8k**	**9k**	88
12	$MeSO_2Cl$ **8l**	**9l**	77
13	(*i*Pr)$_3$SiCl **8m**	**9m**	65

[a] **1a** (2.33 g, 20.0 mmol), DBU (0.30 g, 2.0 mmol), Et_3N (0.86 g, 8.5 mmol), CH_2Cl_2 (50 mL), r. t., 0.5 h; then an acyl chloride **8** (10.5 mmol) in CH_2Cl_2 (20 mL) was added at r. t. and stirred for 15 h.

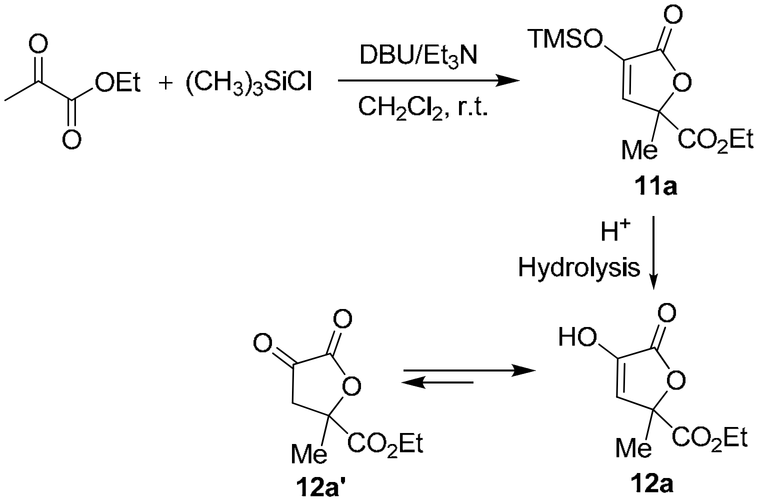
[b] Isolated yield after column chromatography.

[c] Phthaloyl dichloride **8j** (1.12 g, 5.5 mmol) was used.

Gratifyingly, the bis-isotetronic acid derivative **10** could also be furnished by using phthaloyl dichloride **8j** as the electrophile in moderate yield (Table 2, entry 10), even though the product looks rather congested.

The reaction sequence was also successfully extended to tosyl chloride **8k**, methanesulfonyl chloride **8l** and triisopropylsilyl chloride **8m**. Under the standard conditions, the reaction sequence provided good yields of the respective 3-O-protected isotetronic acid derivatives (Table 2, entries 11-13).

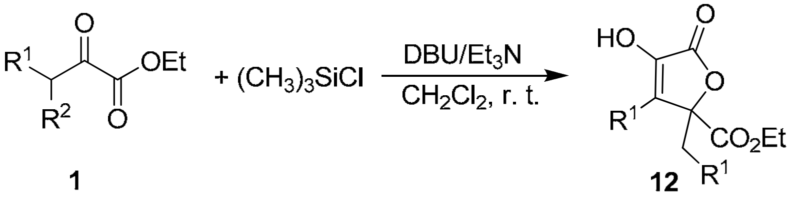
In another experiment, we endeavored the use of trimethylsilyl chloride as the capping agent to get a TMS-protected product **11a**. However, only the 3-OH free product **12a** was isolated in high yield 85% (Table 3, entry 1). In the absence of trimethylsilyl chloride, the unprotected product **12a** was still obtainable, but the yield (determined by GC-Ms) became much inferior (Table 3, entry 2). It could be inferred that trimethylsilyl chloride temporarily protected the hydroxyl group to form the intermediate **11a**, which was prone to desilylation upon the subsequent acidic work-up (Scheme 2). One can also figure out that the O-silylation could favor the homoaldol and lactonization reaction by consuming the hydroxyl-free isotetronic acids. The product **12a** occurs in equilibrium with its dicarbonyl tautomer **12a'** with the former much more pronounced as suggested by the ^{1}H NMR spectra.



Scheme 2

Other workers have noted that it was difficult to isolate the pure OH-free isotetronic acids without protection of the hydroxyl group.[19] In the light of this promising result, we embarked on an investigation of the efficiency and scope of the method with a wide variety of β-substituted 2-oxocarboxylic esters **1b-f**, which were easily accessible from ethyl oxalate using literature methods.[20] The results were collected in Table 3. We pleasingly found that β-mono substituted 2-oxocarboxylic esters **1b-d** behaved as suitable reactants for this process (Table 3, entries 3-5). This demonstrated that the first homo-aldol reaction and the subsequent ring closure occurred for these substituted 2-oxocarboxylic esters without difficulty. As shown by diethyl 2-oxopentanedioate **1d**, the conditions for the reaction were so mild as to permit the coexistence of another ester function in the molecule (Table 3, entry 5). The 3-OH free isotetronic acids were obtained in moderate to high yields. However, a limitation arises when the α-position carries two substitutes (Table 3, entries 6 and 7). Neither the plausible intermediate product nor the final isotetronic acid products **12e-f** could be observed from the reaction mixture. We assume that this was again attributed to the steric hindrance and the poor enolizable property required for the formation of the carbonyl donor. Much stronger base would be a necessity.

Table 3. One-pot synthesis of the unprotected isotetronic acids by using 2-oxocarboxylic esters and trimethylsilyl chloride[a]



Entry	Substrate	R^1	R^2	Product	Yield (%)[b]
1	**1a**	H	H	**12a**	85
2	**1a**	H	H	**12a**	61[c]
3	**1b**	Me	H	**12b**	45
4	**1c**	*n*Pr	H	**12c**	79
5	**1d**	CH_2CO_2Et	H	**12d**	70
6	**1e**	*n*$C_{16}H_{33}$	CO_2Et	-	NR[d]
7	**1f**	Me	Me	-	NR[d]

[a] 2-Oxocarboxylic ester **1** (2.33 g, 20.0 mmol), DBU (0.30 g, 2.0 mmol), Et_3N (0.86 g, 8.5 mmol), CH_2Cl_2 (50 mL), r. t., 0.5 h; then TMSCl (1.13 g, 10.5 mmol) in CH_2Cl_2 (20 mL) was added at r. t. and stirred for 15 h.

[b] Isolated yield by column chromatography.

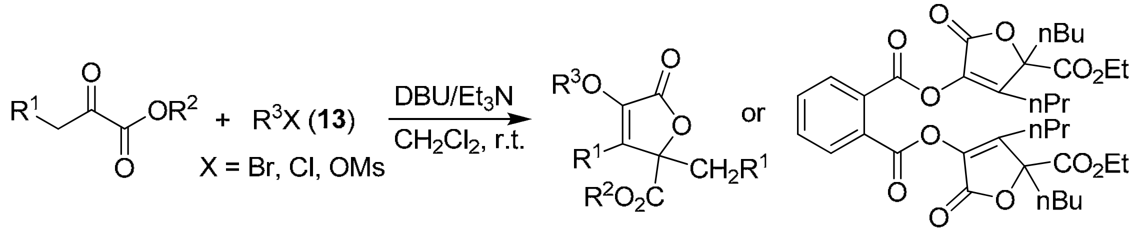
[c] The reaction was carried out without trimethylsilyl chloride.

[d] No reaction.

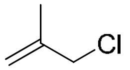
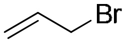
According to the mechanistic rationale, depicted in Scheme 1, we envisioned that the use of other 2-oxocarboxylic esters in the homoaldol-lactonization-alkylation sequence would be capable of affording 4-substituted isotetronic acid derivatives. Thus, several 3-monosubstituted 2-oxocarboxylic esters were examined, however, with only reactive benzyl or allyl halides **13** serving as the eletrophiles. The results were summarized in Table 4. Under similar conditions, moderate to good yields of the highly substituted products **14** were achieved (Table 4, entries 1-6). Again, due to the mildness of the protocol, the reaction sequence allows the existence of additional ester group in the 2-oxocarboxylic esters (Table 4, entries 5 and 6), although the isolated yields seem to be slightly inferior (entry 1 or 3 *vs*. entry 5; entry 4 *vs*. entry 6).

Further work was carried out on butyl methanesulfonate (Table 4, entry 7) and tosyl chloride, and the respective 3-O-protected isotetronic acids were obtained in moderate to good yields (Table 4, entries 8 and 9). The reaction sequence was also extended to phthaloyl dichloride and ethyl 2-oxohexanoate which successfully led to the formation of the highly substituted bis-isotetronic acid **15** in 41% yield (Table 4, entry 10). From these results, it can be concluded that our strategy allows for introducing a wide range of substituents at C-4 and C-5 of the furanone ring just by choosing different suitably substituted 2-oxocarboxylic esters.

Table 4. One-pot synthesis of O-alkylated isotetronic acids using different 2-oxocarboxylic esters **1**[a]



1 **14** **15**

Entry	Substrate	R^1	R^2	R^{3}X	Product	Yield (%)[b]
1	**1b**	Me	Et	BnBr **13a**	**14a**	75
2	**1b**	Me	Et	 **13b**	**14b**	64
3	**1c**	*n*Pr	Et	**13a**	**14c**	72
4	**1c**	*n*Pr	Et	 **13c**	**14d**	75
5	**1d**	CH_2CO_2Et	Et	**13a**	**14e**	65
6	**1g**	CH_2CO_2Me	Me	**13c**	**14f**	48
7	**1c**	*n*Pr	Et	*n*BuOMs **4d**	**14g**	49
8	**1b**	Me	Et	TsCl **8k**	**14h**	69
9	**1c**	*n*Pr	Et	**8k**	**14i**	56
10	**1c**	*n*Pr	Et	**8j**	**15**	41[c]

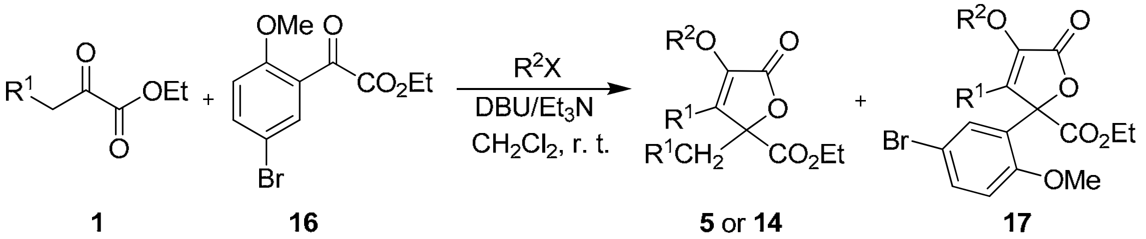
[a] 2-Oxocarboxylic ester **1** (2.33 g, 20.0 mmol), DBU (0.30 g, 2.0 mmol), Et_3N (0.86 g, 8.5 mmol), CH_2Cl_2 (50 mL), r. t., 0.5 h; then R^{3}X (10.5 mmol) in CH_2Cl_2 (20 mL) was added, r. t., 15 h.

[b] Isolated yield by column chromatography.

[c] 1.12 g (5.5 mmol) of phthaloyl dichloride **8j** were used.

In an attempt to extend this chemistry to a cross-aldol version, another study was undertaken starting from the ethyl 2-phenyl-2-oxoacetate **16** which is non-enolizable and hence only capable of being an acceptor in the initial aldol step. Compound **16** was allowed to react with three different 2-oxocarboxylic esters using benzyl bromide or allyl bromide as the electrophile. It was revealed that the reaction proceeded well with good conversion of the substrates. If the aldol donor was ethyl pyruvate **1a** or ethyl 2-oxobutanoate **1b**, the reaction sequence provided a mixture products of **14** and **17**, resulting respectively from the homoaldol of the enolizable 2-oxocarboxylic esters and from the cross-aldol condensation, with the former one significantly pronounced (Table 5, entries 1-3). The mixture could be easily separated by chromatography. On the other hand, if the aldol donor was ethyl 2-oxohexanoate **1c** with a longer carbon chain, the cross-aldol reaction was totally suppressed, and the sole product was **14c** arising from the homo-aldol reaction of **1c**. We are currently exploring other non-enolizable aldol acceptors, such as aromatic and hindered aldehydes, to be involved in our strategy and improvement in the yield by varying the substrate addition sequence.

Table 5. One-pot synthesis of O-alkylated isotetronic acids using two different 2-oxocarboxylic esters[a]



Entry	**1**	R^1	R^2X (**13**)	Product **5** or **14** (% yields)[b]	Product **17** (% yields)[b]
1	**1a**	H	**13c**	**5m** (59)	**17a** (10)
2	**1a**	H	**13a**	**5f** (65)	**17b** (11)
3	**1b**	Me	**13a**	**14a** (60)	**17c** (6)
4	**1c**	*n*Pr	**13a**	**14c** (70)	**17d** (0)

[a] 2-Oxocarboxylic ester **1** (10.0 mmol), **16** (2.85 g, 10.0 mmol), DBU (0.30 g, 2.0 mmol), Et_3N (0.86 g, 8.5 mmol), CH_2Cl_2 (50 mL), r. t., 0.5 h; then alkyl halide **13** (10.5 mmol) in CH_2Cl_2 (20 mL) was added, r. t., 15 h.
[b] Isolated yield after column chromatography.

In summary, we have demonstrated the effectiveness of DBU-Et_3N-promoted homoaldol-lactonization-substitution reaction sequence of 2-oxocarboxylic esters with electrophiles for the rapid assembly of substituted isotetronic acid derivatives. Variation of the types of 2-carboxylic esters and electrophiles were investigated which led the formation of densely functionalized isotetronic acids with structural complexity. The 3-OH unprotected isotetronic acids also became easily accessible simply by prior protection with trimethylsilyl chloride. The attractive features of this protocol include good yields, broad substrate scope, elimination of any expensive reagents, mild reaction conditions and experimental simplicity.

Experimental Section

General Procedures. NMR spectra were recorded on a JEOL ECA-400 spectrometer operating at 400 MHz for proton, and 100 MHz for carbon. ^{1}H chemical shifts (δ) are reported in ppm relative to TMS as internal standard. Coupling constants (J) are given in Hz. ^{13}C chemical shifts were internally referenced to the deuterated solvent signals in $CDCl_3$ (δ 77.00 ppm). Mass spectra were recorded on a HP 5989A mass spectrometer. High resolution mass spectra were recorded on a Finnigan MAT mass spectrometer. Dichloromethane was dried by refluxing and distilling over CaH_2. Triethylamine was distilled from KOH immediately prior to use. Solvents for extraction and chromatography were technical grade, and petroleum ether was distilled and the boiling range of 60-90 ºC was used. Thin layer chromatography was performed on precoated silica gel GF254 (Qingdao Haiyang Chemical Co. Ltd.), and the plates were visualized with UV light. Flash column chromatography was performed using Yantai Jiangyou silica gel (300-400 mesh).

General experimental procedure for the synthesis of *O*-substituted isotetronic acid derivatives

2-Oxocarboxylic ester **1** (20.0 mmol), CH_2Cl_2 (50 mL) were added to an oven dried Schlenk flask and then DBU (0.30 g, 2.0 mmol) and triethylamine (0.86 g, 8.5 mmol) in CH_2Cl_2 (20 mL) were added dropwise to the flask. After the reaction mixture was stirred at room temperature for 0.5 h, electrophile **4** or **8** or **13** (10.5 mmol) in CH_2Cl_2 (20 mL) was added dropwise. Then the reaction mixture was stirred at room temperature overnight. The resulted orange solution was washed sequentially with a saturated ammonium chloride and saturated sodium chloride solution (50 mL), separated and dried over Na_2SO_4. The organic phase was concentrated under high vacuum. The residue was subjected to flash chromatography (silica gel, eluting with petroleum ether/ ethyl acetate) to afford the analytically pure isotetronic acid derivatives **5** or **9** or **14** (Tables 1, 2 and 4).

4-Ethoxy-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (5a). Yellow oil. IR (CH_2Cl_2, cm^{-1}): 1654, 1742, 1788, 3104. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.43 (t, J = 7.1 Hz, 3 H, 4-OCH_2CH_3), 1.72 (s, 3 H, 2-CH_3), 3.98 (q, J = 6.9 Hz, 2 H, 4-OCH_2CH_3), 4.22 (q, J = 6.9 Hz, 2 H, $CO_2CH_2CH_3$), 6.19 (s, 1 H, 3-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 14.0, 23.3, 62.5, 67.4, 82.5, 116.8, 146.5, 166.6, 169.1. HRMS (ESI): Calcd. for $C_{10}H_{14}O_5^+$: 214.0841. Found: 214.0829.

4-(Cinnamyloxy)-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (5b). Yellow oil. IR (CH_2Cl_2, cm^{-1}): 1649, 1742, 1786, 3103. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.71 (s, 3 H, 2-CH_3), 4.19 (q, J = 6.8 Hz, 2 H, CH_2CH_3), 4.62 (d, J = 6.4 Hz, 2 H, 4-OCH_2), 6.14 (s, 1 H, 3-H), 6.30 (dt, J = 16.0, 6.0 Hz, 1 H, CH=CH_2), 6.70 (d, J = 16.0 Hz, 1 H, PhCH), 7.25-7.40 (m, 5 H, C_6H_5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 23.6, 62.6, 72.0, 82.6, 117.7, 121.8, 126.8, 128.5, 128.8, 135.1, 135.8, 146.1, 166.5, 169.1. HRMS (ESI): Calcd. for $C_{17}H_{18}O_5^+$: 302.1154. Found: 302.1164.

2-Methyl-5-oxo-4-(prop-2-ynyloxy)-2,5-dihydrofuran-2-carboxylic acid ethyl ester (5c). Yellow oil. IR (CH_2Cl_2, cm^{-1}): 1655, 1740, 1786, 2125, 3105, 3279. ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 1.76 (s, 3 H, 2-CH_3), 2.62 (t, J = 2.5 Hz, 1 H, $HCCCH_2$), 4.23 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 4.65 (dd, J = 16.0, 2.7 Hz, 1 H), 4.68 (dd, J = 16.0, 2.7 Hz, 1 H) ($HCCCH_2$), 6.34 (s, 1 H, 3-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 23.0, 58.7, 62.6, 75.8, 77.7, 82.6, 119.5, 144.9, 166.1, 168.6. HRMS (ESI): Calcd. for $C_{11}H_{12}O_5^+$: 224.0685. Found: 224.0671.

4-Butoxy-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (5d). Yellow oil. IR (CH_2Cl_2, cm^{-1}): 1653, 1743, 1790, 3105. ^1H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, J = 7.3 Hz, 3 H, 4-$CH_3(CH_2)_3$), 1.29 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.40-1.50 (m, 2 H, 4-$CH_3CH_2(CH_2)_2$), 1.71 (s, 3 H, 2-CH_3), 1.72-1.82 (m, 2 H, 4-$CH_3CH_2CH_2CH_2$), 3.90 (t, J = 6.4 Hz, 2 H, 4-OCH_2), 4.21 (q, J = 7.3 Hz, 2 H, $CO_2CH_2CH_3$), 6.05 (s, 1 H, 3-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 14.1, 19.1, 23.3, 30.6, 62.5, 71.5, 82.5, 116.7, 146.7, 166.6, 169.1. HRMS (ESI): Calcd. for $C_{12}H_{18}O_5^+$: 242.1154. Found: 242.1147.

2-Methyl-5-oxo-4-(3-phenylpropoxy)-2,5-dihydrofuran-2-carboxylic acid ethyl ester (5e). Yellow oil. IR (CH_2Cl_2, cm^{-1}) 1654, 1742, 1789, 3103. ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 1.68 (s, 3 H, 2-CH_3), 2.05-2.18 (m, 2 H, $PhCH_2CH_2$), 2.76 (t, J = 7.8 Hz, 2 H, $PhCH_2$), 3.88 (t, J = 6.4 Hz, 2 H, 4-OCH_2), 4.20 (q, J = 6.8 Hz, 2 H, CH_2CH_3), 6.06 (s, 1 H, 3-H), 7.15-7.30 (m, 5 H, C_6H_5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 23.3, 30.0, 31.8, 62.6, 70.6, 82.6, 117.3, 126.2, 128.5, 128.6, 128.7, 140.9, 146.5, 166.6, 169.0. HRMS (ESI): Calcd. for $C_{17}H_{20}O_5^+$: 304.1311. Found: 304.1299.

4-(Benzyloxy)-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (5f). White solid; m.p. 70-72 ºC. IR (CH_2Cl_2, cm^{-1}): 1454, 1499, 1562, 1650, 1740, 1786, 3103. ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.69 (s, 3 H, 2-CH_3), 4.20 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 5.01 (s, 2 H, $PhCH_2$), 6.11 (s, 1 H, 3-H), 7.33-7.42 (m, 5 H, C_6H_5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 23.2, 62.6, 73.2, 82.5, 118.2, 127.8, 128.8, 134.4, 146.2, 166.4, 169.0. HRMS (ESI): Calcd. for $C_{15}H_{16}O_5^+$: 276.0998. Found: 276.0972.

4-*sec*-Butoxy-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (5g). Yellow oil. IR (CH_2Cl_2, cm^{-1}): 1649, 1743, 1789, 3103. ^1H NMR (400 MHz, $CDCl_3$): δ 0.90-1.00 (m, 3 H, 4-CH_3CH_2), 1.20-1.38 (m, 6 H, 4-CH_3CH & $CO_2CH_2CH_3$), 1.60-1.72 (m, 2 H, 4-CH_3CH_2), 1.72 (s, 3 H, 2-CH_3), 4.03-4.15 (m, 1 H, 4-CH_3CH), 4.23 (q, J = 7.2 Hz, 2 H, $CO_2CH_2CH_3$), 6.01 (s, 1 H, 3-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.6, 14.0, 18.3, 23.2, 28.4, 62.4, 79.7, 81.3, 116.6, 145.4, 167.1, 169.1. HRMS (ESI): Calcd. for $C_{12}H_{18}O_5^+$: 242.1154. Found: 242.1144.

4-(Hexan-2-yloxy)-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (5h). Yellow oil. IR (CH_2Cl_2, cm^{-1}): 1654, 1742, 1793, 3105. ^1H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, J = 6.8 Hz, 3 H, CH_3CH_2), 1.00 (d, J = 6.4 Hz, 3 H, CH_3CH), 1.15-1.50 (m, 9 H, $CH_3(CH_2)_3$ & $CO_2CH_2CH_3$), 1.71 (s, 3 H, 2-CH_3), 3.73-3.75 (m, 1 H, CH_3CH), 4.23 (q, J = 6.6 Hz, 2 H, $CO_2CH_2CH_3$), 6.05 (s, 1 H, 3-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 14.2, 16.8, 20.0, 23.3, 32.4, 35.4, 62.5, 76.8, 81.2, 116.7, 146.8, 166.5, 169.2. HRMS (ESI): Calcd. for $C_{14}H_{22}O_5^+$: 270.1467. Found: 270.1447.

4-(2-Chloroethoxy)-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (5j). Yellow oil. IR ($\mathrm{CH_2Cl_2}$, $\mathrm{cm^{-1}}$): 1656, 1743, 1789, 3104. ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$): δ 1.30 (t, J = 7.3 Hz, 3 H, $\mathrm{CH_2C}H_3$), 1.73 (s, 3 H, 2-$\mathrm{C}H_3$), 3.81 (t, J = 6.2 Hz, 2 H, $\mathrm{ClC}H_2\mathrm{CH_2O}$), 4.18 (t, J = 6.9 Hz, 2 H, $\mathrm{ClCH_2C}H_2\mathrm{O}$), 4.25 (q, J = 7.3 Hz, 2 H, $\mathrm{C}H_2\mathrm{CH_3}$), 6.19 (s, 1 H, 3-H). ^{13}C NMR (100 MHz, $\mathrm{CDCl_3}$): δ 14.0, 23.2, 40.9, 62.7, 71.0, 82.5, 118.2, 145.9, 166.0, 168.7. HRMS (ESI): Calcd. for $\mathrm{C_{10}H_{13}ClO_5^+}$: 248.0452. Found: 248.0454.

Bis-isotetronic acid (6). Yellow oil. IR ($\mathrm{CH_2Cl_2}$, $\mathrm{cm^{-1}}$): 1651, 1743, 1789, 3104. ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$): δ 1.28 (t, J = 7.1 Hz, 6 H, 2 × $\mathrm{CH_2C}H_3$), 1.73 (s, 6 H, 2 × 2-$\mathrm{C}H_3$), 4.22 (q, J = 7.1 Hz, 4 H, 2 × $\mathrm{C}H_2\mathrm{CH_3}$), 4.31 (s, 4 H, $\mathrm{C}H_2\mathrm{C}H_2$), 6.29 (s, 2 H, 2 ×3-H). ^{13}C NMR (100 MHz, $\mathrm{CDCl_3}$): δ 14.0, 23.1, 62.7, 69.3, 82.6, 118.4, 145.9, 16 6.1, 168.7. HRMS (ESI): Calcd. for $\mathrm{C_{18}H_{22}O_{10}^+}$: 398.1213. Found: 398.1206.

Bis-isotetronic acid (7). White solid; m.p. 105-106 ºC. IR ($\mathrm{CH_2Cl_2}$, $\mathrm{cm^{-1}}$): 1653, 1731, 1790, 3103. ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$): δ 1.28 (t, J = 7.1 Hz, 6 H, 2 × $\mathrm{CH_2C}H_3$), 1.72 (s, 6 H, 2 × 2-$\mathrm{C}H_3$), 1.97 (s, 4 H, $\mathrm{CH_2C}H_2\mathrm{C}H_2\mathrm{CH_2}$), 3.98 (s, 4 H, $\mathrm{C}H_2\mathrm{(CH_2)_2C}H_2$), 4.23 (q, J = 7.0 Hz, 4 H, 2 × $\mathrm{C}H_2\mathrm{CH_3}$), 6.12 (s, 2 H, 2 × 3-H). ^{13}C NMR (100 MHz, $\mathrm{CDCl_3}$): δ 14.1, 23.3, 25.3, 62.6, 71.0, 82.5, 117.4, 146.2, 166.4, 168.9. HRMS (ESI): Calcd. for $\mathrm{C_{20}H_{26}O_{10}^+}$: 426.1526. Found: 426.1513.

4-Acetoxy-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (9a). Yellow oil. IR ($\mathrm{CH_2Cl_2}$, $\mathrm{cm^{-1}}$): 1648, 1747, 1786, 3131. ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$): δ 1.30 (t, J = 7.1 Hz, 3 H, $\mathrm{CH_2C}H_3$), 1.77 (s, 3 H, 2-$\mathrm{C}H_3$), 2.33 (s, 3 H, $\mathrm{C}H_3\mathrm{CO}$), 4.24 (q, J = 7.1 Hz, 2 H, $\mathrm{C}H_2\mathrm{CH_3}$), 7.32 (s, 1 H, 3-H). ^{13}C NMR (100 MHz, $\mathrm{CDCl_3}$): δ 14.0, 20.9, 22.5, 62.8, 83.2, 132.9, 137.6, 165.7, 166.8, 167.8. HRMS (ESI): Calcd. for $\mathrm{C_{10}H_{12}O_6^+}$: 228.0634. Found: 228.0629.

2-Methyl-5-oxo-4-(pivaloyloxy)-2,5-dihydrofuran-2-carboxylic acid ethyl ester (9b). Yellow oil. IR ($\mathrm{CH_2Cl_2}$, $\mathrm{cm^{-1}}$): 1647, 1758, 1775, 1794, 3108. ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$): δ 1.22-1.38 (m, 12 H, $\mathrm{(C}H_3\mathrm{)_3C}$ & $\mathrm{CH_2C}H_3$), 1.75 (s, 3 H, 2-$\mathrm{C}H_3$), 4.25 (q, J = 7.4 Hz, 2 H, $\mathrm{C}H_2\mathrm{CH_3}$), 7.25 (s, 1 H, 3-H). ^{13}C NMR (100 MHz, $\mathrm{CDCl_3}$): δ 14.0, 22.6, 26.9, 39.5, 62.8, 83.1, 132.9, 138.1, 165.7, 168.0, 174.7. HRMS (ESI): Calcd. for $\mathrm{C_{13}H_{18}O_6^+}$: 270.1103. Found: 270.1089.

2-Methyl-5-oxo-4-(2-phenylacetoxy)-2,5-dihydrofuran-2-carboxylic acid ethyl ester (9c). Yellow oil. IR ($\mathrm{CH_2Cl_2}$, $\mathrm{cm^{-1}}$): 1648, 1739, 1789, 3110. ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$): δ 1.28 (t, J = 7.3 Hz, 3 H, $\mathrm{CH_2C}H_3$), 1.74 (s, 3 H, 2-$\mathrm{C}H_3$), 3.88 (s, 2 H, $\mathrm{PhC}H_2$), 4.21 (q, J = 7.1 Hz, 2 H, $\mathrm{C}H_2\mathrm{CH_3}$), 7.25 (s, 1 H, 3-H), 7.29-7.40 (m, 5 H, $\mathrm{C_6}H_5$). ^{13}C NMR (100 MHz, $\mathrm{CDCl_3}$): δ 14.0, 22.5, 40.8, 62.9, 83.3, 127.8, 128.9, 129.5, 132.1, 133.1, 138.8, 165.6, 167.8, 167.9. HRMS (ESI): Calcd. for $\mathrm{C_{16}H_{16}O_6^+}$: 304.0947. Found: 304.0951.

4-(4-Ethoxy-4-oxobutanoyloxy)-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (9d). Yellow oil. IR ($\mathrm{CH_2Cl_2}$, $\mathrm{cm^{-1}}$): 1648, 1736, 1794, 3131. ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$): δ 1.20-1.35 (m, 6 H, 2 × $\mathrm{CH_2C}H_3$), 1.76 (s, 3 H, 2-$\mathrm{C}H_3$), 2.71 (t, J = 6.9 Hz, 2 H, $\mathrm{EtOOCC}H_2\mathrm{CH_2}$), 2.91 (t, J = 6.9 Hz, 2 H, $\mathrm{EtOOCCH_2C}H_2$), 4.16 (q, J = 6.9 Hz, 2 H, $\mathrm{CH_3C}H_2\mathrm{OOC}$), 4.25 (q, J = 7.3 Hz, 2 H, 2-$\mathrm{COOC}H_2\mathrm{CH_3}$), 7.33 (s, 1 H, 3-H). ^{13}C NMR (100 MHz, $\mathrm{CDCl_3}$): δ 14.0, 14.1, 22.5, 28.6, 29.1, 61.0, 62.8, 83.2, 133.0, 137.5, 165.5, 167.8, 168.8, 171.7. HRMS (ESI): Calcd. for $\mathrm{C_{14}H_{18}O_8^+}$: 314.1002. Found: 314.1000.

4-(6-Ethoxy-6-oxohexanoyloxy)-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (9e). Yellow oil. IR (CH_2Cl_2, cm^{-1}): 1648, 1735, 1794, 3134. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20-1.45 (m, 6 H, 2 × CH_2CH_3), 1.65-1.75 (m, 4 H, $CH_2CH_2CH_2CH_2$), 1.77 (s, 3 H, 2-CH_3), 2.35 (t, J = 6.9 Hz, 2 H, EtOOCCH_2), 2.62 (t, J = 6.9 Hz, 2 H, 4-OOCCH_2), 4.14 (q, J = 6.9 Hz, 2 H, CH_3CH_2OOC), 4.24 (q, J = 7.4 Hz, 2 H, 2-$CO_2CH_2CH_3$), 7.30 (s, 1 H, 3-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 14.2, 22.6, 23.9, 24.2, 33.7, 33.8, 60.5, 62.9, 83.2, 132.8, 137.7, 165.8, 167.9, 169.4, 173.2. HRMS (ESI): Calcd. for $C_{16}H_{22}O_8^+$: 342.1315. Found: 342.1302.

4-(But-2-enoyloxy)-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (9f). Yellow oil. IR (CH_2Cl_2, cm^{-1}): 1643, 1752, 1794, 3131. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 1.78 (s, 3 H, 2-CH_3), 1.98 (d, J = 7.0 Hz, 3 H, CH_3CH), 4.21 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 6.00 (d, J = 15.4 Hz, 1 H, CHCOO), 7.20-7.32 (m, 1 H, CH_3CH), 7.35 (s, 1 H, 3-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 18.4, 22.5, 62.7, 83.2, 120.4, 132.4, 137.6, 150.1, 162.0, 165.9, 167.9. HRMS (ESI): Calcd. for $C_{12}H_{14}O_6^+$: 254.0790. Found: 254.0792.

4-(Cinnamoyloxy)-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (9g). White solid; m.p. 96-98 ºC. IR (CH_2Cl_2, cm^{-1}): 1450, 1498, 1578, 1631, 1747, 1790, 3136. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.81 (s, 3 H, 2-CH_3), 4.24 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 6.60 (d, J = 16.0 Hz, 1 H, =CHCOO), 7.38-7.58 (m, 6 H, C_6H_5 & 3-H), 7.88 (d, J = 16.0 Hz, 1 H, PhCH=). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 62.9, 83.4, 115.3, 128.7, 129.2, 131.5, 132.4, 133.6, 137.7, 149.0, 162.8, 166.0, 168.0. HRMS (ESI): Calcd. for $C_{17}H_{16}O_6^+$: 316.0947. Found: 316.0932.

4-(4-Chlorobenzoyloxy)-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (9h). White solid; m.p. 75-76 ºC. IR (CH_2Cl_2, cm^{-1}): 1454, 1592, 1649, 1745, 1784, 3139. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.82 (s, 3 H, 2-CH_3), 4.26 (q, J = 6.9 Hz, 2 H, CH_2CH_3), 7.48 (s, 1 H, 3-H), 7.49 (dd, J = 8.7, 2.3 Hz, 2 H), 8.11 (dd, J = 8.7, 2.3 Hz, 2 H) (C_6H_4). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 23.0, 63.0, 83.4, 126.1, 128.5, 130.2, 132.8, 137.7, 141.3, 161.9, 165.6, 167.9. HRMS (ESI): Calcd. for $C_{15}H_{13}ClO_6^+$: 324.0401. Found: 324.0397.

4-(4-Methoxybenzoyloxy)-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (9i). White solid; m.p. 116-118 ºC. IR (CH_2Cl_2, cm^{-1}): 1458, 1509, 1607, 1646, 1735, 1750, 1785, 3134. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.79 (s, 3 H, 2-CH_3), 3.88 (s, 3 H, CH_3O), 4.23 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 6.96 (dd, J = 6.9, 2.3 Hz, 2 H, Ar-H), 7.43 (s, 1 H, 3-H), 8.11 (dd, J = 6.9, 2.3 Hz, 2 H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.7, 55.7, 62.9, 83.3, 114.2, 119.8, 132.3, 132.8, 137.8, 162.3, 164.7, 166.0, 168.1. HRMS (ESI): Calcd. for $C_{16}H_{16}O_7^+$: 320.0896. Found: 320.0885.

Bis(5-(ethoxycarbonyl)-5-methyl-2-oxo-2,5-dihydrofuran-3-yl) phthalate (10). Yellow oil. IR (CH_2Cl_2, cm^{-1}): 1448, 1598, 1649, 1755, 1794, 3130. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, J = 7.1 Hz, 6 H, 2 × CH_2CH_3), 1.74 (s, 6 H, 2 × 2-CH_3), 4.19 (q, J = 7.0 Hz, 4 H, 2 × CH_2CH_3), 7.47 (s, 2 H, 2 × 3-H), 7.67 (dd, J = 5.5, 3.2 Hz, 2 H, Ar-H), 7.88 (dd, J = 5.4, 3.1 Hz, 2 H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.5, 62.9, 83.4, 129.6, 130.4, 133.0, 133.7, 137.4, 162.9, 165.3, 167.7. HRMS (ESI): Calcd. for $C_{24}H_{22}O_{12}^+$: 502.1111. Found: 502.1075.

2-Methyl-5-oxo-4-(tosyloxy)-2,5-dihydrofuran-2-carboxylic acid ethyl ester (9k). White solid; m.p. 56-57 °C. IR ($\mathrm{CH_2Cl_2}$, $\mathrm{cm^{-1}}$): 1390, 1448, 1493, 1597, 1651, 1758, 1797, 3111. ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$): δ 1.27 (t, J = 7.3 Hz, 3 H, $\mathrm{CH_2C}H_3$), 1.72 (s, 3 H, 2-$\mathrm{C}H_3$), 2.47 (s, 3 H, $\mathrm{C}H_3$), 4.21 (q, J = 6.9 Hz, 2 H, $\mathrm{C}H_2\mathrm{CH_3}$), 7.19 (s, 1 H, 3-H), 7.38 (d, J = 8.2 Hz, 2 H), 7.84 (d, J = 8.7 Hz, 2 H) ($\mathrm{C_6}H_4$). ^{13}C NMR (100 MHz, $\mathrm{CDCl_3}$): δ 14.0, 21.9, 22.4, 63.1, 82.9, 128.6, 130.3, 131.3, 134.7, 137.5, 146.9, 164.3, 167.2. HRMS (ESI): Calcd. for $\mathrm{C_{15}H_{16}O_7S^+}$: 340.0617. Found: 340.0625.

2-Methyl-4-(methylsulfonyloxy)-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (9l). White solid; m.p. 43-44 °C. IR ($\mathrm{CH_2Cl_2}$, $\mathrm{cm^{-1}}$): 1380, 1653, 1749, 1794, 3111. ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$): δ 1.30 (t, J = 7.3 Hz, 3 H, $\mathrm{CH_2C}H_3$), 1.78 (s, 3 H, 2-$\mathrm{C}H_3$), 3.37 (s, 3 H, $\mathrm{C}H_3$), 4.26 (q, J = 7.3 Hz, 2 H, $\mathrm{C}H_2\mathrm{CH_3}$), 7.20 (s, 1 H, 3-H). ^{13}C NMR (100 MHz, $\mathrm{CDCl_3}$): δ 14.2, 22.3, 39.6, 63.2, 83.2, 135.9, 137.3, 164.8, 167.0. HRMS (ESI): Calcd. for $\mathrm{C_9H_{12}O_7S^+}$: 264.0304. Found: 264.0300.

2-Methyl-5-oxo-4-(triisopropylsilyloxy)-2,5-dihydrofuran-2-carboxylic acid ethyl ester (9m). Yellow oil. IR ($\mathrm{CH_2Cl_2}$, $\mathrm{cm^{-1}}$): 1654, 1744, 1789, 3101. ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$): δ 1.11 (d, J = 7.3 Hz, 18 H, 3 × ($\mathrm{C}H_3$)$_2$CH), 1.20-1.35 (m, 6 H, 3 × ($\mathrm{CH_3}$)$_2\mathrm{C}H$ & $\mathrm{CH_2C}H_3$), 1.70 (s, 3 H, 2-$\mathrm{C}H_3$), 4.21 (q, J = 7.1 Hz, 2 H, $\mathrm{C}H_2\mathrm{CH_3}$), 6.23 (s, 1 H, 3-H). ^{13}C NMR (100 MHz, $\mathrm{CDCl_3}$): δ 12.3, 14.0, 17.7, 22.8, 62.4, 81.5, 123.8, 143.3, 168.0, 169.0. HRMS (ESI): Calcd. for $\mathrm{C_{17}H_{30}O_5Si^+}$: 342.1863. Found: 342.1857.

4-(Benzyloxy)-2-ethyl-3-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (14a). Yellow oil. IR ($\mathrm{CH_2Cl_2}$, $\mathrm{cm^{-1}}$): 1395, 1457, 1498, 1684, 1736, 1774, 3033. ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$): δ 0.68 (t, J = 7.3 Hz, 3 H, 2-$\mathrm{CH_2C}H_3$), 1.24 (t, J = 7.1 Hz, 3 H, $\mathrm{OCH_2C}H_3$), 1.74 (s, 3 H, 3-$\mathrm{C}H_3$), 1.75-1.83 (m, 1 H), 2.10-2.20 (m, 1 H) (2-$\mathrm{C}H_2\mathrm{CH_3}$), 4.16 (q, J = 7.1 Hz, 2 H, $\mathrm{OC}H_2\mathrm{CH_3}$), 5.25 (d, J = 11.9 Hz, 1 H), 5.33 (d, J = 11.9 Hz, 1 H) ($\mathrm{PhC}H_2$), 7.30-7.45 (m, 5 H, $\mathrm{C_6}H_5$). ^{13}C NMR (100 MHz, $\mathrm{CDCl_3}$): δ 6.7, 9.3, 14.0, 26.9, 62.4, 72.4, 86.9, 128.6, 136.3, 140.3, 140.5, 167.6, 168.2. HRMS (ESI): Calcd. for $\mathrm{C_{17}H_{20}O_5^+}$: 304.1311. Found: 304.1304.

2-Ethyl-3-methyl-4-(2-methylallyloxy)-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (14b). Yellow oil. IR ($\mathrm{CH_2Cl_2}$, $\mathrm{cm^{-1}}$): 1685, 1736, 1775, 3082. ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$): δ 0.86 (t, J = 7.3 Hz, 3 H, 2-$\mathrm{CH_2C}H_3$), 1.28 (t, J = 7.1 Hz, 3 H, $\mathrm{OCH_2C}H_3$), 1.79 (s, 3 H, 3-$\mathrm{C}H_3$), 1.90 (s, 3 H, =$\mathrm{CC}H_3$), 1.85-1.93 (m, 1 H), 2.20-2.30 (m, 1 H) (2-$\mathrm{C}H_2\mathrm{CH_3}$), 4.21 (q, J = 7.1 Hz, 2 H, $\mathrm{OC}H_2\mathrm{CH_3}$), 4.68 (d, J = 11.9 Hz, 1 H), 4.74 (d, J = 11.9 Hz, 1 H) (=$\mathrm{C}H_2$), 4.95 (s, 1 H), 5.02 (s, 1 H) (4-$\mathrm{OC}H_2$). ^{13}C NMR (100 MHz, $\mathrm{CDCl_3}$): δ 6.9, 9.3, 13.9, 19.3, 26.9, 62.3, 73.9, 86.8, 114.2, 138.3, 140.6, 157.9, 167.3, 168.3. HRMS (ESI): Calcd. for $\mathrm{C_{14}H_{20}O_5^+}$: 268.1311. Found: 268.1310.

4-(Benzyloxy)-2-butyl-5-oxo-3-propyl-2,5-dihydrofuran-2-carboxylic acid ethyl ester (14c). Yellow oil. IR ($\mathrm{CH_2Cl_2}$, $\mathrm{cm^{-1}}$): 1465, 1498, 1673, 1736, 1771, 3033. ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$): δ 0.80-0.90 (m, 6 H, 2 × $\mathrm{C}H_3$), 0.90-1.10 (m, 2 H, $\mathrm{C}H_2$), 1.15-1.30 (m, 5 H, $\mathrm{C}H_2$ & $\mathrm{C}H_3$), 1.35-1.45 (m, 2 H, $\mathrm{C}H_2$), 1.75-2.21 (m, 4 H, 2 × $\mathrm{C}H_2$), 4.14 (q, J = 7.0 Hz, 2 H, $\mathrm{OC}H_2\mathrm{CH_3}$), 5.27 (d, J = 11.9 Hz, 1 H), 5.36 (d, J = 11.9 Hz, 1 H) (4-$\mathrm{OC}H_2$), 7.25-7.40 (m, 5 H, $\mathrm{C_6}H_5$). ^{13}C NMR (100 MHz, $\mathrm{CDCl_3}$): δ 13.9, 14.0, 14.2, 20.3, 22.5, 24.6, 26.6, 33.3, 62.3, 72.1, 86.5, 128.5, 128.8, 136.4, 140.8, 143.9, 167.8, 168.6. HRMS (ESI): Calcd. for $C_{21}H_{28}O_5^+$: 360.1937. Found: 360.1934.

4-(Allyloxy)-2-butyl-5-oxo-3-propyl-2,5-dihydrofuran-2-carboxylic acid ethyl ester (14d). Yellow oil. IR (CH_2Cl_2, cm^{-1}): 1465, 1673, 1736, 1774, 3085. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, J = 7.3 Hz, 3 H, CH_3), 0.95 (t, J = 7.8 Hz , 3 H, CH_3), 1.25 (t, J = 7.1 Hz , 3 H, OCH_2CH_3), 1.32-1.40 (m, 4 H, 2 × CH_2), 1.50-1.60 (m, 2 H, CH_2), 1.80-1.90 (m, 1 H), 2.15-2.27 (m, 2 H), 2.28-2.40 (m, 1 H) (2 × CH_2), 4.19 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.75-4.85 (m, 2 H, 4-OCH_2), 5.25 (d, J = 11.9 Hz, 1 H), 5.36 (d, J = 20.5 Hz, 1 H) (=CH_2), 5.90-6.02 (m, 1 H, =CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 14.0, 14.2, 20.4, 22.5, 24.9, 26.6, 33.5, 62.3, 70.9, 86.4, 118.9, 133.1, 141.0, 142.8, 167.6, 168.6. HRMS (ESI): Calcd. for $C_{17}H_{26}O_5^+$: 310.1780. Found: 310.1776.

4-(Benzyloxy)-3-(2-ethoxy-2-oxoethyl)-2-(3-ethoxy-3-oxopropyl)-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (14e). Yellow oil. IR (CH_2Cl_2, cm^{-1}): 1681, 1736, 1778, 3020. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15-1.33 (m, 9 H, 3 × CH_3), 2.12-2.25 (m, 3 H), 2.45-2.55 (m, 1 H) (2 × CH_2), 3.19 (d, J = 17.0 Hz, 1 H), 3.30 (d, J = 17.0 Hz, 1 H) (CH_2), 4.05-4.25 (m, 6 H, 3 × OCH_2), 5.34 (d, J = 11.9 Hz, 1 H), 5.41 (d, J = 11.9 Hz, 1 H) (4-OCH_2), 7.28-7.45 (m, 5 H, C_6H_5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 14.1, 14.2, 27.8, 29.2, 29.8, 60.8, 61.6, 62.8, 72.4, 85.1, 128.4, 128.6, 128.7, 133.8, 136.0, 143.1, 166.2, 167.5, 168.0, 172.0. HRMS (ESI): Calcd. for $C_{23}H_{28}O_9^+$: 448.1733. Found: 448.1696.

4-(Allyloxy)-3-(2-methoxy-2-oxoethyl)-2-(3-methoxy-3-oxopropyl)-5-oxo-2,5-dihydrofuran-2-carboxylic acid methyl ester (14f). Yellow oil. IR (CH_2Cl_2, cm^{-1}): 1680, 1739, 1778, 3002. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20-2.59 (m, 4 H, 2 × CH_2), 3.31 (d, J = 16.5 Hz, 1 H), 3.48 (d, J = 16.5 Hz, 1 H) (3-CH_2), 3.67 (s, 3 H), 3.70 (s, 3 H), 3.76 (s, 3 H) (3 × OCH_3), 4.80-4.95 (m, 2 H, 4-OCH_2), 5.28 (d, J = 10.1 Hz, 1 H), 5.37 (d, J = 17.4Hz, 1 H) (=CH_2), 5.85-6.00 (m, 1 H, =CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.7, 29.2, 29.5, 52.0, 52.5, 53.4, 71.2, 84.9, 119.3, 132.4, 132.6, 143.1, 165.9, 168.0, 168.6, 172.5. HRMS (ESI): Calcd. for $C_{16}H_{20}O_9^+$: 356.1107. Found: 356.1090.

4-Butoxy-2-butyl-5-oxo-3-propyl-2,5-dihydrofuran-2-carboxylic acid ethyl ester (14g). Yellow oil. IR (CH_2Cl_2, cm^{-1}): 1672, 1737, 1774. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85-0.98 (m, 9 H, 3 × CH_3), 1.20-1.38 (m, 7 H, 2 × CH_2 & CH_3), 1.40-1.48 (m, 2 H, CH_2), 1.50-1.60 (m, 2 H, CH_2), 1.60-1.75 (m, 2 H, CH_2), 1.80-1.90 (m, 1 H), 2.15-2.26 (m, 2 H), 2.28-2.35 (m, 1 H) (2 × CH_2), 4.20 (q, J = 7.2 Hz, 2 H), 4.28 (t, J = 6.9 Hz, 2 H) (2 × OCH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 13.9, 14.0, 14.3, 18.9, 20.5, 22.5, 24.9, 26.6, 32.0, 33.6, 62.3, 70.5, 86.4, 141.6, 141.8, 167.7, 168.7. HRMS (ESI): Calcd. for $C_{18}H_{30}O_5^+$: 326.2093. Found: 326.2098.

2-Ethyl-3-methyl-5-oxo-4-(tosyloxy)-2,5-dihydrofuran-2-carboxylic acid ethyl ester (14h). Yellow oil. IR (CH_2Cl_2, cm^{-1}): 1459, 1493, 1597, 1686, 1743, 1793, 3057. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 7.3 Hz, 3 H, 2-CH_2CH_3), 1.29 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 2.05 (s, 3 H, 3-CH_3), 1.96-2.04 (m, 1 H), 2.25-2.34 (m, 1 H) (2-CH_2CH_3), 2.46 (s, 3 H, ArCH_3), 4.26 (q, J = 6.9 Hz, 2 H), 7.37 (d, J = 8.2 Hz, 2 H), 7.87 (d, J = 8.2 Hz, 2 H) (C_6H_4). ^{13}C NMR (100 MHz,

$CDCl_3$): δ 6.8, 10.7, 14.1, 21.9, 27.0, 62.9, 87.6, 128.7, 130.1, 132.2, 134.3, 146.4, 152.1, 165.0, 167.1. HRMS (ESI): Calcd. for $C_{17}H_{20}O_7S^+$: 368.0930. Found: 368.0901.

2-Butyl-5-oxo-3-propyl-4-(tosyloxy)-2,5-dihydrofuran-2-carboxylic acid ethyl ester (14i). Yellow oil. IR (CH_2Cl_2, cm^{-1}): 1383, 1466, 1597, 1674, 1743, 1791. ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, J = 6.9 Hz, 3 H, CH_3), 0.97 (t, J = 6.9 Hz, 3 H, CH_3), 1.20-1.42 (m, 7 H, 2 × CH_2 & OCH_2CH_3), 1.55-1.70 (m, 2 H, CH_2), 1.91-1.99 (m, 1 H), 2.20-2.55 (m, 3 H) (2 × CH_2), 2.47 (s, 3 H, $ArCH_3$), 4.24 (q, J = 6.9 Hz, 2 H, OCH_2CH_3), 7.38 (d, J = 7.8 Hz, 2 H), 7.91 (d, J = 7.8 Hz, 2 H) (C_6H_4). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 14.0, 14.1, 19.8, 21.8, 22.5, 24.7, 27.4, 33.2, 62.9, 87.3, 128.7, 129.9, 132.6, 134.6, 146.3, 155.3, 165.3, 167.4. HRMS (ESI): Calcd. for $C_{21}H_{28}O_7S^+$: 424.1556. Found: 424.1562.

Bis(5-butyl-5-(ethoxycarbonyl)-2-oxo-4-propyl-2,5-dihydrofuran-3-yl) phthalate (15). Yellow oil. IR (CH_2Cl_2, cm^{-1}): 1466, 1597, 1689, 1741, 1790, 3371. ^1H NMR (400 MHz, $CDCl_3$): δ 0.85-1.00 (m, 12 H, 4 × CH_3), 1.25-1.45 (m, 14 H, 2 × OCH_2CH_3 & 4 × CH_2), 1.50-1.62 (m, 4 H), 1.90-2.03 (m, 2 H), 2.25-2.39 (m, 4 H), 2.40-2.50 (m, 2 H) (6 × CH_2), 4.26 (q, J = 7.1 Hz, 4 H, 2 × OCH_2CH_3), 7.73 (dd, J = 5.4, 3.2 Hz, 2 H), 8.01 (dd, J = 5.5, 3.3 Hz, 2 H) (C_6H_4). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 14.1, 14.2, 20.5, 22.3, 25.4, 27.4, 33.9, 62.4, 87.6, 130.2, 130.3, 132.6, 135.4, 152.0, 163.2, 165.8, 168.8. HRMS (ESI): Calcd. for $C_{36}H_{46}O_{12}^+$: 670.2989. Found: 670.2981.

General experimental procedure for preparation of 3-OH unprotected isotetronic acids (12)

2-Oxocarboxylic ester **1** (20.0 mmol), CH_2Cl_2 (50 mL) were added to an oven dried Schlenk flask and then DBU (0.30 g, 2.0 mmol) and triethylamine (0.86 g, 8.5 mmol) in CH_2Cl_2 (20 mL) were added dropwise to the flask. After the reaction mixture was stirred at room temperature for 0.5 h, a solution of trimethylsilyl chloride (1.13 g, 10.5 mmol) in CH_2Cl_2 (20 mL) was added dropwise to the reaction. The mixture was stirred further at room temperature overnight, washed sequentially with a saturated ammonium chloride and saturated sodium chloride solution (50 mL), separated and dried over Na_2SO_4. The organic phase was concentrated under high vacuum. The residue was subjected to flash chromatography (silica gel, eluting with petroleum ether/ ethyl acetate) to afford the analytically pure isotetronic acid derivatives **12** (Table 3).

4-Hydroxy-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (12a). Yellow oil. IR (CH_2Cl_2, cm^{-1}): 1658, 1740, 1782, 3109, 3317. ^1H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.65 (s, 3 H, 2-CH_3), 4.14 (q, J = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 6.19 (s, 1 H, 3-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.9, 62.6, 83.2, 119.4, 143.0, 169.0, 169.3. HRMS (ESI): Calcd. for $C_8H_{10}O_5^+$: 186.0528. Found: 186.0521.

2-Methyl-4,5-dioxo-tetrahydrofuran-2-carboxylic acid ethyl ester (12a'). ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ 1.29 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.86 (s, 3 H, 2-CH_3), 2.76 (d, J = 19.7 Hz, 1 H), 3.18 (d, J = 19.7 Hz, 1 H) (3-CH_2), 4.25 (q, J = 7.1 Hz, 2 H, $CO_2CH_2CH_3$).

2-Ethyl-4-hydroxy-3-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (12b). Yellow oil. IR (CH_2Cl_2, cm^{-1}): 1739, 1778, 3355. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 7.1 Hz, 3 H, 2-CH_2CH_3), 1.29 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.75-1.95 (m, 4 H), 2.15-2.30 (m, 1

H) (2-CH_2CH$_3$ & 3-CH_3), 4.23 (q, J = 7.3 Hz, 2 H, CO$_2$CH_2CH$_3$), 6.04 (br s, 1 H, 4-OH). ^{13}C NMR (100 MHz, CDCl$_3$): δ 7.0, 8.9, 14.1, 27.1, 62.4, 88.0, 130.1, 138.6, 168.4, 169.7. HRMS (ESI): Calcd. for $C_{10}H_{14}O_5^+$: 214.0841. Found: 214.0828.

2-Butyl-4-hydroxy-5-oxo-3-propyl-2,5-dihydrofuran-2-carboxylic acid ethyl ester (12c). Yellow oil. IR (CH$_2$Cl$_2$, cm^{-1}): 1736, 1754, 3342. ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.82 (t, J = 6.9 Hz, 3 H, CH_3), 0.88 (t, J = 6.8 Hz, 3 H, CH_3), 1.05-1.30 (m, 7 H, 2 × CH_2 & OCH$_2$CH_3), 1.45-1.61 (m, 2 H), 1.70-1.82 (m, 1 H), 2.10-2.30 (m, 3 H) (3 × CH_2), 4.13 (q, J = 7.1 Hz, 2 H, OCH_2CH$_3$), 7.10 (br s, 1 H, OH). ^{13}C NMR (100 MHz, CDCl$_3$): δ 13.8, 14.0, 14.2, 19.9, 22.5, 24.9, 26.5, 33.6, 62.4, 87.8, 133.8, 138.8, 168.6, 170.2. HRMS (ESI): Calcd. for $C_{14}H_{22}O_5^+$: 270.1467. Found: 270.1457.

3-(2-Ethoxy-2-oxoethyl)-2-(3-ethoxy-3-oxopropyl)-4-hydroxy-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (12d). Yellow oil. IR (CH$_2$Cl$_2$, cm^{-1}): 1736, 1783, 3319. ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.05-1.30 (m, 9 H, 3 × OCH$_2$CH_3), 2.10-2.35 (m, 3 H), 2.40-2.50 (m, 1 H) (2 × CH_2), 3.34 (d, J = 18.8 Hz, 1 H), 3.42 (d, J = 18.8 Hz, 1 H) (CH_2), 3.95-4.20 (m, 6 H, 3 × OCH_2CH$_3$). ^{13}C NMR (100 MHz, CDCl$_3$): δ 14.0, 14.0, 14.1, 27.9, 29.2, 30.4, 61.0, 62.3, 62.9, 85.2, 121.9, 141.4, 167.5, 167.9, 170.7, 172.4. HRMS (ESI): Calcd. for $C_{16}H_{22}O_9^+$: 358.1264. Found: 358.1269.

General procedure for the cross aldol-lactonization-alkylation reaction

2-Oxocarboxylic ester **1** (10.0 mmol), (5-bromo-2-methoxy-phenyl)-oxo-acetic acid ethyl ester **16** (2.85 g, 10.0 mmol), CH$_2$Cl$_2$ (50 mL) were added to an oven dried Schlenk flask and then DBU (0.30 g, 2.0 mmol) and triethylamine (0.86 g, 8.5 mmol) in CH$_2$Cl$_2$ (20 mL) were added dropwise to the flask. After the mixture was stirred at room temperature for 0.5 h, an electrophile **4** or **8** or **13** (10.5 mmol) in CH$_2$Cl$_2$ (20 mL) was added dropwise to the reaction. The mixture was stirred further at room temperature overnight. The resulted orange solution was washed sequentially with a saturated ammonium chloride and saturated sodium chloride solution (50 mL), separated and dried over Na$_2$SO$_4$. The organic phase was concentrated under high vacuum. The residue was subjected to flash chromatography (silica gel, eluting with petroleum ether/ ethyl acetate) to afford the analytically pure isotetronic acid derivatives **5** or **14** and **17** (Table 5).

4-(Allyloxy)-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (5m). Yellow oil. IR (CH$_2$Cl$_2$, cm^{-1}): 1654, 1742, 1786, 3103. ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.28 (t, J = 7.1 Hz, 3 H, CO$_2$CH$_2$CH_3), 1.71 (s, 3 H, 2-CH_3), 4.22 (q, J = 7.1 Hz, 2 H, CO$_2$CH_2CH$_3$), 4.48 (d, J = 6.0 Hz, 2 H, 4-OCH_2), 5.34 (d, J = 10.5 Hz, 1 H), 5.41 (d, J = 17.3 Hz, 1 H) (=CH_2), 5.93-6.03 (m, 1 H, =CH), 6.10 (s, 1 H, 3-H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 14.0, 23.1, 62.4, 72.0, 82.4, 117.6, 119.4, 130.9, 146.0, 166.3, 168.9. HRMS (ESI): Calcd. For $C_{11}H_{14}O_5^+$: 226.0841. Found: 226.0834.

4-(Allyloxy)-2-(5-bromo-2-methoxyphenyl)-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (17a). Yellow oil. IR (CH$_2$Cl$_2$, cm^{-1}): 1487, 1595, 1655, 1747, 1789, 3104. ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.24 (t, J = 7.1 Hz, 3 H, CO$_2$CH$_2$CH_3), 3.83 (s, 3 H, OCH_3), 4.23 (q, J = 6.9 Hz, 2 H, CO$_2$CH_2CH$_3$), 4.50-4.60 (m, 2 H, 4-OCH_2), 5.37 (d, J = 11.9 Hz, 1 H), 5.45 (d, J = 17.0 Hz, 1 H) (=C*H*$_2$), 5.95-6.05 (m, 1 H, =C*H*), 6.43 (s, 1 H, 3-H), 6.82 (d, *J* = 8.2 Hz, 1 H), 7.44-7.52 (m, 2 H) (C$_6$*H*$_3$). ^{13}C NMR (100 MHz, CDCl$_3$): δ 14.1, 56.1, 62.7, 72.2, 83.6, 113.1, 113.2, 116.2, 119.7, 127.3, 129.5, 131.0, 133.5, 146.1, 156.0, 166.2, 167.8. HRMS (ESI): Calcd. for $C_{17}H_{17}BrO_6^+$: 396.0209. Found: 396.0188.

4-(Benzyloxy)-2-(5-bromo-2-methoxyphenyl)-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (17b). Yellow oil. IR (CH$_2$Cl$_2$, cm^{-1}): 1487, 1594, 1654, 1747, 1787, 3105. ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.20 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H*$_3$), 3.79 (s, 3 H, OC*H*$_3$), 4.18 (q, *J* = 7.1 Hz, 2 H, CO$_2$C*H*$_2$CH$_3$), 5.02 (d, *J* = 11.9 Hz, 1 H), 5.12 (d, *J* = 11.9 Hz, 1 H) (4-OC*H*$_2$), 6.38 (s, 1 H, 3-H), 6.78 (d, *J* = 8.7 Hz, 1 H), 7.21 (d, *J* = 2.3 Hz, 1 H), 7.35-7.43 (m, 6 H) (Ar-*H*). ^{13}C NMR (100 MHz, CDCl$_3$): δ 14.1, 56.1, 62.7, 73.3, 83.5, 113.1, 116.6, 127.3, 127.9, 128.9, 129.0, 129.7, 133.6, 134.3, 146.3, 156.1, 166.1, 167.9. HRMS (ESI): Calcd. for $C_{21}H_{19}BrO_6^+$: 446.0365. Found: 446.0369.

4-Benzyloxy-2-(5-bromo-2-methoxyphenyl)-3-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (17c). Yellow oil. IR (CH$_2$Cl$_2$, cm^{-1}): 1486, 1593, 1677, 1737, 1774, 3102. ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.20 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H*$_3$), 1.82 (s, 3 H, 3-C*H*$_3$), 3.77 (s, 3 H, OC*H*$_3$), 4.20 (q, *J* = 7.1 Hz, 2 H, CO$_2$C*H*$_2$CH$_3$), 5.30 (d, *J* = 11.9 Hz, 1 H), 5.39 (d, *J* = 11.9 Hz, 1 H) (4-OC*H*$_2$), 6.76-6.83 (m, 2 H), 7.30-7.42 (m, 5 H), 7.43 (dd, *J* = 8.7, 2.3 Hz, 1 H) (Ar-*H*). ^{13}C NMR (100 MHz, CDCl$_3$): δ 10.8, 14.2, 56.1, 62.5, 72.6, 85.2, 113.1, 113.5, 126.3, 128.8, 128.9, 130.8, 136.0, 139.8, 141.9, 156.7, 166.9, 167.4. HRMS (ESI): Calcd. for $C_{22}H_{21}BrO_6^+$: 460.0522. Found: 460.0538.

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