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Grob-type fragmentation of 5-oxabicyclo[2.1.1]hexane system: a strategy for synthesis of annulated and 2,2,5-trisubstituted tetrahydrofurans

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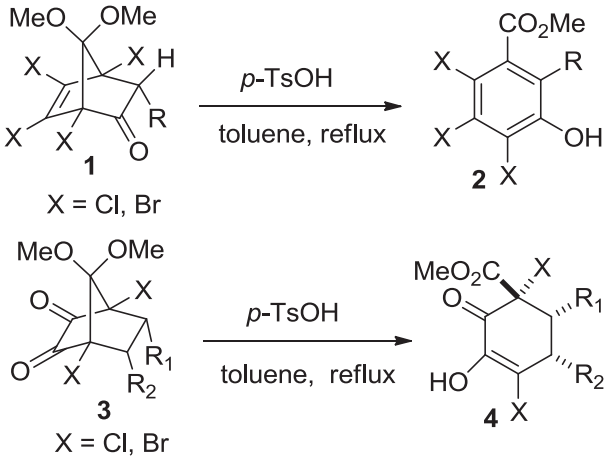
ABSTRACT

Acid mediated, efficient Grob-type fragmentation reaction facilitated by vicinal ketal and ester moieties in variety of 5-oxabicyclo[2.1.1]hexanes leading to the corresponding annulated and 2,2,5-trisubstituted tetrahydrofurans is reported. Among the Brønsted and Lewis acids tested, $BF_3{\cdot}OEt_2$ appears to give the best results, furnishing near quantitative yield (>99%) of tetrahydrofuran tricarboxylate derivatives under mild reaction condition. In case of unsymmetrical monosubstituted 5-oxabicyclo[2.1.1]hexanes two regioisomeric products are obtained. A strategy to transform one of the ester groups of the title compounds to protected hydroxymethyl moiety was evolved, which allows access to differentially protected 2-hydroxymethyl THF derivatives upon fragmentation. Employing $TiCl_4$/*R* or *S*-BINOL as chiral Lewis acid, an enantioselective fragmentation (up to 66% ee) was described for the *meso* bis-furan derivative.

1. Introduction

Grob fragmentations are heterolytic sigma bond cleavage reactions involving a five-atom system. These fragmentation reactions have been widely explored since their study was started 60 years ago.[1] The selectivity and high efficiency makes them more attractive to synthetic chemists. This reaction was extensively utilized to construct variety of organic frameworks,[2a,b] and served as the key step in numerous multistep syntheses of complex natural products.[2c,d] Among these heterolytic fragmentations, base or nucleophile induced fragmentations in molecules containing groups derived from 1,3-diol,[2e,f] β-hydroxy ketone[2g] are most common. Although Barluenga et al.[3a] and others[3b,c,4] reported, Lewis acid-mediated or catalyzed Grob fragmentation reactions are not much known in the literature due to their lack of selectivity in polyfunctional molecules. However, the routine Grob fragmentations culminate with the formation of carbon–carbon multiple bonds and such examples are abound.[1] Recently, Charette and Lemonnier reported a Tf_2O-mediated Grob-fragmentation of azabicyclo[2.2.2]octane leading to substituted piperidines via a reactive dihydropyridinium intermediate.[5]

Our previous works on acid-mediated Grob fragmentation–aromatization reactions of 1,4,5,6-tetrahalo-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-one (R=alkyl or aryl) **1** to obtain trihalo phenols **2** is represented in Scheme 1.[6a] In continuation of this work we also reported recently, Grob-fragmentation of symmetrically and asymmetrically substituted 1,4-dihalo-7,7-dimethoxybicyclo[2.2.1]heptane-2,3-diones **3** (R^1, R^2=H, alkyl, aryl or ring substituents etc.) to form six membered α-keto enol **4**.[6a] A variety of trihalo phenol derivatives and substituted aromatic



Scheme 1. Our previous work on acid-mediated Grob-fragmentation.

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compounds were efficiently synthesized by successful utilization of fragmentation protocol. In addition to this, our group has recently reported the utility of afore-mentioned reaction (**1** to **2**) for the synthesis of marine originated brominated alkaloids.[6b]

Development of new stereoselective strategy for synthesis of heterocyclic molecules having many stereocenters is one of the challenging, as well as attractive area of research. Among these, 2,2,5-trisubstituted tetrahydrofurans,[7a,b] hexahydroisobenzofurans (2-oxabicyclo[4.3.0]nonane),[7c,d] 2,5-di- and 2,2,5-trisubstituted 3,4-dihydroxy-tetrahydrofurans[7e–g] having importance, because of their presence as structural motifs in various biologically active natural products. This saturated heterocycles could be routinely made from cyclization of unsaturated[8a–e] or epoxy alcohols.[8f,g] Plumet et al.[9a] reported ring-opening cross-metathesis of 2-substituted 7-oxabicyclo[2.2.1]-5-heptenes leading to 2,3,5-trisubstituted tetrahydrofurans. Recently, Martin and Benjamin reported similar strategy leading to 2,2,5-tri and 2,2,5,5-tetrasubstituted tetrahydrofurans starting from [4+2] cycloaddition of substituted furan with chiral vinyl sulphoxide.[9b] However, these methods are not elaborated to 3,4-substituted or annulated tetrahydrofurans because of less or moderate diastereoselectivity in cycloaddition step.[9c] In this paper we describes the new stereoselective route to access highly substituted tetrahydrofurans from oxa-bridged compounds, which are readily and easily preparable from commercial reagents via diastereoselective Diels–Alder reaction. Some naturally occurring annulated and 2,2,5-trisubstituted tetrahydrofurans are shown in Fig. 1.[10]

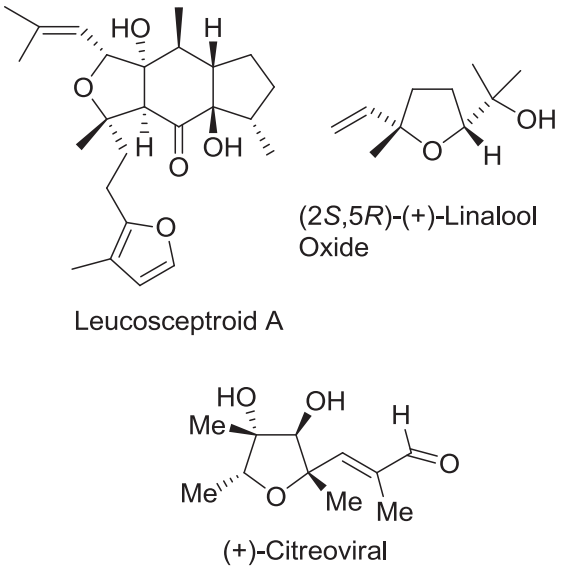
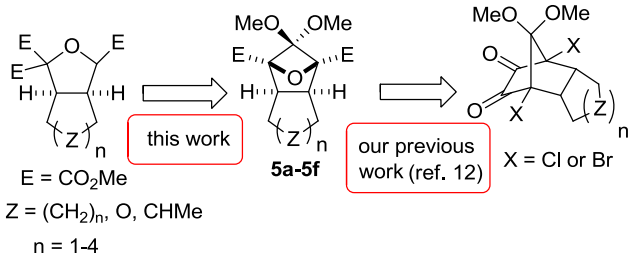


Fig. 1. Some naturally occurring annulated and 2,2,5-trisubstituted tetrahydrofurans.

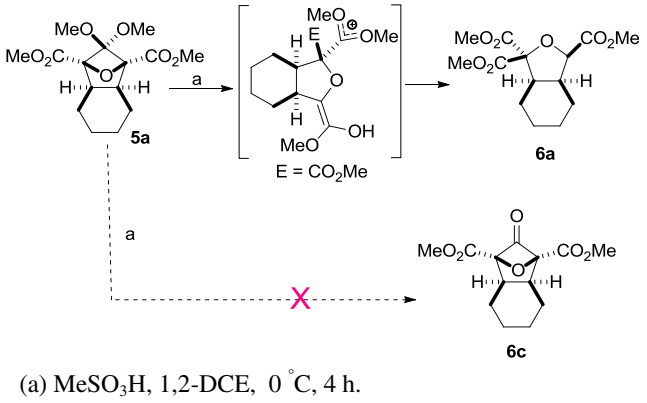
In continuation of our journey on exploring the chemistry of norbornyl α-diketones[11a] for the synthesis of various organic templates[11b–d] and natural products,[11e,f] we previously reported synthesis of novel constrained oxa-bridged molecules, such as **5**.[12] Herein, we wish to report an efficient Lewis acid-mediated Grob-type fragmentation reaction involving ester as a nucleofuge group and dimethoxy as an electrofuge group of constrained oxa-bridged molecules to access annulated and 2,2,5-trisubstituted tetrahydrofuran building blocks. The oxa-bridged bicyclo[2.1.1]hexane systems with a variety of substituents could be obtained expeditiously as shown in Scheme 2.



Scheme 2. Our stereoselective two step strategy for the synthesis of highly substituted tetrahydrofurans from norbornyl α-diketones.

2. Result and discussion

During our study on oxa-bridged compounds,[13] we subjected compound **5a** for deprotection of ketal with $MeSO_3H$ (2.5 equiv). Instead of expected ketone **6c** we found the fragmented bicyclic tetrahydrofuran tricarboxylate **6a**, *albeit*, in low (38%) yield. This observation prompted us to study and explore the fragmentation reaction due to potentially wide synthetic applications of the substituted tetrahydrofuran building blocks thus formed (Scheme 3).

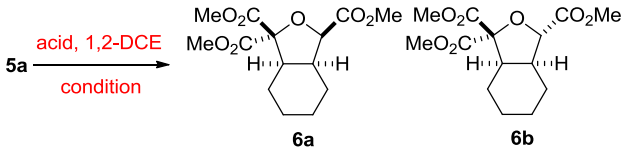


Scheme 3. Initial observation of Grob-type fragmentation reaction.

We have chosen the compound **5a** as a reference starting material for the optimization purpose and treated it with various Brønsted and Lewis acids, the obtained results are summarized in Table 1. Due to our interest in PTSA-mediated Grob fragmentation reactions,[6a] we first carried out fragmentation of **5a** with PTSA in refluxing toluene. Under these conditions, the fragmented products **6a**,**b** were obtained in 83% yield and the two isomers were found to be in 71:29 ratio, respectively. When $MeSO_3H$ (4 equiv) and TFA (6 equiv) were used, complete conversion of starting material was not observed (Table 1, entries 2 and 3). Next, we turned our attention to see the efficiency of fragmentation reaction with Lewis acids. Compound **5a** was treated with $BF_3{\cdot}OEt_2$, $TiCl_4$, $In(OTf)_3$, and $Cu(OTf)_2$ and the results are shown in Table 1 (entries 4–10). Among the Lewis acids tested, $BF_3{\cdot}OEt_2$ appeared to be good in terms of yield while $TiCl_4$ with regard to selectivity.

This straightforward route to access substituted bicyclic tetrahydrofurans via an interesting Grob-type fragmentation reaction inspired us to elaborate the fragmentation protocol for various oxa-bridged derivatives. The result of $BF_3{\cdot}OEt_2$-mediated Grob-type fragmentation reactions for various symmetric tricyclic oxa-bridged compounds is depicted in Table 2. The annulated and 2,2,5-tricarboxylate tetrahydrofurans **6a**,**b** to **11a**,**b** were obtained nearly quantitative yield (>99%) through Grob-type fragmentation

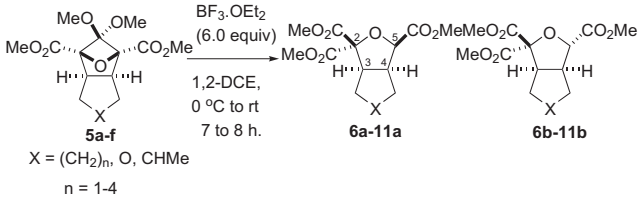
Table 1
Screening of Grob-type fragmentation reaction of compound **5a** with Brønsted and Lewis acids



Entry	Acid (equiv)	Reaction condition	Time (h)	Yield (%)[a] (**6a**/**6b**)[b]
1[c]	*p*-TsOH (2)	Reflux	3	83 (71:29)
2[d]	$MeSO_3H$ (4)	0–5 °C	4	82 (85:15)
3[d]	TFA (6)	Reflux	8	47 (83:17)
4[d]	$BF_3{\cdot}OEt_2$ (4)	0 °C to rt	8	94 (77:23)
5	$BF_3{\cdot}OEt_2$ (6)	0 °C to rt	8	>99 (75:25)
6[d,e]	$TiCl_4$ (1.3)	0 °C	3	92 (94:06)
7[d,e]	$TiCl_4$ (1.4)	0 °C	3	94 (94:06)
8[d]	$In(OTf)_3$ (1.5)	rt	8	94 (67:33)
9	$In(OTf)_3$ (2)	rt	6	97 (71:29)
10	$Cu(OTf)_2$ (1.5)	70 °C	2	92 (74:26)

[a] Isolated yields.
[b] The ratios of epimers (**6a** and **6b**) were determined by ^1H NMR analysis of the crude reaction mixtures.
[c] Dry toluene is used as a solvent.
[d] Complete consumption of starting material was not observed and the amount of minor isomers were determined from ^1H NMR.
[e] Freshly prepared 0.05 M solution of $TiCl_4$ in 1,2-DCE was used for fragmentation.

Table 2
$BF_3{\cdot}OEt_2$-mediated fragmentation of various tricyclic oxa-bridged compounds

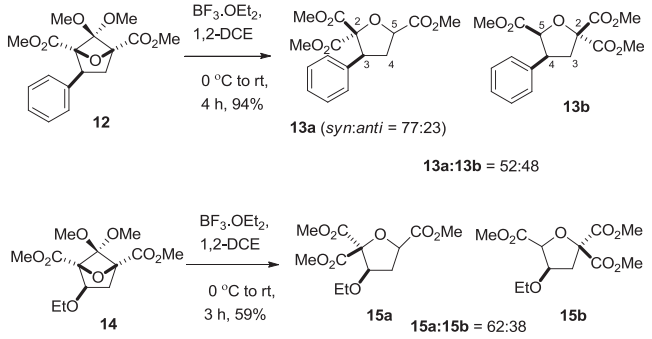


Entry[a]	Substrate [**5a**–**f**]	Products	Yield[b] (%)	**6a**–**11a**/**6b**–**11b** [ratio of epimers][c]
1	**5a**, X=–$(CH_2)_2$–	**6a**,**b**	>99	75:25
2	**5b**, X=–(CH_2)–	**7a**,**b**	>99	95:05
3	**5c**, X=–$(CH_2)_3$–	**8a**,**b**	>99	88:12
4	**5d**, X=–$(CH_2)_4$–	**9a**,**b**	>99	84:16
5	**5e**, X=–O–	**10a**,**b**	>99	86:14
6	**5f**, X=–CHMe–	**11a**,**b**	>99	84:16

[a] All fragmentation reactions (entries 1–6) were performed by treating oxa-bridged compounds [**5a**–**f**] with 6.0 equiv of $BF_3{\cdot}OEt_2$ at 0 °C to rt in dry 1,2-DCE solvent under argon atmosphere.
[b] Isolated yields.
[c] The ratios of epimers were determined by ^1H NMR of crude reaction mixture.

of the corresponding symmetric oxa-bridged derivatives **5a**–**f**. The ^1H and ^{13}C NMR spectra of the products (**6a**,**b** to **11a**,**b**), obtained simply after a short filtration through a SiO_2 column, showed that the samples are fairly clean and do not require extensive chromatographic purification. A detailed analysis of ^1H NMR of the bicyclic tetrahydrofurans (**6a**,**b**–**10a**,**b**), revealed shielding (0.03–0.27 ppm) of C5 proton of the minor isomer. This observation is consistent with the assigned structure wherein C5 proton is *syn* to C3 and C4 ring substituents. To rule out any ambiguity, NOE (for **6a** and **6b**, for details, see S56–S59 in Supplementary data) and single crystal X-ray analysis (for **6a**) experiments were carried out to confirm the relative stereochemistry of C5 proton. In addition to this, in case of compounds **11a**,**b**, contrary to other cases, C5 proton of the major isomer is observed at slightly high field (0.04 ppm), because due to presence of *cis* methyl substituent at annulated cyclopentane ring. Further evidence was obtained by NOE experiments for compound **11a** (see S59–S60 in Supplementary data), which clearly suggest *cis* relative stereochemistry of C4 and C5 protons as similar to previous cases (**6a**,**b**–**10a**,**b**).

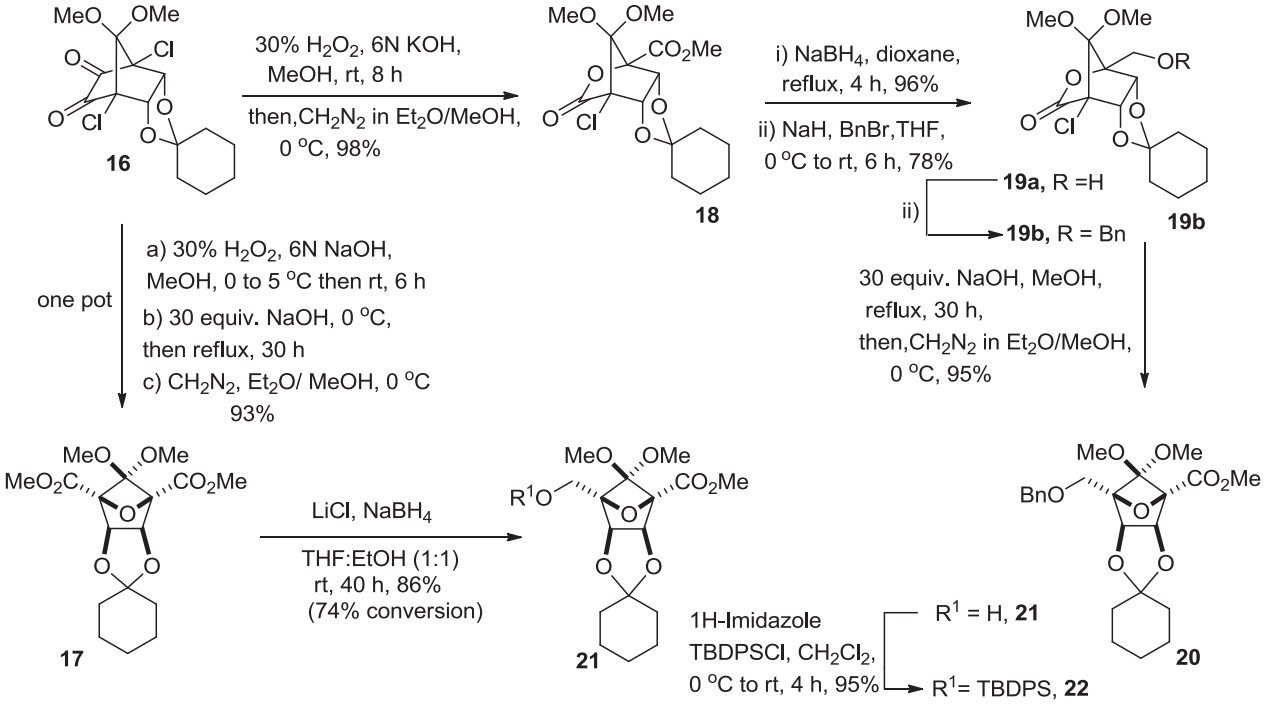
Due to the presence of two competing nucleofuge groups for fragmentation reaction, we were interested to investigate regioselectivity of this transformation. With this consideration, we extended the fragmentation protocol to monosubstituted oxa-bridged derivatives. $BF_3{\cdot}OEt_2$-mediated Grob-type fragmentation reaction of these compounds is depicted in Scheme 4. The ratios of regioisomers were determined by the integration of ^1H NMR for H-5 proton of the tetrahydrofurans (**13a**,**b** and **15a**,**b**). For the sensitive ethoxy substituted compound **14**, moderate yield of 59% was obtained. These experiments demonstrate that there is little or no regioselectivity in case of monosubstituted derivatives.



Scheme 4. $BF_3{\cdot}OEt_2$-mediated fragmentation of bicyclic monosubstituted oxa-bridged compounds.

The presence of highly substituted oxygenated tetrahydrofuran natural products,[7e,10d] and also to further demonstrate the practical utility of our methodology, we elaborated the fragmentation reaction to highly oxygenated 5-oxabicyclo[2.1.1]hexane systems **17**, **20**, and **22**. The details for the synthesis of compounds **17**, **20**, and **22** from symmetric norbornyl α-diketone **16** are depicted in Scheme 5. One pot transformation of α-diketone **16** to symmetric oxa-bridged compound **17** was accomplished by oxidative cleavage of α-diketone with alkaline 30% H_2O_2, followed by refluxing with 30 equiv of NaOH and esterification of resultant dicarboxylic acids with CH_2N_2 in Et_2O/MeOH at 0 °C afforded compound **17** in 93% yield. At this stage, we were interested to synthesize oxa-bridged monoester derivative of compound **17**, by focusing our attention to our previously reported synthesis of oxa-bridged compounds via bridge-head lactone in two step protocol. The synthesis involves conversion of α-diketone **16** to bridged-lactone **18** in 98% yield. The chemoselective reduction of bridge-head ester with $NaBH_4$ in dioxane at reflux condition afforded alcohol **19a** in 97% yield and subsequent protection of alcohol as benzyl ether gave **19b** in 78% yield. Then bridged-lactone **19b** was successfully converted into oxa-bridged monoester **20** by refluxing with 30 equiv of NaOH in MeOH, followed by CH_2N_2 treatment of resultant mono carboxylic acid in Et_2O/MeOH at 0 °C in 95% yield. The *meso* diester **17** was subjected to partial reduction[14] with $NaBH_4$ in THF/EtOH (1:1) using LiCl to afford a monoalcohol **21** in 86% yield. Subsequently, the resultant monoalcohol **21** was protected with TBDPS group with 95% yield gave oxa-bridged monoester derivative **22** in two steps from compound **17**.

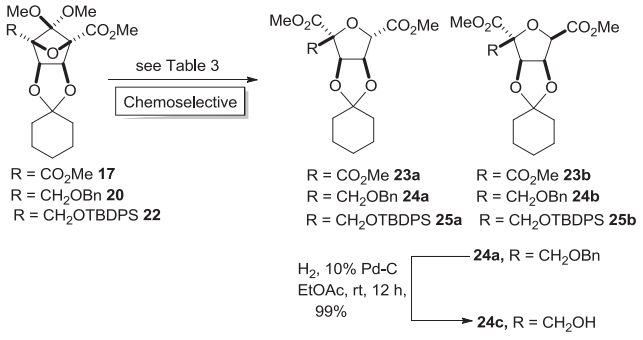
Having di and monoester derivatives (**17**, **20**, and **22**) of 5-oxabicyclo[2.1.1]hexane system in hand, we focused our attention to see the efficiency of these substrates to form tetrahydrofurans via fragmentation reaction. The presence of sensitive cyclohexylidene protection on constrained bicyclic core would be



Scheme 5. Synthesis of highly oxygenated 5-oxabicyclo[2.1.1]hexane systems **17**, **20**, and **22** from norbornyl α-diketone **16**.

additional factor of curiosity for these substrates selectively undergo fragmentation reaction. The details of fragmentations of compounds **17**, **20**, and **22** are summarized in Table 3. Treatment of compound **17** with 3.0 equiv of $BF_3{\cdot}OEt_2$ for 9 h forms tetrahydrofurans **23a**,**b** with 97% yield (ratio of epimers 88:12). On the other hand, $In(OTf)_3$ gave moderate yield for the fragmentation of compounds **17** and **20**, despite of products (epimers) selectivity in case of monoesters (compounds **20** and **22**). The chemoselectivity in the presence of an acid sensitive cyclohexylidene group is the consequence of non-nucleophilic reaction conditions and efficiency of the system to undergo fragmentation.

Table 3
Chemoselective Grob-type fragmentation of compounds **17**, **20**, and **22**



Lewis acid[a] (equiv)	Substrate	Condition	Time (h)	Yield %[b] (ratio of epimers)[c]
$BF_3{\cdot}OEt_2$ (3.0)	**17**	0 °C to rt	9	97 (**23a**/**23b**=88:12)
$BF_3{\cdot}OEt_2$ (3.0)	**20**	0 °C to rt	4	86 (**24a**/**24b**=57:43)
$In(OTf)_3$ (2.0)	**17**	rt	7	66 (**23a**/**23b**=82:18)
$In(OTf)_3$ (2.0)	**20**	rt	4	71 (**24a**/**24b**=55:45)
$BF_3{\cdot}OEt_2$ (3.0)	**22**	0 °C to rt	5	94 (**25a**/**25b**=46:54)
TMSOTf (3.0)	**17**	0 °C	2	72 (**23a**/**23b**=97:03)

[a] All the reactions were carried out in dry 1,2-DCE solvent under argon atmosphere.
[b] Isolated yields.
[c] The ratios of epimers were determined by analyzing ^1H NMR of the crude reaction mixture.

Debenzylation of compound **24a** with H_2, 10% Pd–C afford an alcohol **24c** in 99% yield. Access to **24c** having oxaquaternary stereocenter, which is attractive from the view point of being a potential precursor in natural product synthesis, could not have been possible via a direct chemoselective reduction of one of the three ester groups of **23**. When 3.0 equiv of TMSOTf was employed, compound **17** underwent chemoselective fragmentation to furnish two epimers **23a**,**b** (ratio 97:03) in 72% yield. The reaction was found to be relatively faster compared to $BF_3{\cdot}OEt_2$ and $In(OTf)_3$-mediated fragmentations.

Due to the reverse in R_f values of major isomer (**23a**) in comparison with major isomer (**6a**) in TLC we anticipated, the relative stereochemistry of C4 and C5 proton might be reverse in former case (**23a**). By keeping this in mind, single crystal X-ray analysis was carried out for the compound **23a**, the X-ray pictures of compounds **6a** and **23a** are shown in Fig. 2.[16] The structure shows that C4 and C5 protons having *trans* relationship in case of compound **23a**. The inversion of stereochemistry at C5 stereocenter for the compound **23a** might be due to overlaying chair conformation of cyclohexylidene protection on tetrahydrofuran ring affect the enolate intermediate to form 4,5-*trans* substituted tetrahydrofuran **23a** (major isomer).

We thought of exploring the possibility of enantioselective Grob-type fragmentation of symmetric oxa-bridged compounds by using cheap chiral auxiliaries (*R* or *S*-BINOL). Literature survey[15] reveals that, 1:1 of BINOL and Ti-Lewis acid have more acidity to bind with substrate. Our initial effort for enantioselective fragmentation of **5a** with $TiCl_4$/*R*-BINOL (1:1) resulted in 12.9% ee. Next, our attention was turned on tricyclic bis-furan substrate for the study of asymmetric Grob-type fragmentation reaction. The results of enantioselective fragmentation of *meso* substrate **5e** with $TiCl_4$/*R* or *S*-BINOL in various reaction conditions are depicted in Table 4. After treating the compound **5e** with in situ generated chiral Lewis acid, 3.0 equiv of $TiCl_4$ were generally used as a promoter for

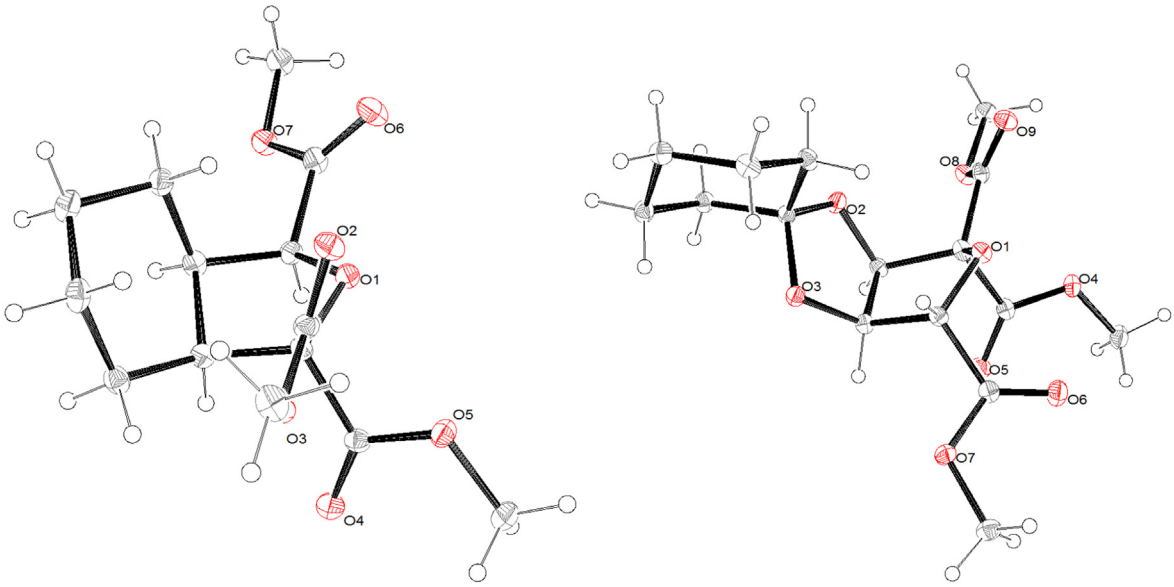
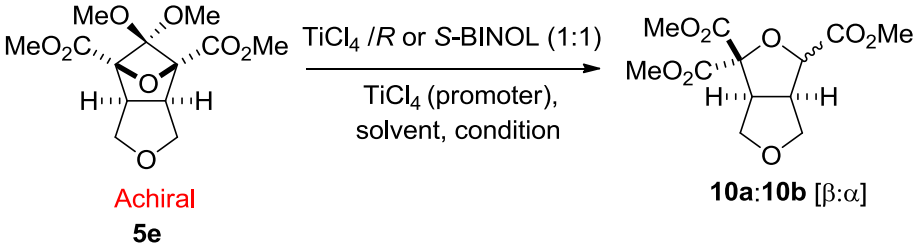


Fig. 2. X-ray crystal structures of compound **6a** and **23a** depicting *cis* relationship of C4–C5 protons in case of **6a** and *trans* relationship of C4–C5 protons in case of **23a**. Displacement ellipsoids are shown at the 30% probability level.

Table 4
Enantioselective Grob-type fragmentation reaction of bis-furan (**5e**) with $TiCl_4$/*R* or *S*-BINOL



Entry[a]	$TiCl_4$/ligand [ratios]	Condition	Time[b]	Promoter (equiv)	Time[c] (h)	Yield[d] (%)	**10a**/**10b**[e]	ee[f] for **10a**
1	$TiCl_4$/*R*-BINOL (1:1)	0 °C to rt	1 h	$TiCl_4$ (3.0)	2	97	87:13	20
2	$TiCl_4$/*R*-BINOL (1.5:1)	−5 °C	0.5 h	$TiCl_4$ (3.0)	3	96	88:12	37
3	$TiCl_4$/*R*-BINOL (1:1)	−5 °C	1 h	$TiCl_4$ (2.0)	2.5	95	90:10	45
4	$TiCl_4$/*R*-BINOL (1:1)	−5 °C	0.5 h	$TiCl_4$ (3.0)	2	97	90:10	55
5[g,h]	$TiCl_4$/*R*-BINOL (1:1)	−20 °C	0.5 h	$TiCl_4$ (3.0)	3	71	88:12	57
6[g,h,i]	$TiCl_4$/*R*-BINOL (1:1)	−20 °C	0.5 h	$TiCl_4$ (3.0)	2	67	89:11	66
7[j]	$TiCl_4$/*R*-BINOL (1:1)	−5 °C	15 min	$TiCl_4$ (3.0)	2	95	89:11	64
8	$TiCl_4$/*S*-BINOL (1:1)	0 °C	0.5 h	$TiCl_4$ (3.0)	2	97	88:12	34
9[g,h]	$TiCl_4$/*S*-BINOL (1:1)	−20 °C	0.5 h	$TiCl_4$ (3.0)	4	70	91:09	66

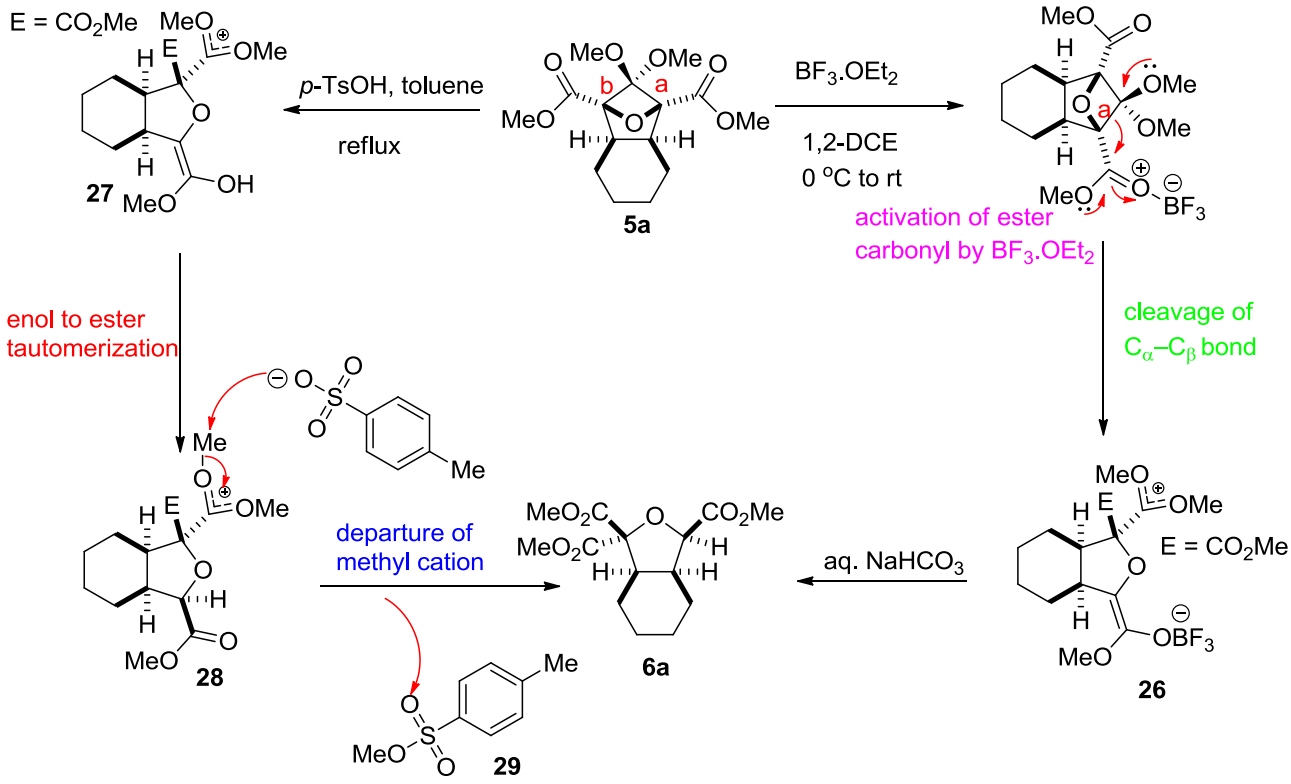
[a] Unless otherwise specified, all reactions were carried out using 2 equiv of freshly prepared 0.1 M $TiCl_4$ in dry 1,2-DCE and 2 equiv *R* or *S*-BINOL in 1,2-DCE solvent.
[b] Time of reaction carried with $TiCl_4$ and *R* or *S*-BINOL chiral Lewis acid.
[c] Time of reaction carried after addition of 3.0 equiv of $TiCl_4$ (promoter).
[d] Isolated yields.
[e] Ratios of **10a** and **10b** were determined from analysis of ^{1}H NMR of crude reaction mixtures.
[f] ee was determined by preparative HPLC equipped with JAIGEL-OA4100 column at detector wave length 230 nm.
[g] Yield was determined from ^{1}H NMR due to incomplete conversion of starting material.
[h] 0.1 M $TiCl_4$ in CH_2Cl_2 and CH_2Cl_2 used as a solvent.
[i] 3.0 equiv of 0.1 M $TiCl_4$ in CH_2Cl_2 and *R*-BINOL is used.
[j] 3.0 equiv of 0.1 M $TiCl_4$ in 1,2-DCE and *R*-BINOL is used.

fragmentation reaction. When compound **5e** was treated with 1:1 $TiCl_4$/*R* or *S*-BINOL as chiral Lewis acid at −20 °C in CH_2Cl_2 gave up to 66% ee. The reason for higher ee (up to 66% ee) in the case of compound **5e** compared to **5a** might be due to the presence of a hetero atom in the attached ring, which provides additional binding site for the chiral Lewis acid. Though moderate, but to the best of our knowledge this is the first enantioselective Grob-type fragmentation reaction reported so far and further exploration of this reaction is under way in our group.

A plausible mechanism is depicted in Scheme 6. The Grob-type fragmentation can take place by cleavage of either bond a or b of compound **5a**. The fragmentation reaction is initiated from activation of carbonyl functionality of ester (**5a**) by Lewis acid and rapture of C_α–C_β bond to generate ester enolate oxonium intermediate (**26**). In the case of *p*-TsOH, protonation of carbonyl of one of the ester groups followed by cleavage of C_α–C_β leads to enol **27**. Tautomerization of enol **27** to ester **28** and subsequent departure of methyl cation as 4-

methylbenzenesulfonate (**29**) gives tetrahydrofuran tricarboxylate **6a**. The byproduct 4-methylbenzenesulfonate (**29**), which supports the mechanistic proposal, was isolated and characterized.

carried to determine the relative stereochemistry of the THF compounds. The IR spectra were recorded as KBr pellets (solids) or as thin films (liquids). The mass spectrometry analysis was done ESI, EI or APCI mode. The CHN analysis was carried using CE-440



Scheme 6. Mechanism of $BF_3{\cdot}OEt_2$ and PTSA-mediated Grob-type fragmentation reaction of compound **5a**.

3. Conclusion

In conclusion, a straightforward stereoselective strategy for the synthesis of annulated and 2,2,5-trisubstituted tetrahydrofurans via an efficient Grob-type fragmentation of abundantly available 5-oxabicyclo[2.1.1]hexane derivatives is developed. A useful methodology for the conversion of one of the ester groups of the title compounds to protected hydroxymethyl moiety was evolved, which allows access to differently protected 2-hydroxymethyl THF derivatives. In case of bis-furan derivative, an enantioselectivity (upto 66% ee) during Grob-type fragmentation is observed using chiral auxiliaries (*R* or *S*-BINOL) by in situ generated chiral Lewis acid with $TiCl_4$.

4. Experimental section

4.1. General methods

^1H and proton decoupled ^{13}C NMR spectra were recorded in 400 and 100 MHz, respectively, unless at field strength of 500 (^1H NMR) and 125 MHz (^{13}C NMR). The samples for NMR were made by dissolving in $CDCl_3$ and TMS is used as an internal standard, the δ value for the peaks in ^1H NMR were reported in terms of parts per million with reference to TMS (0 ppm) peak and the coupling constants were reported in hertz. The multiplicity are reported as follows br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. The chemical shift in ^{13}C NMR is assigned by fixing middle peak of $CDCl_3$ at 77.00 ppm. The NOE experiments were Elemental Analyzer of Exeter analytical Inc (at IITK). Melting points are uncorrected. The crystal structures of compounds **6a** and **23a** were solved using SIR-92 and refined using SHELXL-97.[17]

4.2. General procedure 1 for $BF_3{\cdot}OEt_2$-mediated Grob-type fragmentation reaction of oxa-bridged compounds

To a stirred solution of oxa-bridged compounds (1 mmol) in dry 1,2-DCE (5 mL) was added $BF_3{\cdot}OEt_2$ (6.0 mmol) at 0 °C, then the reaction mixture was slowly brought to rt. After completion of reaction (monitored by TLC), the reaction mixture was quenched with aqueous saturated $NaHCO_3$ solution (3 mL) at 0 °C and 1,2-DCE was evaporated under reduced pressure. To the obtained residue was added H_2O (3 mL), aqueous part was extracted with EtOAc (3×20 mL), the combined organic layers were washed once with brine solution (6 mL), organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The silica gel column chromatography purification of the crude reaction mixture (EtOAc/Hexane solvent system as eluent) afforded the analytically pure tetrahydrofuran derivatives.

4.3. Experimental procedure for $TiCl_4$ promoted Grob-type fragmentation reaction of oxa-bridged compound 5a

To a solution of oxa-bridged compound **5a** (62 mg, 0.197 mmol) in dry 1,2-DCE (6 mL) was added drop wise freshly prepared 0.05 M $TiCl_4$ (5.52 mL, 0.276 mmol, 1.4 equiv) in 1,2-DCE at 0 °C. After 3 h, the reaction mixture was quenched by addition of H_2O (2 mL) and

then 1,2-DCE was evaporated on rotary evaporator, the aqueous part was extracted with EtOAc (2×20 mL), the combined organic layers were washed once with brine solution (6 mL), then organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Then the residue was purified by silica gel column chromatography (20–30% EtOAc in Hexane eluent, v/v) afforded **6a**,**b**, yield 94%, ratio of epimers 94:06.

4.4. Experimental procedure for enantioselective Grob-type fragmentation of compound 5e with $TiCl_4$/*R*-BINOL

To a stirred solution of 0.1 M $TiCl_4$ (1.72 mL, 32.6 mg, 0.172 mmol) in 1,2-DCE (1 mL) was added *R*-BINOL (49.2 mg, 0.172 mmol) at −5 °C, after 5 min, compound **5e** (26 mg, 0.086 mmol) in 1,2-DCE (1.5 mL) was added to reaction mixture via cannula. After additional stirring of reaction mixture for 30 min at same temperature, was added $TiCl_4$ (49 mg, 0.258 mmol) drop wise. After 2 h, the reaction mixture was quenched with H_2O (2 mL) and concentrated to remove 1,2-DCE, aqueous layer was extracted with EtOAc (2×20 mL), washed with brine (4 mL), dried over Na_2SO_4, and concentrated. Chromatography of the crude residue on silica gel [30–60% EtOAc in Hexane, v/v] afforded **10a**,**b**. Yield 97% (24.0 mg, 0.083 mmol), **10a**/**10b**=90:10, $[\alpha]_D^{25}$ +17.7 (*c* 0.27, $CHCl_3$), for **10a** 55% ee.

4.5. Trapping of methyl cation during PTSA-mediated fragmentation reaction of compound 5a

p-TsOH·H_2O (68 mg, 0.356 mmol) in anhydrous toluene (2 mL) was refluxed for 10 min, then solution of compound **5a** (56 mg, 0.178 mmol) in toluene (2 mL) was added drop wise to reaction mixture at reflux condition. After 2 h, the reaction mixture was cooled to 0 °C, quenched with aqueous saturated $NaHCO_3$ solution (2 mL) and solvent was evaporated under reduced pressure. To the obtained residue was added H_2O (2 mL) and the aqueous layer was extracted with EtOAc (3×15 mL), the combined organic layers were washed once with brine solution (3 mL), finally dried over Na_2SO_4, and concentrated. The SiO_2 column chromatography for the obtained crude afforded the analytically pure tetrahydrofuran derivatives **6a**,**b**, yield 79% (42.2 mg, 0.140 mmol) and methyl 4-methylbenzenesulfonate (**29**), yield 80% (21 mg, 0.112 mmol, based on **6a**,**b**).

*4.5.1. (±)-(3R,3aS,7aR)-Trimethyl hexahydroisobenzofuran-1,1,3(3H)-tricarboxylate (**6a**).* The general procedure 1 mentioned above was followed, when compound **5a** (67 mg, 0.213 mmol) was treated with $BF_3\cdot OEt_2$ (158 μL, 1.28 mmol) for 8 h to afford **6a**,**b**, yield >99% (55.4 mg, 0.212 mmol), ratio of epimers 75:25, major isomer (**6a**), colorless liquid (solidified after cooling, Mp 62–64 °C), R_f=0.45 (30% EtOAc in Hexane, silica gel TLC); ^{1}H NMR (400 MHz, $CDCl_3$); δ 4.60 (d, 1H, *J*=8.3 Hz), 3.83 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.06 (q, 1H, *J*=6.7 Hz), 2.72–2.77 (m, 1H), 1.51–1.75 (m, 4H), 1.20–1.34 (br m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 169.2, 168.3, 89.1, 80.1, 53.1, 52.7, 52.0, 43.2, 40.5, 22.6, 22.2, 22.0, 21.8; IR ν_{max} (neat) 2950, 2870, 1744, 1473, 1283, 1217, 1101, 1088 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{21}O_7$ $[M+H]^+$ 301.1287; found 301.1280.

*4.5.2. (±)-(3S,3aS,7aR)-Trimethyl hexahydroisobenzofuran-1,1,3(3H)-tricarboxylate (**6b**).* Minor isomer, colorless liquid (solidified after cooling, Mp 66–68 °C); R_f=0.5 (30% EtOAc in Hexane, silica gel TLC); ^{1}H NMR (400 MHz, $CDCl_3$); δ 4.57 (d, 1H, *J*=10.2 Hz), 3.81 (s, 3H), 3.78 (s, 3H), 3.72 (s, 3H), 2.92–2.97 (m, 1H), 2.67–2.71 (m, 1H), 1.49–1.87 (m, 5H), 1.22–1.41 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 168.8, 167.9, 91.0, 79.5, 53.0, 52.6, 52.2, 43.3, 42.0, 23.8, 23.4, 22.9, 20.7; IR ν_{max} (neat) 2935, 2861, 1745, 1436, 1240, 1202, 1088, 1032 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{20}O_7Na$ $[M+Na]^+$ 323.1101; found 323.1101.

*4.5.3. (±)-(3R,3aS,6aR)-Trimethyl tetrahydro-1H-cyclopenta[c]furan-1,1,3(3H,3aH)-tricarboxylate (**7a**).* The general procedure 1 mentioned above was followed when compound **5b** (52 mg, 0.173 mmol) was treated with $BF_3\cdot OEt_2$ (129 μL, 1.04 mmol) for 7 h to afford **7a**,**b**, yield >99% (49.3 mg, 0.172 mmol), colorless liquid, ratio of epimers 95:05, R_f=0.5 (30% EtOAc in Hexane, silica gel TLC); major isomer (**7a**), ^{1}H NMR (400 MHz, $CDCl_3$); δ 4.42 (d, 1H, *J*=7.8 Hz), 3.75 (s, 3H), 3.71 (s, 3H), 3.70 (s, 3H), 3.38 (q, 1H, *J*=8.5 Hz), 2.99–3.07 (m, 1H), 1.61–1.84 (m, 3H), 1.18–1.39 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 168.7, 167.1, 89.8, 80.1, 53.1, 52.6, 51.9, 49.0, 46.0, 30.1, 29.6, 27.1; IR ν_{max} (neat) 1957, 2873, 1741, 1438, 1286, 1237, 1114 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_7$: C, 54.54; H, 6.34. Found: C, 54.47; H, 6.22.

*4.5.4. (±)-(3R,3aS,8aR)-Trimethyl hexahydro-1H-cyclohepta[c]furan-1,1,3(3H,3aH)-tricarboxylate (**8a**).* The general procedure 1 mentioned above was followed when compound **5c** (80 mg, 0.243 mmol) was treated with $BF_3\cdot OEt_2$ (181 μL, 1.46 mmol) for 7 h to afford **8a**,**b**, yield >99% (75.9 mg, 0.241 mmol), colorless liquid, ratio of epimers 88:12, R_f=0.6 (30% EtOAc in Hexane, silica gel TLC); major isomer (**8a**), ^{1}H NMR (400 MHz, $CDCl_3$); δ 4.58 (d, 1H, *J*=7.8 Hz), 3.81 (s, 3H), 3.77–3.78 (br s 6H), 3.20–3.27 (m, 1H), 2.78–2.83(m, 1H), 1.76–1.86 (m, 4H), 1.54–1.57 (m, 1H), 1.18–1.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 169.6, 168.0, 90.8, 82.0, 53.0, 52.6, 51.8, 49.0, 46.5, 31.0, 28.7, 28.0, 27.2, 26.1; IR ν_{max} (neat): 2929, 2856, 1742, 1438, 1276, 1231, 1120 cm^{-1}; Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.32; H, 7.05. Found: C, 57.19; H, 6.90.

*4.5.5. (±)-(3R,3aS,9aR)-Trimethyl octahydrocycloocta[c]furan-1,1,3(3H)-tricarboxylate (**9a**).* The general procedure 1 mentioned above was followed when compound **5d** (80 mg, 0.233 mmol) was treated with $BF_3\cdot OEt_2$ (173 μL, 1.40 mmol) for 7 h to afford **9a**,**b**, yield >99% (76.0 mg, 0.231 mmol), colorless liquid, ratio of epimers 84:16, R_f=0.5 (30% EtOAc in Hexane, silica gel TLC); major isomer (**9a**), ^{1}H NMR (400 MHz, $CDCl_3$); δ 4.57 (d, 1H, *J*=7.3 Hz), 3.74 (s, 3H), 3.71 (s, 6H), 2.93–2.96 (br t, 1H), 2.60–2.65 (br q, 1H), 1.56–1.63 (m, 4H), 1.18–1.52 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 169.2, 168.3, 89.1, 80.1, 53.1, 52.7, 51.9, 48.4, 45.0, 28.9, 28.5, 25.4, 25.2, 23.6, 23.6; IR ν_{max} (neat) 2928, 2854, 1743, 1439, 1278, 1105, 1035 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{16}H_{25}O_7$ $[M+H]^+$ 329.1600; found 329.1602.

*4.5.6. (±)-(3R,3aR,6aS)-Trimethyl tetrahydrofuro[3,4-c]furan-1,1,3(3H)-tricarboxylate (**10a**).* The general procedure 1 mentioned above was followed when compound **5e** (60 mg, 0.198 mmol), was treated with $BF_3\cdot OEt_2$ (147 μL, 1.19 mmol) for 7 h to afford **10a**,**b**, yield >99% (56.8 mg, 0.197 mmol), colorless liquid, ratio of epimers 86:14, R_f=0.5 (40% EtOAc in Hexane, silica gel TLC); major isomer (**10a**), ^{1}H NMR (400 MHz, $CDCl_3$); δ 4.72 (d, 1H, *J*=7.8 Hz), 3.79–4.05 (m, 2H), 3.84 (s, 3H), 3.80 (s, 6H), 3.63–3.68 (m, 1H), 3.46–3.55 (m, 2H), 3.27–3.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 168.2, 166.6, 88.9, 79.3, 70.5, 70.4, 53.4, 53.0, 52.3, 50.0, 46.9; IR ν_{max} (neat): 2957, 2860, 1744, 1438, 1267, 1240, 1108 cm^{-1}; Anal. Calcd for $C_{12}H_{16}O_8$: C, 50.00; H, 5.59. Found: C, 50.16; H, 5.68.

*4.5.7. (±)-(3R,3aS,5S,6aR)-Trimethyl 5-methyltetrahydro-1H-cyclopenta[c]furan-1,1,3(3H,3aH)-tricarboxylate (**11a**).* The general procedure 1 mentioned above was followed when compound **5f** (75 mg, 0.238 mmol) was treated with $BF_3\cdot OEt_2$ (177 μL, 1.43 mmol) for 8 h to afford **11a**,**b**, yield >99% (70.8 mg, 0.236 mmol), ratio of epimers 84:16, major isomer (**11a**), colorless liquid, R_f=0.5 (30%

EtOAc in Hexane, silica gel TLC); ^{1}H NMR (500 MHz, $CDCl_3$); δ 4.46 (d, 1H, J=7.9 Hz), 3.82 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.44–3.49 (m, 1H), 3.08–3.15 (m, 1H), 1.81–1.95 (m, 3H), 0.97 (d, 3H, J=6.1 Hz), 0.83–0.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 168.7, 167.1, 89.3, 79.7, 53.2, 52.7, 52.0, 49.1, 46.0, 38.3, 37.8, 36.3, 18.1; IR ν_{max} (neat): 2955, 2871, 1741, 1437, 1233, 1117, 1055 cm^{-1}. HRMS (ESI): m/z calcd for $C_{14}H_{21}O_7$ $[M+H]^+$ 301.1287, found 301.1281.

*4.5.8. (±)-(3S,3aS,5S,6aR)-Trimethyl 5-methyltetrahydro-1H-cyclopenta[c]furan-1,1,3(3H,3aH)-tricarboxylate (**11b**).* Minor isomer, colorless liquid, R_f=0.55 (30% EtOAc in Hexane, silica gel TLC); ^{1}H NMR (500 MHz, $CDCl_3$); δ 4.50 (d, 1H, J=5.7 Hz), 3.80 (s, 3H), 3.80 (s, 3H), 3.69 (s, 3H), 3.49–3.55 (m, 1H), 2.98–3.04 (m, 1H), 2.26–2.31 (m, 1H), 1.99–2.05 (m, 1H), 1.80–1.85 (m, 1H), 1.21–1.27 (m, 1H), 1.03 (d, 3H, J=6.3 Hz), 0.96–1.00 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 168.7, 168.1, 90.3, 85.8, 53.1, 52.6, 52.1, 50.4, 48.7, 41.2, 37.2, 37.2, 19.0; IR ν_{max} (neat): 2955, 2871, 1745, 1436, 1291, 1233 cm^{-1}. HRMS (ESI): m/z calcd for $C_{14}H_{20}O_7Na$ $[M+Na]^+$ 323.1101; found 323.1101.

*4.5.9. (±)-(3S,5R)-Trimethyl 3-phenyldihydrofuran-2,2,5(3H)-tricarboxylate (**13a**,syn).* The general procedure 1 mentioned above was followed when compound **12** (200 mg, 0.594 mmol) was treated with $BF_3{\cdot}OEt_2$ (0.44 mL, 3.57 mmol) for 4 h to afford mixture of regioisomers **13a**,**b**, yield 94% (180 mg, 0.558 mmol), ratio of regioisomers **13a**,**b**=52:48, the regioisomers were separated by LC-908W preparative HPLC [JAIGEL-OA4100 (column), 1% EtOH in Hexane eluent (v/v)]. Major regioisomer *syn*/*anti*=77:23, compound **13a**,*syn*, colorless liquid; R_f=0.4 (30% EtOAc in Hexane, silica gel TLC), ^{1}H NMR (500 MHz, $CDCl_3$); δ 7.25–7.35 (m, 5H, aromatic), 4.74 (dd, 1H, J=9.3, 7.5 Hz), 4.29 (dd, 1H, J=10.3, 7.9 Hz), 3.86 (s, 3H), 3.80 (s, 3H), 3.30 (s, 3H), 2.70–2.74 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 168.4, 167.7, 136.0, 128.3, 127.8, 90.5, 77.7, 53.1, 52.5, 52.2, 50.0, 35.0; IR ν_{max} (neat) 2954, 2849, 1740, 1436, 1289, 1230, 1116, 1052 cm^{-1}. HRMS (ESI): m/z calcd for $C_{16}H_{19}O_7$ $[M+H]^+$ 323.1131, found 323.1130.

*4.5.10. (±)-(4S,5S)-Trimethyl 4-phenyldihydrofuran-2,2,5(3H)-tricarboxylate (**13b**).* Minor regioisomer (**13b**), colorless liquid, R_f=0.4 (30% EtOAc in Hexane, silica gel TLC); ^{1}H NMR (500 MHz, $CDCl_3$); δ 7.18–7.30 (m, 5H, aromatic), 4.93 (d, 1H, J=8.5 Hz), 3.94–3.99 (m, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.27 (s, 3H), 3.19 (dd, 1H, J=13.0, 12.7 Hz), 2.74 (dd, 1H, J=13.3, 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 169.9, 168.6, 134.7, 128.5 (2C), 127.8, 127.7 (2C), 87.2, 83.0, 53.3, 53.2, 51.5, 47.3, 36.4; IR ν_{max} (neat) 2955, 2849, 1746, 1498, 1436, 1214, 1093 cm^{-1}. HRMS (ESI): m/z calcd for $C_{16}H_{19}O_7$ $[M+H]^+$ 323.1131, found 323.1132.

*4.5.11. The inseparable tricarboxylate tetrahydrofuran derivatives (**15a** and **15b**).* The general procedure 1 mentioned above was followed when compound **14** (80 mg, 0.263 mmol) was treated with $BF_3{\cdot}OEt_2$ (195 μL, 1.58 mmol) for 3 h to afford **15a**,**b**, yield 59% (45.0 mg, 0.155 mmol), colorless liquid, ratio of regioisomers **15a**/**15b**=62:38, R_f=0.5 (40% EtOAc in Hexane, silica gel TLC); From the mixture, major isomer (**15a**): ^{1}H NMR (400 MHz, $CDCl_3$); δ 4.70 (dd, 1H, J=8.5, 4.1 Hz), 4.57 (dd, 1H, J=4.6, 3.2 Hz), 3.81 (s, 3H), 3.78 (s, 6H), 3.41–3.50 (m, 2H), 2.44–2.62 (m, buried with signal of minor isomer, 2H), 1.07–1.10 (t, 3H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 168.7, 167.9, 91.1, 81.1, 77.8, 65.5, 53.1, 52.7, 52.4, 34.9, 15.0. Minor isomer (**15b**): ^{1}H NMR (400 MHz, $CDCl_3$); δ 4.81 (d, 1H, J=5.1 Hz), 4.37 (q, 1H, J=5.1 Hz), 3.84 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 3.51–3.57 (m, 2H), 2.92 (dd, 1H, J=13.5, 4.5 Hz), 2.44–2.62 (m, buried with signal of major isomer, 1H), 1.09–1.13 (t, 3H, J=6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 168.8, 166.5, 86.4, 82.2, 78.9, 65.5, 53.3, 53.2, 52.0, 38.0, 15.0; IR ν_{max} (neat) 2956, 2851, 1745, 1438, 1291, 1235, 1100, 1032 cm^{-1}; HRMS (ESI): m/z calcd for $C_{12}H_{19}O_8$ $[M+H]^+$ 291.1080; found 291.1085.

4.5.12. Cyclohexylidene protection of endo diol (1,4,5,6-tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-ene-2,3-diol). To a solution of *endo* diol (4.37 g, 13.488 mmol) in dry benzene (90 mL) were added cyclohexanone (1.68 mL, 16.186 mmol) and *p*-TsOH.H_2O (257 mg, 1.35 mmol) at rt. Then reaction mixture was refluxed to remove H_2O azeotropically by using Dean–stark apparatus. After 15 h, the reaction mixture was cooled to ≈10 °C and 6 mL cold saturated aqueous $NaHCO_3$ solution was added sequentially. After evaporation of solvent under reduced pressure, H_2O (10 mL) was added to residue and the aqueous layer was extracted with EtOAc (3×50 mL), the combined EtOAc layers were washed with brine (20 mL), EtOAc layer was separated, dried over Na_2SO_4 and solvent was evaporated. The silica gel column chromatography for the crude reaction mixture affords **15c** (compound numbered in Supplementary data). The resultant compound was further purified by fractional crystallization with CH_2Cl_2/Hexane (10:1) to afford crystalline compound **15c**. Yield 98% (5.34 g, 13.21 mmol); R_f=0.9 (10% EtOAc in Hexane, silica gel TLC), Mp 120–122 °C, ^{1}H NMR (500 MHz, $CDCl_3$); δ 4.81 (s, 2H), 3.55 (s, 3H), 3.53 (s, 3H), 1.56–1.58 (m, 4H), 1.51–1.52 (m, 4H), 1.34 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.6 (2C), 116.7, 114.1, 85.3 (2C), 77.6 (2C), 52.5, 51.7, 35.4, 35.1, 24.9, 23.5, 23.3; IR ν_{max} (KBr) 2949, 2846, 1602, 1449, 1371, 1194, 1106 cm^{-1}. HRMS (ESI): m/z calcd for $C_{15}H_{19}Cl_4O_4$ $[M+H]^+$ 403.0037, found 403.0038.

*4.5.13. Oxidation of vicinal dichloro alkene **15c** to norbornyl α-diketone **16**.* To a vigorously stirred solution of compound dichloro alkene **15c** (5.34 g, 13.21 mmol) in MeCN (100 mL) were added RuLDH [529 mg, 0.9 mol % $RuCl_3{\cdot}3H_2O$ loaded on layer double hydroxide (LDH)] and $NaIO_4$ (4.52 g, 21.13 mmol) sequentially, followed by addition of 16.6 mL H_2O at rt. After 4 h, the reaction mixture was quenched with *i*-PrOH (7 mL) and stirred for 1 h. Then the black residue was filtered through sintered crucible under vacuum, washed with EtOAc, the combined filtrate was concentrated on rotary evaporator. The obtained residue was dissolved in EtOAc and H_2O (20 mL) was added, the product was extracted with EtOAc (3×60 mL) and the combined organic layers were washed with saturated aqueous $Na_2S_2O_3$ (20 mL), followed by brine (25 mL), organic layer was separated, dried over Na_2SO_4 and solvent was evaporated on a rotary evaporator. The silica gel column chromatography for the crude reaction mixture afforded yellow solid **16**, yield 95% (4.58 g, 12.55 mmol), R_f=0.5 (10% EtOAc in Hexane, silica gel TLC), Mp=194–196 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 4.93 (s, 2H), 3.64 (s, 3H), 3.47 (s, 3H), 1.46 (br s, 6H), 1.38–1.40 (m, 2H), 1.27–1.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.4 (2C, −C=O), 116.7, 105.2, 81.8 (2C), 78.2 (2C), 52.4, 52.3, 35.0, 33.3, 24.6, 23.3, 23.1; IR ν_{max} (KBr) 2956, 2866, 1771, 1453, 1218, 1093 cm^{-1}. HRMS (ESI): m/z calcd for $C_{15}H_{19}Cl_2O_6$ $[M+H]^+$ 365.0558, found 365.0556.

*4.5.14. One pot synthesis of oxa-bridged compound **17** from norbornyl α-diketone **16**.* To a stirred solution of α-diketone **16** (4.87 g, 13.33 mmol) in MeOH (100 mL) was added 30% H_2O_2 (15.4 mL), followed by the slow addition of 6 N NaOH solution (6.2 mL) at 0–5 °C. Then the resultant solution was stirred at rt, after 6 h the reaction mixture was cooled to 0 °C and 30 equiv of NaOH (16.0 g in 10 mL H_2O) was added slowly. After completion of addition, the reaction mixture was refluxed for 30 h. Then the reaction mixture was cooled to 0–5 °C, acidified up to pH≈5 with 5% HCl solution, then the organic components were extracted with EtOAc (3×60 mL), washed with brine solution (20 mL), finally dried over Na_2SO_4, and concentrated. The obtained crude dicarboxylic acid dissolved in MeOH (20 mL), treated with CH_2N_2/Et_2O at 0 °C, the excess of CH_2N_2 was quenched with acetic acid and solution was

concentrated, the resultant residue was purified by silica gel column chromatography with 20% EtOAc in Hexane as eluent to afford **17**, yield 93% (4.61 g, 12.39 mmol), colorless solid, Mp 106–108 °C, R_f=0.55 (30% EtOAc in Hexane, silica gel TLC); ^{1}H NMR (400 MHz, $CDCl_3$); δ 5.10 (s, 2H), 3.86 (s, 6H), 3.40 (s, 3H), 3.32 (s, 3H), 1.73–1.76 (m, 2H), 1.56 (br s, 6H), 1.35 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 116.7, 114.0, 89.2, 81.6, 52.7, 51.8, 51.7, 35.8, 35.1, 24.9, 23.7, 23.6; IR ν_{max} (neat) 2939, 2854, 1728, 1443, 1385, 1209 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_{17}H_{24}O_9$ 372.1420, found 372.1425.

*4.5.15. Synthesis of bridged lactone **18**.* To a stirred solution of α-diketone **16** (810 mg, 2.218 mmol) in MeOH (20 mL) was added 30% H_2O_2 solution (1.55 mL), followed by drop wise addition of 6 N KOH (479 mg in 1.4 mL H_2O) at 0 °C, then reaction mixture was stirred at rt. After 8 h, the reaction mixture was acidified up to pH≈5 with 5% HCl at 0 °C. Then the product was extracted with EtOAc (3×30 mL), washed with brine (4 mL), the combined organic layers were dried over Na_2SO_4 and solvent was evaporated. The crude carboxylic acid was treated with CH_2N_2 in Et_2O/MeOH (1:1), after quenching excess of CH_2N_2 with acetic acid, the solvent was evaporated and the silica gel column chromatography for the residue afforded the compound **18**, yield 98% (819 mg, 2.173 mmol), colorless crystalline compound, Mp 182–184 °C, R_f=0.6 (40% EtOAc in Hexane, silica gel TLC), ^{1}H NMR (500 MHz, $CDCl_3$); δ 5.31 (d, 1H, *J*=7.3 Hz), 4.81 (d, 1H, *J*=7.3 Hz), 3.87 (s, 3H), 3.56 (s, 3H), 3.36 (s, 3H), 1.64–1.67 (m, 2H), 1.51–1.58 (m, 6H), 1.33–1.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 164.5, 117.2, 111.0, 83.5, 80.6, 79.9, 76.2, 53.4, 51.9, 51.5, 35.1, 34.9, 24.8, 23.5, 23.3; IR ν_{max} (KBr) 2948, 2866, 1824, 1745, 1450, 1322, 1188, 1104 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_{16}H_{21}ClO_8$ 376.0925, found 376.0923.

*4.5.16. Chemoselective reduction of bridge-head ester **18**.* To a stirred solution of compound **18** (1.4 g, 3.715 mmol) in dry 1,4-dioxane (30 mL), was added $NaBH_4$ (422 mg, 11.145 mmol) at rt, then reaction mixture was refluxed. After 4 h, the reaction mixture was cooled to 0 °C and quenched with H_2O (4 mL), the solvent was evaporated under reduced pressure. For the obtained crude H_2O (6 mL) was added, product was extracted with EtOAc (3×30 mL), washed with H_2O (4 mL) and brine (8 mL), organic layer was dried over Na_2SO_4 and concentrated. The crude residue was purified on silica gel column chromatography (20–40% EtOAc in Hexane eluent), afforded compound **19a**, yield 96% (1.24 g, 3.56 mmol), colorless solid, Mp 98–100 °C, R_f=0.4 (50% EtOAc in Hexane, silica gel TLC), ^{1}H NMR (400 MHz, $CDCl_3$); δ 4.87 (d, 1H, *J*=7.3 Hz), 4.78 (d, 1H, *J*=7.3 Hz), 4.04–4.12 (m, 2H), 3.55 (s, 3H), 3.51(s, 3H), 2.21 (br s, 1H), 1.67–1.70 (m, 2H), 1.57–1.62 (m, 6H), 1.36–1.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 116.8, 109.4, 87.3, 80.9, 77.6, 75.8, 58.5, 52.0, 51.8, 35.2, 34.8, 24.8, 23.6, 23.4; IR (KBr) 3501 (br), 2941, 2852, 1817, 1450, 1371, 1267, 1250 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_{15}H_{21}ClO_7$ 348.0976; found 348.0973.

*4.5.17. Benzylation of alcohol **19a**.* NaH (688 mg, 17.20 mmol, 60% dispersion in mineral oil) was taken in a flame dried 100 mL two necked round bottomed flask under argon atmosphere. The oily NaH washed with dry hexane (4 mL) and solvent was removed through syringe. Then dry THF (20 mL) was added to NaH and cooled to 0 °C, the solution of alcohol **19a** (3 g, 8.60 mmol) in dry THF (40 mL) was added, followed by addition of benzyl bromide (2.05 mL, 17.20 mmol). Then reaction mixture was slowly brought to rt. After 6 h, the reaction mixture was cooled to 0 °C and quenched with H_2O (3 mL), the product was extracted with EtOAc (three times), the combined organic layers were washed once with brine (8 mL), dried over Na_2SO_4 and solvent was evaporated. The residue was purified by silica gel (100–200 mesh) column chromatography with 10–20% EtOAc in hexane eluent afforded compound **19b**. Yield 78% (2.94 g, 6.71 mmol), colorless solid, Mp 104–106 °C, R_f=0.7 (20% EtOAc in Hexane, silica gel TLC); ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.23 (m, 5H), 4.87 (d, 1H, *J*=7.5 Hz), 4.70 (d, 1H, *J*=7.3 Hz), 4.57 (dd, 2H, *J*=59.6, 11.8 Hz), 3.83 (dd, 2H, *J*=53.7, 11.7 Hz), 3.43 (s, 3H), 3.38 (s, 3H), 1.64 (t, 2H, *J*=6.1 Hz), 1.50–1.55 (m, 6H), 1.30–1.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 137.3, 128.3, 127.8, 116.5, 109.3, 87.6, 81.0, 80.9, 75.8, 74.9, 64.5, 51.9, 51.8, 35.2 34.8, 24.9, 23.6, 23.4; IR ν_{max} (KBr) 2941, 2861, 1814, 1450, 1373, 1299, 1219, 1123 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_{22}H_{27}ClO_7$ 438.1445; found 438.1446.

*4.5.18. Synthesis of oxa-bridged compound **20** from bridged lactone **19b**.* To a solution of compound **19b** (1.3 g, 2.962 mmol) in MeOH (25 mL) was added 30 equiv of NaOH (3.55 g in 4 mL H_2O, 88.86 mmol) at 0–5 °C, then the reaction mixture was refluxed, after completion of starting material (monitored by TLC) 30 h, the reaction mixture was cooled to 0 °C and acidified up to pH≈5 with 5% HCl, then immediately product was extracted with EtOAc (3×30 mL), washed with brine (8 mL), the resultant organic layer was dried over Na_2SO_4 and concentrated. The crude acid was dissolved in dry EtOAc (10 mL) and treated with CH_2N_2/Et_2O at 0 °C. The excess of CH_2N_2 was quenched with acetic acid and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (100–200 mesh) with 20% EtOAc in hexane eluent afforded compound **20**. Yield 95% (1.22 g, 2.814 mmol), colorless liquid, R_f=0.55 (25% EtOAc in Hexane, silica gel TLC); ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.26–7.33 (m, 5H, aromatic), 5.06 (1H, d, *J*=5.8 Hz), 4.89 (d, 1H, *J*=5.8 Hz), 4.60 (dd, 2H, *J*=28.3, 11.7 Hz), 3.83 (s, 3H, CO_2*Me*), 3.77 (dd, 2H, *J*=77.5, 10.2 Hz), 3.32 (s, 3H, OMe), 3.30 (s, 3H, OMe), 1.69–1.73 (m, 2H), 1.54–1.58 (m, 6H), 1.29–1.36 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 137.6, 128.2, 127.7, 115.9, 112.1, 91.5, 89.6, 81.7, 79.0, 73.7, 62.4, 52.6, 51.9, 51.5, 35.9, 35.3, 25.1, 23.8; IR (neat) 1940, 2859, 1755, 1450, 1266, 1101 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{23}H_{31}O_8$ $[M+H]^+$ 435.2019, found 435.2011.

*4.5.19. Partial reduction of meso diester **17**.* To a stirred solution of oxa-bridged compound **17** (100 mg, 0.268 mmol) in dry THF/EtOH (3:3 mL) was added LiCl (29 mg, 0.671 mmol), followed by addition of $NaBH_4$ (25 mg, 0.671 mmol) at rt, after reaction mixture was stirred for 40 h, quenched with saturated NH_4Cl (4 mL), product was extracted with EtOAc (3×15 mL), the combined organic layers were washed once with brine (8 mL), dried over Na_2SO_4 and solvent was evaporated. The silica gel column chromatography for the crude residue afforded monoalcohol **21**, yield 86% (66 mg, 0.192 mmol, based on starting material recovery), solidified after cooling, colorless solid, Mp 86–88 °C, R_f=0.5 (40% EtOAc in Hexane, silica gel TLC); ^{1}H NMR (400 MHz, $CDCl_3$); δ 5.08 (d, 1H, *J*=5.4 Hz), 4.84 (d, 1H, *J*=5.4 Hz), 4.01 (qd, 2H, *J*=14.5, 5.4 Hz), 3.86 (s, 3H), 3.37 (s, 3H), 3.32 (s, 3H), 2.47–2.52 (m, 1H), 1.69–1.77 (m, 2H), 1.52–1.58 (m, 6H), 1.31–1.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 116.4, 112.5, 92.3, 89.5, 81.9, 79.5, 57.3, 52.7, 51.8, 51.7, 35.8, 35.2, 25.0, 23.8, 23.7; IR ν_{max} (neat) 3501, 2935, 2851, 1749, 1441, 1200, 1130 cm^{-1}. HRMS (APCI): *m*/*z* calcd for $C_{16}H_{28}NO_8$ $[M+NH_4]^+$ 362.1815, found 362.1806.

*4.5.20. TBDPS ether protection of monoalcohol **21**.* To a solution of alcohol **21** (114 mg, 0.331 mmol) in dry CH_2Cl_2 (12 mL) was added 1*H*-imidazole (68 mg, 0.993 mmol), followed by addition of TBDPSCl (137 mg, 0.496 mmol) at 0 °C, then reaction mixture was stirred at rt. After 4 h, the reaction mixture was diluted with H_2O (6 mL), product was extracted with CH_2Cl_2 (3×15 mL), the combined organic layers were washed once with brine (8 mL), dried over Na_2SO_4 and solvent was evaporated. The silica gel column chromatography for the crude reaction mixture afforded monoester **22**, yield 95% (183 mg, 0.314 mmol), obtained as colorless liquid, R_f=0.6 (25% EtOAc in Hexane, silica gel TLC); ^{1}H

NMR (400 MHz, $CDCl_3$); δ 7.66–7.72 (m, 4H), 7.34–7.44 (m, 6H), 5.13 (d, 1H, J=5.9 Hz), 5.03 (d, 1H, J=5.4 Hz), 3.93 (dd, 2H, J=76, 10.2 Hz), 3.82 (s, 3H), 3.39 (s, 3H), 3.36 (s, 3H), 1.71–1.77 (m, 2H), 1.53–1.68 (m, 7H), 1.21–1.28 (m, 1H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 135.7 (2C), 135.5 (2C), 132.9, 132.5, 129.8, 129.7, 127.7 (2C), 127.6 (2C), 115.9, 112.3, 92.7, 89.4, 81.7, 78.6, 56.5, 52.6, 52.1, 51.5, 36.0, 35.3, 26.7 (3C, *t*-Bu), 25.1, 23.9, 23.8, 19.2. IR ν_{max} (neat) 2937, 2857, 1758, 1735, 1438, 1362, 1208, 1092 cm^{-1}. HRMS (APCI): m/z calcd for $C_{32}H_{46}NO_8Si$ $[M+NH_4]^+$ 600.2993, found 600.2964.

*4.5.21. (±)-(3a′R,6′S,6a′S)-Trimethyl dihydrospiro[cyclohexane-1,2′-furo[3,4-d][1,3]dioxole]-4′,4′,6′(3a′H)-tricarboxylate **23a**.* To a stirred solution of **17** (1.36 g, 3.65 mmol) in dry 1,2-DCE (20 mL) was added $BF_3\cdot OEt_2$ (1.35 mL, 10.95 mmol) drop wise at 0 °C, after addition completed the reaction mixture was slowly brought to rt. After 9 h, the reaction mixture was cooled to 0 °C and quenched with cold saturated aqueous $NaHCO_3$ solution (8 mL) and 1,2-DCE was evaporated under reduced pressure. To the obtained crude H_2O (6 mL) was added, aqueous part was extracted with EtOAc (3×30 mL), the combined organic layers were washed once with brine solution (10 mL), organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The SiO_2 column chromatography for the crude reaction mixture (20–30% EtOAc in Hexane solvent as eluent) afforded the analytically pure tetrahydrofurans **23a**,**b**, yield 97% (1.26 g, 3.54 mmol), ratio of epimers 88:12, major isomer (**23a**), white solid, Mp 102–103 °C, R_f=0.6 (30% EtOAc in Hexane, silica gel TLC); ^{1}H NMR (500 MHz, $CDCl_3$); δ 5.46 (d, 1H, J=6.1 Hz), 5.08 (dd, 1H, J=5.9, 1.3 Hz), 4.89 (br s, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.73 (s, 3H), 1.68–1.70 (br m, 2H), 1.55 (br s, 6H), 1.37 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 167.3, 165.3, 114.9, 91.2, 84.7, 83.4, 83.1, 53.2, 52.9, 52.4, 35.7, 34.6, 24.8, 23.8, 23.6; IR ν_{max} (KBr) 2945, 2853, 1780, 1760, 1726, 1441, 1227, 1110 cm^{-1}; Anal. Calcd for $C_{16}H_{22}O_9$: C, 53.63; H, 6.19. Found: C, 53.70; H, 6.18.

*4.5.22. (±)-(3a′R,6′R,6a′S)-Trimethyl dihydrospiro[cyclohexane-1,2′-furo[3,4-d][1,3]dioxole]-4′,4′,6′(3a′H)-tricarboxylate **23b**.* Minor isomer (**23b**), colorless liquid (solidified after cooling, Mp 68–70 °C), R_f=0.5 (30% EtOAc in Hexane, silica gel TLC); ^{1}H NMR (500 MHz, $CDCl_3$); δ 5.34 (d, 1H, J=5.7 Hz), 5.12 (dd, 1H, J=5.8, 4.5 Hz), 4.47 (d, 1H, J=4.5 Hz), 3.86 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 1.65–1.68 (m, 2H), 1.49–1.53 (m, 6H), 1.33 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 166.4, 164.6, 115.1, 89.7, 83.0, 81.2, 81.0, 83.0, 81.2, 81.0, 53.3, 52.9, 52.3, 35.4, 35.3, 24.8, 23.8, 23.7; IR ν_{max} (neat) 2940, 2855, 1776, 1741, 1438, 1369, 1266, 1122, 1038 cm^{-1}. HRMS (ESI): m/z calcd for $C_{16}H_{22}O_9Na$ $[M+Na]^+$ 381.1156, found 381.1160.

*4.5.23. (±)-(3a′R,4′R,6′S,6a′S)-Dimethyl 4′-((benzyloxy)methyl)tetrahydrospiro[cyclohexane-1,2′-furo[3,4-d][1,3]dioxole]-4′,6′-dicarboxylate (**24a**).* Experimental procedure is similar to compounds **23a**,**b**, when compound **20** (95 mg, 0.218 mmol) was treated with $BF_3\cdot OEt_2$ (81 μL, 0.656 mmol) for 4 h to afford **24a**,**b**, yield 86% (78.8 mg, 0.187 mmol), ratio of epimers 57:43, the two isomers were separated by column chromatography (silica gel, 100–200 mesh, 15% EtOAc in Hexane as eluent). Major isomer (**24a**), colorless liquid, R_f=0.5 (25% EtOAc in Hexane, silica gel TLC); ^{1}H NMR (500 MHz, $CDCl_3$); δ 7.26–7.37 (m, 5H, aromatic), 5.20 (d, 1H, J=5.8 Hz), 5.12 (dd, 1H, J=5.8, 1.5 Hz), 4.59 (d, 1H, J=1.5 Hz), 4.58 (dd, 2H, J=37.4, 12.4 Hz), 3.90 (dd, 2H, J=26.4, 9.0 Hz), 3.74 (s, 3H), 3.73 (s, 3H), 1.66–1.69 (m, 2H), 1.56–1.62 (m, 6H), 1.39 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.1, 137.8, 128.2 (2C), 127.6 (2C), 127.5, 114.0, 89.4, 84.1, 83.5, 81.8, 73.5, 69.3, 52.5, 52.3, 36.1, 34.6, 24.9, 23.9, 23.6; IR ν_{max} (neat) 2937, 2860, 1759, 1736, 1451, 1283, 1228, 1105 cm^{-1}. HRMS (ESI): m/z calcd for $C_{22}H_{28}O_8Na$ $[M+Na]^+$ 443.1676, found 443.1683.

*4.5.24. (±)-(3a′R,4′R,6′R,6a′S)-Dimethyl 4′-((benzyloxy)methyl)tetrahydrospiro[cyclohexane-1,2′-furo[3,4-d][1,3]dioxole]-4′,6′-dicarboxylate (**24b**).* Minor isomer, colorless liquid; R_f=0.4 (25% EtOAc in Hexane, silica gel TLC); ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.19–7.25 (m, 5H, aromatic), 4.97 (d, 1H, J=5.8 Hz), 4.92 (dd, 1H, J=5.8, 4.6 Hz), 4.49 (d, 1H, J=4.6 Hz), 4.44–4.63 (dd, 1H, J=65.1, 12.2 Hz), 3.90 (dd, 2H, J=71.9, 10.2 Hz), 3.71 (s, 3H), 3.68 (s, 3H), 1.55–1.58 (m, 2H), 1.40–1.47 (m, 6H), 1.26–1.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 167.2, 137.8, 128.2 (2C), 127.7 (2C), 127.5, 114.5, 89.4, 82.6, 81.5, 80.9, 73.4, 69.9, 52.6, 52.0, 35.5, 34.9, 24.9, 23.8, 23.7; IR ν_{max} (neat) 2973, 1742, 1628, 1442, 1368, 1221, 1101 cm^{-1}. HRMS (EI): m/z calcd for $C_{22}H_{28}O_8$ 420.1784; found 420.1787.

*4.5.25. Debenzylation of compound **24a**, (±)-(3a′R,4′R,6′S,6a′S)-dimethyl 4′-(hydroxymethyl)tetrahydrospiro[cyclohexane-1,2′-furo[3,4-d][1,3]dioxole]-4′,6′-dicarboxylate (**24c**).* To a stirred solution of compound **24a** (34 mg, 0.081 mmol) in EtOAc (4 mL), was added 10% Pd/C (5 mg) and reaction mixture was stirred under hydrogen atmosphere at rt, after 12 h the reaction mixture was directly filtered through a small Celite pad, washed with EtOAc and the resultant solution was concentrated. The obtained residue was purified on silica gel column chromatography (silica gel, 100–200 mesh, 30–50% EtOAc in Hexane as eluent), afforded compound **24c**. Yield 99% (26 mg, 0.08 mmol), colorless liquid, R_f=0.4 (50% EtOAc in Hexane, silica gel TLC). ^{1}H NMR (400 MHz, $CDCl_3$); δ 5.22 (d, 1H, J=6.1 Hz), 5.15 (dd, 1H, J=6.1, 1.4 Hz), 4.68 (d, 1H, J=1.4 Hz), 3.96–4.13 (m, 2H), 3.78 (s, 3H), 3.75 (s, 3H), 2.31 (br s, 1H), 1.74–1.77 (m, 2H), 1.54–1.67 (m, 6H), 1.37–1.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 169.9, 114.5, 89.6, 83.9, 83.6, 82.1, 63.5, 52.6, 52.4, 35.9, 34.2, 24.9, 23.9, 23.6; IR ν_{max} (neat) 3489, 2940, 2859, 1738, 1441, 1369, 1283, 1223, 1102 cm^{-1}. HRMS (EI): m/z calcd for $C_{15}H_{22}O_8$ 330.1315, found 330.1316.

*4.5.26. (±)-(3a′R,4′R,6′S,6a′S)-Dimethyl 4′-(((tert-butyldiphenylsilyl)oxy)methyl)tetrahydrospiro[cyclohexane-1,2′-furo[3,4-d][1,3]dioxole]-4′,6′-dicarboxylate (**25a**).* Experimental procedure is similar to compounds **23a**,**b**, when compound **22** (73 mg, 0.125 mmol) was treated with $BF_3\cdot OEt_2$ (47 μL, 0.376 mmol) for 5 h to afford **25a**,**b**, yield 94% (67 mg, 0.117 mmol), ratio of epimers 46:54, the two isomers were separated by column chromatography (silica gel, 100–200 mesh, 10% EtOAc in Hexane as eluent). Minor epimer **25a**, colorless liquid, R_f=0.5 (20% EtOAc in Hexane, silica gel TLC); ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.66–7.73 (4H, m), 7.34–7.44 (m, 6H), 5.34 (d, 1H, J=5.9 Hz), 5.15 (dd, 1H, J=5.9, 2 Hz), 4.53 (d, 1H, J=2 Hz), 4.14 (s, 2H), 3.81 (s, 3H), 3.73 (s, 3H), 1.48–1.72 (m, 9H), 1.37 (br s, 1H), 1.0 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.4, 135.6 (2C), 135.5 (2C), 133.0, 132.9, 129.7, 129.6, 127.6 (2C), 127.5 (2C), 114.0, 90.0, 84.6, 84.0, 81.0, 62.7, 52.4, 52.3, 36.3, 34.8, 26.5 (3C, *t*-Bu), 25.0, 23.8, 23.7, 19.2; IR ν_{max} (neat) 2940, 2857, 1739, 1435, 1234, 1108 cm^{-1}. HRMS (APCI): m/z calcd for $C_{31}H_{44}NO_8Si$ $[M+NH_4]^+$ 586.2836, found 586.2819.

*4.5.27. (±)-(3a′R,4′R,6′R,6a′S)-Dimethyl 4′-(((tert-butyldiphenylsilyl)oxy)methyl)tetrahydrospiro[cyclohexane-1,2′-furo[3,4-d][1,3]dioxole]-4′,6′-dicarboxylate (**25b**).* Major epimer, colorless liquid, R_f=0.45 (20% EtOAc in Hexane, silica gel TLC); ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.69–7.71 (m, 4H), 7.35–7.44 (m, 6H), 5.2 (d, 1H, J=5.9 Hz), 5.04–5.06 (m, 1H), 4.47 (d, 1H, J=4.4 Hz), 4.17 (dd, 2H, J=67.5, 9.8 Hz), 3.79 (s, 3H), 3.78 (s, 3H), 1.36–1.59 (m, 9H), 1.25–1.29 (m, 1H), 1.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 167.3, 135.7 (2C), 135.5 (2C), 133.2, 132.8, 129.7, 129.6, 127.6 (2C), 127.6 (2C), 114.3, 89.5, 81.5, 81.3, 80.9, 63.6, 52.4, 52.0, 35.5, 35.1, 26.5 (3C,

t-Bu), 24.9, 23.7, 23.7, 19.2; IR ν_{max} (neat) 2936, 2858, 1767, 1739, 1436, 1222, 1111 cm^{-1}. HRMS (APCI): *m*/*z* calcd for $C_{31}H_{44}NO_8Si$ $[M+NH_4]^+$ 586.2836, found 586.2816.

*4.5.28. Methyl 4-methylbenzenesulfonate (**29**).* CAS RN [80-48-8] Lit. reported:[18] ^1H NMR ($CDCl_3$); δ 7.79 (dt, 2H, *J*=8.5, 2.0 Hz), 7.35 (m, 2H), 3.74 (s, 3H), 2.45 (s, 3H). IR ν_{max} (neat) 2956, 1599, 1360, 1179, 993, 767 cm^{-1}. Observed: ^1H NMR (400 MHz, $CDCl_3$); δ 7.79 (d, 2H, *J*=8.3 Hz), 7.36 (d, 2H, *J*=8.3 Hz), 3.74 (s, 3H), 2.45 (s, 3H); IR ν_{max} (neat) 2955, 1598, 1360, 1177, 992, 766 cm^{-1}.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.07.005.

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