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Stereoselective synthesis of *cis*- or *trans*-2,4-disubstituted butyrolactones from Wynberg lactone

Ashok Ganta, Julia L. Shamshina, Lauren R. Cafiero, Timothy S. Snowden *

Department of Chemistry, The University of Alabama, Box 870336, Tuscaloosa, AL 35487-0336, United States

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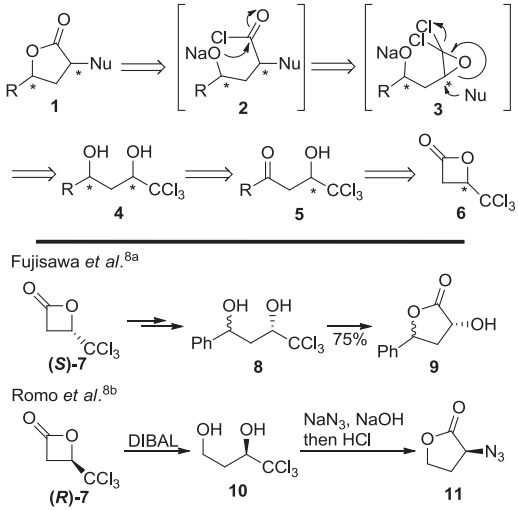
ABSTRACT

(*R*)-Wynberg lactone was used to prepare various asymmetric 2,4-disubstituted butyrolactones in three to four steps. Attainment of any possible stereoisomer, based upon commencement from (*R*)- or (*S*)-4-trichloromethyl-2-oxetanone, and the capacity to install disparate substituents at C_2 make this approach particularly versatile.

1. Introduction

Heteroatom-substituted butyrolactones serve as multipurpose intermediates in organic synthesis, providing direct access to highly functionalized carbonyl compounds or alcohols through standard transformations. Substituted butyrolactones also find application in the preparation of liquid crystals,[1] and several exhibit biological activity including cytotoxicity[2] and hunger modulation.[3] It has been estimated that asymmetric butyrolactones exist as components of about 10% of all natural products.[4] Considering the importance of these structures in chemistry, biology, and materials science, we intended to devise an expedient approach to variably 2,4-disubstituted butyrolactones taking advantage of our experience with reactions involving *gem*-dichloroepoxide intermediates.[5] We also planned to offer a method where any one of the four possible stereoisomers is equally and predictably attainable.

We reasoned that asymmetric 2,4-disubstituted lactones (**1**) would be accessible in a single operation from a chiral 1-trichloromethyl-1,3-diol (**4**) (Scheme 1). Treatment of **4** with base in protic media would initiate a reaction cascade where asymmetric *gem*-dichloroepoxide **3** would form after deprotonation of a trichloromethyl carbinol. Inclusion of the desired nucleophile for installation at C_2 would promote regioselective substitution with stereospecific inversion of configuration followed by acid chloride generation. The acyl chloride would be subject to intramolecular nucleophilic acyl substitution by the tethered alkoxide (**2**) to afford the decorated butyrolactone in a one-pot operation. We envisioned the requisite *syn*- or *anti*-1,3-diols could arise from substrate-directed borohydride reductions, whereby a newly formed *R*- or *S*-stereocenter would be furnished based upon the absolute stereochemistry of the carbinol substrate. Hence, we required con-



Scheme 1. Conceptualized route to asymmetric 2,4-disubstituted butyrolactones and related examples.

* Corresponding author. E-mail address: snowden@bama.ua.edu (T.S. Snowden).

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venient and affordable access to asymmetric 3-ketotrichloromethyl carbinols **5**, bearing disparate 'R-groups', to initiate the approach.

The research groups of Fujisawa and Romo took advantage of the chirality resident in (*S*)- or (*R*)-4-trichloromethyl-2-oxetanone[6] (Wynberg lactone **7**)[7] to synthesize select 3-hydroxytrichloromethyl carbinols (**8** and **10**, Scheme 1).[8] Each group also described a single example of substituted butyrolactone preparation by an approach involving *gem*-dichloroepoxides. Fujisawa briefly noted the formation of C_4 epimeric **9** in 75% yield after treatment of 1-trichloromethyl-1,3-diol (**8**) in basic media. However, no reaction details or other examples were disclosed. Romo prepared monosubstituted (*S*)-2-azidolactone **11** starting from Wynberg lactone. Notably, **11** was formed with only 2.5% racemization under the reaction conditions employed. Inspired by these successes, we elected to exploit **7** for entry to **5** with the intention of preparing stereodefined lactones (**1**). We expected the proposed route to be particularly powerful given the variety of substituents amenable to incorporation at C_2 and C_4 of **1**.

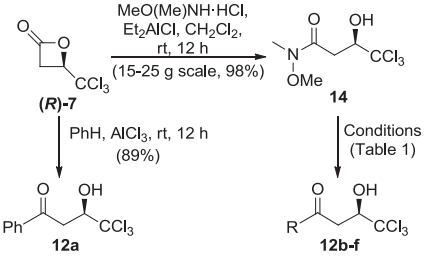
2. Results and discussion

2.1. Preparation of chiral trichloromethyl β-hydroxyketones

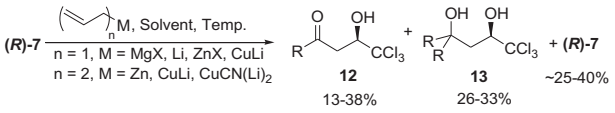
We began by investigating formation of the requisite ketones (**5**) by addition of common organometallic reagents to (*R*)-**7**.[9] Although **7** smoothly undergoes Lewis acid-mediated Friedel–Crafts acylation with aromatic substrates (entry 1, Table 1),[10] we discovered that treatment with 1.0 equiv of an allyl lithium, magnesium, zinc, or copper reagent afforded roughly equal mixtures of **12** and **13** and (*R*)-**7** (Scheme 2). Attempted Sakurai allylation using allyltrimethylsilane and $BF_3{\cdot}Et_2O$ also proved unsatisfactory. These results suggest that the carbonyl reforms after addition to **7** with concomitant β-lactone ring opening. The resultant β-alkoxy ketone, presumably activated by metal-chelation, shows comparable reactivity to **7** thereby precluding selective addition to the oxetanone.

We resorted to Weinreb amidation of **7** to deter regeneration of the carbonyl following the initial addition to **14**, thereby inhibiting the formation of **13**.[11] We found that amidations conducted under Lewis acidic conditions afforded **14** in excellent yields, even on multigram scales (Table 1).[12] This preparation proved superior in reaction time, yields, and scalability to amidations using DIEA.

Table 1
Preparations of β-hydroxyketones **12**



Entry	R	Conditions	Product	Yield (%)
1	Ph	PhH, $AlCl_3$, rt, 12 h directly from (*R*)-7	**12a**	89
2	2-Furyl	1.0 equiv *i*-PrMgCl, then 1.25 equiv furyl lithium, THF, −15 °C, 4 h;	**12b**	85
3	2-Thienyl	1.0 equiv *i*-PrMgCl, then 1.25 equiv thienyl lithium, THF, −15 °C, 4 h;	**12c**	87
4	Allyl	1.0 equiv *i*-PrMgCl, then 1.25 equiv allylMgCl, THF, −15 °C, 4 h;	**12d**	88
5	Vinyl	1.0 equiv *i*-PrMgCl, then 1.25 equiv vinylMgBr, THF, −15 °C, 4 h;	**12e**	73
6	n-C_6H_{13}	2.25 equiv hexylMgBr, PhMe, −15 °C, 4 h	**12f**	68



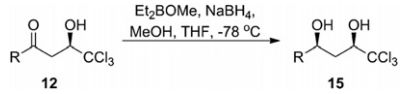
Scheme 2. Additions to Wynberg lactone (*R*)-**7**.

The Weinreb amide was reliably converted to asymmetric β-hydroxyketones by treatment with excess of any of several freshly prepared organolithium or commercial Grignard reagents (Table 1). We found that preliminary hydroxyl deprotonation by introduction of *i*-PrMgCl, followed by addition of the desired nucleophile offered superior yields in most cases (entries 2–5).[13] Maintaining reaction temperatures *below* −10 °C was critical, because higher temperatures permitted some double addition. It was necessary to quench cold reaction mixtures of **12d** and **12e** by rapid transfer through a chilled solution of 1 N $HCl_{(aqueous)}$ to circumvent *N*-methoxymethanamide conjugate addition to the newly formed enone in **12e** and to the crotonyl ketone resulting from *N*-methoxymethanamide-promoted alkene isomerization in **12d**.[14]

2.2. Directed reductions to *syn*- or *anti*-1,3-diols

Next we explored directed *syn*- and *anti*-1,3-reductions of ketones **12** to establish the γ-stereocenter in the prospective substituted butyrolactones. After surveying several methods, we found that diethylmethoxyborane and $NaBH_4$ in cold methanol/THF furnished *syn*-diols (**15**) in 79–97% yields and with good to exceptional diastereoselectivities (Table 2).[15] *anti*-Diols (**16**) were rendered with comparable results using Evans' triacetoxyborohydride/anhydrous acetic acid protocol (Table 3).[16] In both reactions, the minor diastereomers were easily separated by column chromatography affording diols of high enantiopurity.

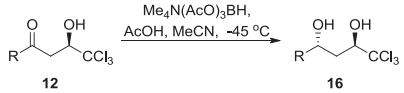
Table 2
Directed *syn*-reductions of **12**



Entry	R	*syn*-Diol	Yield[a] (%)	dr[b]
1	Ph	**15a**	97	>98:2
2	2-Furyl	**15b**	88	91:9
3	2-Thienyl	**15c**	94	>98:2
4	$H_2C{=}CHCH_2-$	**15d**	79	93:7
5	$H_2C{=}CH-$	**15e**	79	92:8
6	n-C_6H_{13}	**15f**	85	87:13

[a] Yield of purified *major diastereomer*.
[b] Established from ^1H NMR spectra of crude reaction mixtures.

Table 3
Directed *anti*-reductions of **12**



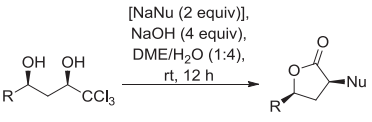
Entry	R	*anti*-Diol	Yield[a] (%)	dr[b]
1	Ph	**16a**	85	94:6
2	2-Furyl	**16b**	89	91:9
3	2-Thienyl	**16c**	80	> 98:2
4	$H_2C{=}CHCH_2-$	**16d**	79	90:10
5	$H_2C{=}CH-$	**16e**	77	90:10
6	n-C_6H_{13}	**16f**	92	94:6

[a] Yield of purified *major diastereomer*.
[b] Established from ^1H NMR spectra of crude reaction mixtures.

2.3. Preparation of *cis*-2,4-disubstituted butyrolactones

Targeted *cis*-2,4-disubstituted lactones were prepared by dissolving the corresponding diols in DME/H_2O, adding 4.0 equiv of NaOH followed by 2.0 equiv of the desired nucleophile for incorporation at C_2, and mixing at ambient temperature for 12 h (Table 4). Notably, the relatively high nucleophilicity of azide in protic media allows for its, rather than the solvated hydroxide's, selective substitution with **3**.[17] The workup procedure has a critical impact on yield, because the products exist as a mixture of disubstituted lactones and carboxylates prior to acidification. Hence, the reaction mixture was quenched by addition of HCl to afford an aqueous solution of pH=2–3. This was mixed vigorously for 1–4 h to promote lactonization (readily monitored by TLC analysis), then the products were extracted to furnish **17** in uniformly high yields, independent of the selected nucleophile.[18] As expected, the dichloroepoxide substitution occurred with stereospecific inversion of configuration. Gratifyingly, little or no epimerization occurred after cyclization, with **17f** exhibiting only 5–7% epimerization in the worst case.

Table 4
Preparation of *cis*-disubstituted butyrolactones **17**



15 17

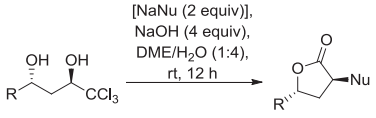
Entry	R	Nu	*cis*-Lactone[a]	Yield[b] (%)	dr[c]
1	Ph[d]	N_3	**17a**	98	>98:2
2		OH	**17b**	93	95:5
3	2-Furyl	N_3	**17c**	72	94:6
4		OH	**17d**	66	94:6
5	2-Thienyl	N_3	**17e**	98	>98:2
6		OH	**17f**	90	93:7
7	Allyl	N_3	**17g**	93	>98:2
8		OH	**17h**	95	>98:2
9	Vinyl	N_3	**17i**	69	94:6
10		OH	**17j**	69	94:6
11	*n*-C_6H_{13}[d]	N_3	**17k**	90	>98:2
12		OH	**17l**	95	96:4

[a] Reactions conducted by dissolving 1 mmol of **15** in 5 mL DME/H_2O (1:4 v/v) then adding 4 mmol of NaOH followed by 2 mmol of desired nucleophile (NaOH or NaN_3) with rapid mixing at rt for 12 h. Workup by extraction at pH 2–3.
[b] Yield of purified *major diastereomer*.
[c] Established from ^{1}H spectra of crude reaction mixtures.
[d] Reactions required 24 h to reach completion due to limited solubility in DME/H_2O.

2.4. Preparation of *trans*-2,4-disubstituted butyrolactones

The *trans*-2,4-disubstituted lactones (**18**) were generated in an analogous manner with one important exception. When cyclization of the *anti*-diols (**16**) was conducted at a 0.2 M substrate concentration, significant quantities of epimerized products were obtained. We found that decreasing the *anti*-diol concentration to 0.05 M in DME/H_2O offered meaningful decreases in epimerization (Table 5, entries 1–3). We anticipated that reactions involving higher concentrations of diol and base (Table 5, entries 1 and 2) would feature a higher rate of enolization, thereby partially equilibrating more of the *trans*-disubstituted lactone to the lower energy *cis*-diastereomer **17**, vide infra, during the course of the reaction. At the 0.05 M substrate concentration, lactones **18** were prepared in good yields and with acceptable diastereoselectivities (Table 5, entries 3–14).[18] As with the diastereomeric diols, the major *cis*- and *trans*-lactone stereoisomers were readily separated by chromatography, with the exception of **18h** and **18j**, which could not be purified to homogeneity. Importantly, the α-azido lactones may be converted to the corresponding α-amino derivatives by Staudinger reduction in excellent reported yields.[19]

Table 5
Preparation of *trans*-disubstituted butyrolactones **18**

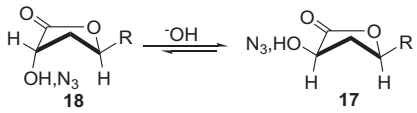


16 18

Entry	R	Nu	*trans*-Lactone[a]	Yield[b] (%)	dr[c]
1	Ph[d]	N_3 (0.2 M)	**18a**	—	70:30
2		N_3 (0.125 M)	**18a**	—	78:22
3		N_3 (0.05 M)	**18a**	70	86:14
4		OH	**18b**	69	85:15
5	2-Furyl	N_3	**18c**	60	84:16
6		OH	**18d**	52	75:25
7	2-Thienyl	N_3	**18e**	83	84:16
8		OH	**18f**	71	80:20
9	Allyl	N_3	**18g**	88	90:10
10		OH	**18h**	78[e]	88:12
11	Vinyl	N_3	**18i**	55	82:18
12		OH	**18j**	—[f]	80:20
13	*n*-C_6H_{13}[d]	N_3	**18k**	74	84:16
14		OH	**18l**	69	80:20

[a] Reactions conducted by dissolving 1 mmol of **16** in 20 mL DME/H_2O (1:4 v/v) then adding 4 mmol of NaOH followed by 2 mmol of desired nucleophile (NaOH or NaN_3) with rapid mixing at rt for 12 h. Workup by extraction at pH 2–3.
[b] Yield of purified *major diastereomer*.
[c] Established from ^{1}H spectra of crude reaction mixtures.
[d] Reactions required 24 h to reach completion due to limited solubility in DME/H_2O.
[e] The yield is reported for the mixture of inseparable diastereomers.
[f] Product could not be purified to homogeneity.

Portions of both the *cis*- and *trans*-disubstituted lactones are deprotonated to form enolates under the basic reaction conditions—although once the lactones are hydrolyzed to the β-hydroxycarboylates, enolization is precluded based upon the reduced acidity of the carboxylate α-methyne position. The different extents of epimerization between the *cis*- and *trans*-disubstituted lactones may be rationalized by considering the relative stabilities of the configurational isomers,[20] and not the relative susceptibilities of each to α-deprotonation, since the cis diastereomers are presumably more acidic than the trans because of the favorable alignment of the α-C–H σ-bond and the carbonyl π* orbital in **17**. The *cis*-2,4-disubstituted lactones **17** assume an envelope conformation where the cis-substituents preferentially reside in pseudoequatorial positions (Fig. 1). Conversely, the *trans*-epimers (**18**) have one substituent in a pseudoaxial position, thereby experiencing some interaction with the alternate pseudoaxial hydrogen. Hence, **18** are more susceptible to isomerization, because the enolate from the trans-diastereomer is funneled toward the lower energy cis-isomer during reprotonation, although only partial equilibration of the *trans*-lactones is attained during the reaction. This rationale also explains, at least in part, the greater epimerization of the α-hydroxy-substituted lactones compared to the α-azido products, since hydroxyl groups are highly solvated in protic media exacerbating the interaction with the pseudoaxial hydrogen relative to the trans-products bearing an azide.[21] Intramolecular hydrogen bond stabilization of 2-hydroxylactones in **17** relative to **18** may also play a role, although such an interaction may be mitigated by the polar protic media. Another possible explanation



18 17

Fig. 1. Configurational partial equilibration in **18**.

for the greater extent of epimerization of **18** relative to **17** is the higher susceptibility of **17** to nucleophilic acyl substitution with hydroxide on steric grounds. If such a rate difference is significant, lactones **18** will have a longer lifetime in the reaction milieu, and a greater opportunity for α-deprotonation–reprotonation leading to more extensive epimerization than **17**.

3. Conclusions

We devised a versatile route to any of the four possible stereoisomers of 2,4-disubstituted butyrolactones from (*R*)- or (*S*)-Wynberg lactone in just three or four steps.[9] The approach is amenable to installation of varied carbon substituents at C_4 and heteroatom functionalities at C_2 and should be attractive for diversity-oriented or target-directed synthesis applications.

4. Experimental section

4.1. General information

The ^{1}H and ^{13}C NMR spectra were recorded at 360 or 500 MHz and 90 or 125 MHz, respectively, and were referenced to acetone-d_6 (2.05 and 30.83 ppm) or $CDCl_3$ (7.26 and 77.0 ppm). High-resolution mass spectra were recorded on an AutoSpec-Ultima™ NT mass spectrometer using electron ionization (EI) at 70 eV. All melting points are uncorrected. TLC visualization was achieved by UV light (254 nm) or $KMnO_4$ staining. Commercial alkyl, allyl, and vinyl Grignard reagents were purchased as 1.0 or 2.0 M solutions in THF or diethyl ether from Aldrich and were used without titration. Thienyl lithium was used directly from a Sure-seal bottle that was purchased as a 1 M solution in hexanes from Aldrich. Alkyl lithium reagents (e.g., butyllithium) were titrated using the procedure of Kofron and Baclawski.[22]

Acetonitrile and benzene were dried over 4 Å molecular sieves prior to use. Diisopropylethyl amine was used directly from a Sure-seal bottle that was purchased from Aldrich. THF and Et_2O were distilled from sodium benzophenone ketyl radical. Dichloromethane was distilled from calcium hydride. Chloral was purchased from Riedel-de Haën and distilled neat onto 4 Å molecular sieves. Acetyl chloride was distilled from one-tenth the volume of *N*,*N*-dimethylaniline. Anhydrous acetic acid was prepared by stirring a 1:1 mixture of acetic acid with acetic anhydride for 1 h, and then the acetic acid was distilled onto 4 Å molecular sieves.

4.2. Synthesis of (*R*)-7 and 14

*4.2.1. (R)-4-Trichloromethyl-2-oxetanone ((R)-**7**).* (*R*)-4-Trichloromethyl-2-oxetanone ((*R*)-**7**) is occasionally commercially available from Aldrich, or it can be prepared on a 250 mmol scale using the following protocol.[7,23] A dry 1 L three-neck round-bottom flask was fitted with two dry addition funnels under a blanket of argon. The three-neck round-bottom flask was charged with quinidine (1.25 mmol, 406 mg) and freshly distilled diethyl ether (165 mL). Anhydrous diisopropylethyl amine (287.5 mmol, 47.5 mL) was added and the solution was cooled to −15 °C. A solution of freshly distilled chloral (250 mmol, 24.4 mL) in 115 mL of anhydrous diethyl ether was added to one of the addition funnels. A solution of freshly distilled acetyl chloride (250 mmol, 17.8 mL) in 115 mL of anhydrous diethyl ether was added to the other addition funnel. The chloral and the acetyl chloride solutions were added to the reaction mixture simultaneously over 1 h at approximately equal rates. After the addition was complete, the reaction mixture was stirred for an additional 2 h. Aqueous 1 N HCl (125 mL) was added and the reaction mixture was warmed to room temperature. The phases were separated, and the aqueous phase was extracted with diethyl ether (3×30 mL). The combined organic phases were washed with aqueous 1 N HCl (3×25 mL) and then dried with $MgSO_4$ and concentrated. The crude product was purified by bulb-to-bulb distillation at 82 °C and 0.2 mmHg to obtain 4-trichloromethyl-2-oxetanone (**7**) as a white solid, which was a mixture of enantiomers. $[\alpha]^{20}_{578}$ −10.7 (*c* 1.0, cyclohexane). The major enantiomer was isolated by recrystallization from methylcyclohexane to obtain white solid (*R*)-**7** (29.4 g, 62% yield), mp 51–52 °C, $[\alpha]^{20}_{578}$ −15.6 (*c* 1.0, cyclohexane), equal to 98% ee.[7a] ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm: 5.00 (dd, *J*=5.7, 3.6 Hz, 1H), 3.72 (dd, *J*=5.7, 11.4 Hz, 1H), 3.60 (dd, *J*=3.6, 11.4 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ ppm: 163.8, 96.7, 76.1, 42.5.

*4.2.2. (R)-4,4,4-Trichloro-3-hydroxy-N-methoxy-N-methylbutanamide (**14**).* (*R*)-4,4,4-Trichloro-3-hydroxy-*N*-methoxy-*N*-methylbutanamide was prepared by a modified Shimizu and Nakata method.[12] A two-neck flask was charged with a solution of Me_2AlCl (1.0 M in hexane, 150 mmol, 150 mL) (CAUTION: pyrophoric!) and diluted with CH_2Cl_2 (150 mL). Then *N*,*O*-dimethylhydroxylamine hydrochloride (150 mmol, 14.5 g) was added portionwise over a 15 min period under argon at 0 °C. The mixture was warmed to room temperature and stirred for 1 h. Then, a solution of (*R*)-**7** (75 mmol, 4.2 g) in DCM (750 mL) was added portionwise over a period of 10 min via syringe. After mixing at room temperature for 12 h, the reaction mixture was added to a saturated aqueous solution of NH_4Cl (3 mL per 1 mmol of Me_2AlCl) at 0 °C, and stirring was continued for 10 min. The reaction mixture was diluted with DCM, filtered through a pad of Celite, and then the Celite was washed thoroughly with DCM. The aqueous layer was extracted with DCM (3×5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel flash column chromatography using 6:4 hexanes/EtOAc as the eluent to give (*R*)-4,4,4-trichloro-3-hydroxy-*N*-methoxy-*N*-methylbutanamide (**14**) as a white solid (18.5 g, 98% yield), mp 47–48 °C, $[\alpha]^{20}_{D}$ +39.0 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 5.12 (d, *J*=4.3 Hz, 1H), 4.64–4.61 (m, 1H), 3.69 (s, 3H), 3.17 (s, 3H), 3.04 (d, *J*=16.1 Hz, 1H), 2.92 (dd, *J*=16.1, 9.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 170.9, 102.7, 79.0, 61.3, 34.3, 32.0; FTIR: 3373 (s), 2978 (m), 2943 (s), 1635 (s), 1462 (s) cm^{-1}; HRMS *m*/*z* calcd for $C_7H_9Cl_3O_2$ 248.9726; found 248.9721.

4.3. Synthesis of (*R*)-β-ketotrichloromethyl carbinols (12)

*4.3.1. (R)-4,4,4-Trichloro-3-hydroxy-1-phenylbutan-1-one (**12a**).* Compound **12a** was prepared by a modification of Fujisawa's reported procedure.[8a] To a solution of powdered $AlCl_3$ (3.75 mmol, 500 mg) in benzene (20.0 mL) was added a solution of (*R*)-**7** (1 mmol, 189 mg) in benzene (10 mL) at 0 °C. The mixture was warmed to room temperature and stirred. After 12 h, the reaction mixture was cooled to 0 °C and quenched with aqueous saturated NH_4Cl (~20 mL). The aqueous layer was extracted with benzene (3×5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel flash column chromatography using 8:2 hexanes/Et_2O as the eluent to give (*R*)-4,4,4-trichloro-3-hydroxy-1-phenylbutan-1-one (**12a**) as a white solid (239 mg, 89% yield), mp 62–63 °C, $[\alpha]^{20}_{D}$ +35.2 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm: 7.98–7.96 (m, 2H), 7.61–7.57 (m, 1H), 7.46 (t, *J*=7.6 Hz, 2H), 4.91 (ddd, *J*=8.7, 5.0, 2.1 Hz, 1H), 4.39 (d, *J*=5.0 Hz, 1H), 3.62 (dd, *J*=17.4, 2.1 Hz, 1H), 3.52 (dd, *J*=17.4, 8.7 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ ppm: 197.1, 136.3, 133.9, 128.8, 128.3, 102.5, 79.0, 40.7; FTIR: 3464 (m), 3055 (m), 2927 (w), 1686 (s), 1446 (w) cm^{-1}; HRMS *m*/*z* calcd for $C_{10}H_9Cl_3O_2$ 265.9668; found 247.9562, which corresponds to $[M-H_2O]^+$.

*4.3.2. (R)-4,4,4-Trichloro-1-(furan-2-yl)-3-hydroxybutan-1-one (**12b**).* *n*-Butyllithium (500 μL of a 2.5 M solution in hexanes, 1.25 mmol) was added slowly to a stirred solution of furan (100 μL, 1.38 mmol) in dry THF (0.55 mL) at −78 °C under a blanket of argon.

The solution was allowed to warm to 0 °C, stirred for an additional 30 min, and then cooled to −40 °C. To a solution of Weinreb amide **14** (251 mg, 1 mmol) in anhydrous THF (2 mL) in a separate round-bottom flask at −15 °C, was added isopropylmagnesium chloride (2 M in THF, 0.96 mmol, 0.48 mL). After 1 h, the −40 °C furyl lithium solution (2.5 M in THF, 1.25 mmol) was added dropwise via cannula and the reaction mixture was stirred for an additional 4 h at −15 °C. The cold reaction was quenched by transferring it through a 0 °C 1 M aqueous HCl solution via cannula. The temperature was allowed to rise to room temperature, the mixture was diluted with EtOAc, and the layers were separated. The aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel flash column chromatography using 8:2 hexanes/Et_2O as the eluent to give the (*R*)-4,4,4-trichloro-1-(furan-2-yl)-3-hydroxybutan-1-one (**12b**) as a white solid (219 mg, 85% yield), mp 66–67 °C, $[\alpha]_D^{20}$ +30.8 (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.64 (dd, *J*=0.5, 1.5 Hz, 1H), 7.29 (dd, *J*=0.5, 3.5 Hz, 1H), 6.58 (dd, *J*=3.5, 1.5 Hz, 1H), 4.83 (ddd, *J*=2.0, 4.0, 9.0 Hz, 1H), 3.67 (d, *J*=4.0 Hz, 1H), 3.50 (dd, *J*=2.0, 17.0 Hz, 1H), 3.37 (dd, J=9.0, 17.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 185.6, 152.2, 147.1, 118.3, 112.6, 102.5, 78.7, 40.6; FTIR: 3400 (m), 3054 (m), 2986 (m), 1670 (m), 1421 (m) cm^{-1}; HRMS *m*/*z* calcd for $C_8H_7Cl_3O_3$ 255.9461; found 255.9461.

*4.3.3. (R)-4,4,4-Trichloro-3-hydroxy-1-(thiophen-2-yl)butan-1-one (**12c**).* To a solution of Weinreb amide **14** (251 mg, 1 mmol) in anhydrous THF (2 mL) at −15 °C, was added isopropylmagnesium chloride (2 M in THF, 0.96 mmol, 0.48 mL) and the reaction mixture was stirred for 1 h. Thienyl lithium (1 M in hexanes, 1.25 mmol, 1.25 mL) was added and reaction mixture was stirred for an additional 4 h. The −15 °C reaction was quenched by transferring it through a 0 °C 1 M aqueous HCl solution via cannula. The temperature was allowed to rise to room temperature, the mixture was diluted with EtOAc, and the layers were separated. The aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel flash column chromatography using 8:2 hexanes/Et_2O as the eluent to give (*R*)-4,4,4-trichloro-3-hydroxy-1-(thiophen-2-yl)butan-1-one (**12c**) as a yellow oil (238 mg, 87% yield), $[\alpha]_D^{20}$ +30.0 (*c* 0.50, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$) δ ppm: 7.81 (dd, *J*=3.9, 1.1 Hz, 1H), 7.72 (dd, *J*=5.0, 1.1 Hz, 1H), 7.17 (dd, *J*=5.0, 3.9 Hz, 1H), 4.84 (ddd, *J*=9.0, 4.4, 2.1 Hz, 1H), 3.69 (dd, *J*=4.4, 0.7 Hz, 1H), 3.58 (ddd, *J*=16.8, 2.1, 0.7 Hz, 1H), 3.43 (dd, *J*=16.8, 9.0 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ ppm: 189.7, 143.3, 134.9, 133.1, 128.3, 102.5, 78.9, 41.3; FTIR: 3437(s), 3053 (w), 2981 (w), 1660 (s), 1421(m) cm^{-1}; HRMS *m*/*z* calcd for $C_8H_7Cl_3O_2S$ 271.9232; found 271.9231.

*4.3.4. (R)-7,7,7-Trichloro-6-hydroxyhept-1-en-4-one (**12d**).* To a solution of Weinreb amide **14** (251 mg, 1 mmol) in anhydrous THF (2 mL) at −15 °C, was added isopropylmagnesium chloride (2 M in THF, 0.96 mmol, 0.48 mL) and the reaction mixture was stirred for 1 h. Allylmagnesium chloride (2 M in THF, 1.25 mmol, 0.625 mL) was added, and the reaction mixture was stirred for an additional 4 h. The −15 °C reaction was quenched by transferring it through a 0 °C 1 M aqueous HCl solution via cannula. The temperature was allowed to rise to room temperature, the mixture was diluted with EtOAc, and the layers were separated. The aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel flash column chromatography using 8:2 hexanes/Et_2O as the eluent to give (*R*)-7,7,7-trichloro-6-hydroxyhept-1-en-4-one (**12d**) as a yellow oil (204 mg, 88% yield), $[\alpha]_D^{20}$ +33.6 (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 5.92–5.81 (m, 1H), 5.20–5.11 (m, 2H), 4.63 (dd, *J*=9.0, 2.1 Hz, 1H), 4.45 (br s, 1H), 3.24 (d, *J*=6.9 Hz, 2H), 3.07 (dd, *J*=17.4, 2.1 Hz, 1H), 2.93 (dd, *J*=17.4, 9.0 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ ppm: 205.7, 129.4, 119.6, 102.5, 78.3, 48.3, 44.1; FTIR: 3421 (s), 3055 (w), 2962 (w), 1716 (m), 1417 (m) cm^{-1}; HRMS *m*/*z* calcd for $C_7H_9Cl_3O_2$ 229.9668; found 113.0599, which corresponds to [M−CCl_3].

*4.3.5. (R)-6,6,6-Trichloro-5-hydroxyhex-1-en-3-one (**12e**).* To a solution of Weinreb amide **14** (251 mg, 1 mmol) in anhydrous THF (2 mL) at −15 °C was added isopropylmagnesium chloride (2 M in THF, 0.96 mmol, 0.48 mL). The reaction mixture was stirred for 1 h, then vinylmagnesium chloride (1 M in THF, 1.25 mmol, 1.25 mL) was added, and the reaction mixture was stirred for an additional 4 h. The −15 °C reaction was quenched by transferring it through a 0 °C 1 M aqueous HCl solution via cannula. The temperature was allowed to rise to room temperature, the mixture was diluted with EtOAc, and the layers were separated. The aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel flash column chromatography using 8:2 hexanes/Et_2O to give (*R*)-6,6,6-trichloro-5-hydroxyhex-1-en-3-one (**12e**) as a white solid (159 mg, 73% yield), mp 36–37 °C, $[\alpha]_D^{20}$ +29.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$) δ ppm: 6.42 (dd, *J*=17.7, 10.1 Hz, 1H), 6.32 (dd, *J*=17.7, 1.2 Hz, 1H), 5.96 (dd, *J*=10.1, 1.2 Hz, 1H), 4.73 (ddd, *J*=8.9, 4.6, 2.1 Hz, 1H), 3.73 (dd, *J*=4.6, 1.0 Hz, 1H), 3.26 (ddd, *J*=17.3, 2.1, 1.0 Hz, 1H), 3.12 (dd, *J*=17.3, 8.9 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ ppm: 197.4, 136.1, 130.2, 102.5, 78.5, 41.4; FTIR: 3460 (s), 3055 (s), 2987 (m), 2306 (m), 1709 (s), 1421 (s) cm^{-1}; HRMS *m*/*z* calcd for $C_6H_7Cl_3O_2$ 215.9512, found 99.0520, which corresponds to [M−CCl_3].

*4.3.6. (R)-1,1,1-Trichloro-2-hydroxydecan-4-one (**12f**).* To a solution of Weinreb amide **14** (251 mg, 1 mmol) in anhydrous toluene (5 mL) at −15 °C, was added hexylmagnesium bromide (2 M in diethyl ether, 2.26 mmol, 1.13 mL), and the reaction mixture was stirred for an additional 12 h. The −15 °C reaction was quenched by transferring it through a 0 °C 1 M aqueous HCl solution via cannula. The temperature was allowed to rise to room temperature, the mixture was diluted with EtOAc, and the layers were separated. The aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel flash column chromatography using 8:2 hexanes/Et_2O as the eluent to give (*R*)-1,1,1-trichloro-2-hydroxydecan-4-one (**12f**) as a yellow oil (186 mg, 68% yield), $[\alpha]_D^{20}$ +25.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 4.65 (ddd, *J*=9.1, 4.4, 2.0 Hz, 1H), 3.74 (d, *J*=4.4 Hz, 1H), 3.07 (dd, *J*=17.3, 2.0 Hz, 1H), 2.90 (dd, *J*=17.3, 9.1 Hz, 1H), 2.50 (t, *J*=7.5 Hz, 2H), 1.69 (br s, 1H), 1.62–1.59 (m, 1H), 1.32–1.29 (m, 6H), 0.88 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 208.2, 102.5, 78.8, 44.3, 43.9, 31.5, 28.7, 23.5, 22.4, 14.0; FTIR: 3423 (m), 3055 (m), 2986 (m), 2859 (m), 1716 (m) cm^{-1}; HRMS *m*/*z* calcd for $C_{10}H_{17}Cl_3O_2$ 274.0294, found 274.0302.

4.4. General procedure for the synthesis of *syn*-diols (15)

The *syn*-diols (**15**) were prepared by a modification of the procedure reported by Prasad et al.[15] To a solution of a β-ketotrichloromethyl carbinol **12** (1 mmol) in freshly distilled THF (10 mL) and anhydrous methanol (2 mL) at room temperature under argon was added diethylmethoxyborane (0.14 mL, 1.2 mmol) via syringe. The reaction mixture was stirred at room temperature for 30 min and then cooled to −70 °C. Sodium borohydride (53 mg, 1.4 mmol) was added under positive pressure of argon. The mixture was stirred for 12 h at −70 °C then quenched at −70 °C by addition of 0.5 mL of 30% aqueous H_2O_2. The mixture was allowed to warm slowly to ambient temperature then concentrated. The residue was dissolved in water (2 mL) and extracted with EtOAc (3×5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated.

The mixture was purified by flash chromatography on silica gel to afford the corresponding *syn*-diol (**15**) as outlined below.

*4.4.1. (1S,3R)-4,4,4-Trichloro-1-phenylbutane-1,3-diol (**15a**).* The crude material was purified by silica gel flash chromatography using 6:4 hexane/Et_2O as the eluent. The indicated compound was obtained as a yellow oil (261 mg, 97% yield), mp 120–121 °C, $[\alpha]_D^{20}$ +41.2 (*c* 1.0, CH_2Cl_2). ^1H NMR (360 MHz, acetone-d_6) δ ppm: 7.45–7.26 (m, 5H), 5.88 (d, *J*=5.3 Hz, 1H), 5.04–4.99 (m, 1H), 4.73 (d, *J*=3.5 Hz, 1H), 4.02–3.97 (m, 1H), 2.44–2.38 (m, 1H), 2.25–2.17 (m, 1H); ^{13}C NMR (90 MHz, acetone-d_6) δ ppm: 146.2, 130.1, 129.3, 128.0, 106.0, 82.8, 73.6, 42.8; FTIR: 3415 (s), 3055 (w), 2987 (w), 1641 (s), 1421 (w) cm^{-1}; HRMS *m*/*z* calcd for $C_{10}H_{11}Cl_3O_2$ 267.9825; found 267.9818.

*4.4.2. (1S,3R)-4,4,4-Trichloro-1-(furan-2-yl)butane-1,3-diol (**15b**).* The crude material was purified by silica gel flash chromatography using 6:4 hexane/Et_2O as the eluent. The indicated compound was obtained as a white solid (228 mg, 88% yield), mp 102–103 °C, $[\alpha]_D^{20}$ +9.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.41 (dd, *J*=1.8, 0.8 Hz, 1H), 6.37 (dd, *J*=3.2, 1.8 Hz, 1H), 6.34 (d, *J*=3.2 Hz, 1H), 5.06–5.02 (m, 1H), 4.22 (ddd, *J*=10.0, 3.8, 2.0 Hz, 1H), 3.85 (dd, *J*=3.8, 0.8 Hz, 1H), 2.83 (d, *J*=3.8 Hz, 1H), 2.64–2.60 (m, 1H), 2.31–2.25 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 154.7, 142.5, 110.3, 106.7, 102.7, 81.7, 66.4, 36.7; FTIR: 3428 (m), 3054 (m), 2986 (m), 1421 (m) cm^{-1}; HRMS *m*/*z* calcd for $C_8H_9Cl_3O_3$ 257.9671; found 257.9626.

*4.4.3. (1S,3R)-4,4,4-Trichloro-1-(thiophen-2-yl)butane-1,3-diol (**15c**).* The crude material was purified by silica gel flash chromatography using 6:4 hexane/Et_2O as the eluent. The indicated compound was obtained as a yellow oil (259 mg, 94% yield), $[\alpha]_D^{20}$ +10.0 (*c* 0.6, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$) δ ppm: 7.31 (d, *J*=5.0 Hz, 1H), 7.06 (d, *J*=3.0 Hz, 1H), 7.00 (dd, *J*=5.0, 3.6 Hz, 1H), 5.32–5.27 (m, 1H), 4.25–4.21 (m, 1H), 3.78 (d, *J*=3.7 Hz, 1H), 2.89 (d, *J*=2.7 Hz, 1H), 2.57 (dd, *J*=14.2, 3.7 Hz, 1H), 2.36–2.29 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ ppm: 146.6, 126.8, 125.3, 124.3, 102.7, 81.9, 69.0, 40.3; FTIR: 3417 (s), 3055 (s), 2987 (m), 2306 (m), 1423 (m) cm^{-1}; HRMS *m*/*z* calcd for $C_8H_9Cl_3O_2S$ 273.9389; found 273.9372.

*4.4.4. (2R,4R)-1,1,1-Trichlorohept-6-en-2,4-diol (**15d**).* The crude material was purified by silica gel flash chromatography using 6:4 hexane/Et_2O as the eluent. The indicated compound was obtained as a colorless oil (184 mg, 79% yield), $[\alpha]_D^{20}$ +41.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$) δ ppm: 5.88–5.77 (m, 1H), 5.22–5.16 (m, 2H), 4.31 (dt, *J*=10.0, 2.1 Hz), 4.23 (d, *J*=2.1 Hz, 1H), 4.05–3.97 (m, 1H), 2.59 (d, *J*=2.1 1H), 2.42–2.25 (m, 3H), 1.88–1.79 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 133.4, 119.2, 102.8, 82.7, 70.1, 42.2, 37.3; FTIR: 3581 (m), 3055 (s), 2985(s), 2306 (m), 1423 (s) cm^{-1}; HRMS *m*/*z* calcd for $C_7H_{11}Cl_3O_2$ 231.9825; found 115.0757, which corresponds to $[M-CCl_3]^+$.

*4.4.5. (2R,4S)-1,1,1-Trichlorohex-5-en-2,4-diol (**15e**).* The crude material was purified by silica gel flash chromatography using 6:4 hexane/Et_2O as the eluent. The indicated compound was obtained as a white solid (173 mg, 79% yield), mp 40–41 °C, $[\alpha]_D^{20}$ +5.9 (*c* 1.0, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$) δ 6.05–5.88 (m, 1H), 5.35 (m, 1H), 5.25–5.17 (m, 1H), 4.52–4.41 (m, 1H), 4.29 (d, *J*=9.9 Hz, 1H), 3.93 (s, 1H), 2.41 (s, 1H), 2.30 (ddd, *J*=14.4, 4.0, 2.0 Hz, 1H), 1.99–1.90 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 139.3, 116.1, 102.8, 82.0, 71.9, 37.7; FTIR: 3584 (m), 3055 (s), 2987 (s), 2306 (m), 1425 (m) cm^{-1}; HRMS *m*/*z* calcd for $C_6H_9Cl_3O_2$ 217.9668; found 101.0603, which corresponds to $[M-CCl_3]^+$.

*4.4.6. (2R,4R)-1,1,1-Trichlorodecane-2,4-diol (**15f**).* The crude material was purified by silica gel flash chromatography using 6:4 hexane/Et_2O as the eluent. The indicated compound was obtained as a colorless oil (236 mg, 85% yield), $[\alpha]_D^{20}$ +20.0 (*c* 5.0, CH_2Cl_2), ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 4.94 (s, 1H), 4.26 (d, *J*=9.7 Hz, 1H), 3.93–3.89 (m, 1H), 3.35 (s, 1H), 2.21 (dt, *J*=14.5, 2.2 Hz, 1H), 1.77 (dt, *J*=14.5, 9.8 Hz, 1H), 1.57–1.46 (m, 2H), 1.35–1.21 (m, 8H), 0.87 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 103.0, 82.8, 71.4, 37.8, 37.5, 31.7, 29.2, 25.1, 22.5, 14.0; FTIR: 3403 (m), 3054 (m), 2986 (m), 2868 (m), 1421 (m) cm^{-1}; *m*/*z* calcd for $C_{10}H_{19}Cl_3O_2$ 258.0345; found 258.0344, which corresponds to $[M-H_2O]^+$.

4.5. General procedure for the synthesis of *anti*-diols (16)

The *anti*-diols (**16**) were prepared by a modification of the method reported by Evans et al.[16] To a solution of tetramethylammonium triacetoxyborohydride (2.148 g, 8 mmol) in anhydrous acetonitrile (4.5 mL) was added anhydrous acetic acid (4.5 mL). The mixture was stirred at room temperature for 1 h. The mixture then was cooled to less than −45 °C (we found that diastereoselectivity was severely compromised when the bath temperature exceeded −4 °C), and a solution of β-ketotrichloromethyl carbinol **12** (1 mmol) in anhydrous acetonitrile (1.5 mL) was added slowly via syringe. The mixture was stirred at −45 to −50 °C for 18–36 h. The reaction was quenched with 15 mL of 0.5 N aqueous sodium potassium tartrate and warmed slowly to room temperature. After diluting with dichloromethane, the layers were separated. The organic phase was then washed with a saturated solution of aqueous sodium bicarbonate. The aqueous phase was back extracted with dichloromethane (4×5 mL), and the combined organic layers were washed with a saturated solution of aqueous sodium bicarbonate until pH >7. The resultant organics were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel to afford the corresponding *anti*-diol (**16**) as outlined below.

*4.5.1. (1R,3R)-4,4,4-Trichloro-1-phenylbutane-1,3-diol (**16a**).* The crude material was purified by silica gel flash chromatography using 6:4 hexane/Et_2O as the eluent. The indicated compound was obtained as a white solid (228 mg, 85% yield), mp 105–10 °C, $[\alpha]_D^{20}$ +65.7 (*c* 2.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.42–7.30 (m, 5H), 5.11 (d, *J*=9.5 Hz, 1H), 4.43 (dd, *J*=9.5, 2.7 Hz, 1H), 3.34 (d, *J*=3.7 Hz, 1H), 2.45 (dd, *J*=14.3, 9.5 Hz, 1H), 2.35 (d, *J*=3.5 Hz, 1H), 2.09–2.04 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 143.7, 128.7, 127.9, 125.5, 103.8, 79.9, 70.9, 40.2; FTIR: 3410 (m), 3055 (m), 2986 (m), 1643 (m), 1423 (m) cm^{-1}; HRMS *m*/*z* calcd for $C_{10}H_{11}Cl_3O_2$ 267.9825; found 267.9828.

*4.5.2. (1R,3R)-4,4,4-Trichloro-1-(furan-2-yl)butane-1,3-diol (**16b**).* The crude material was purified by silica gel flash chromatography using 6:4 hexane/Et_2O as the eluent. The indicated compound was obtained as a white solid (231 mg, 89% yield), mp 81–82 °C, $[\alpha]_D^{20}$ +25.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.40 (d, *J*=2.0 Hz, 1H), 6.36 (dd, *J*=2.0, 3.0 Hz, 1H), 6.32 (d, *J*=3.0 Hz, 1H), 5.11–5.07 (m, 1H), 4.49–4.46 (m, 1H), 3.13 (dd, *J*=1.5, 5.0 Hz, 1H), 2.63–2.57 (m, 1H), 2.28 (d, *J*=6.0 Hz, 1H), 2.17–2.12 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ ppm: 155.6, 142.3, 110.3, 106.2, 103.6, 79.6, 64.6, 36.7; FTIR: 3421 (m), 3054 (m), 2987 (m), 1647 (m), 1421 (m) cm^{-1}; HRMS *m*/*z* calcd for $C_8H_9Cl_3O_3$ 257.9671; found 257.9619.

*4.5.3. (1R,3R)-4,4,4-Trichloro-1-(thiophen-2-yl)butane-1,3-diol (**16c**).* The crude material was purified by silica gel flash chromatography using 6:4 hexane/Et_2O as the eluent. The indicated compound was obtained as a white solid (220 mg, 80% yield), mp 119–12 °C, $[\alpha]_D^{20}$ +41.3 (*c* 2.2, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$) δ ppm: 7.28 (dd, *J*=5.0, 1.3 Hz, 1H), 7.06–7.03 (m, 1H), 7.00 (dd, *J*=5.0, 3.5 Hz, 1H), 5.40–5.32 (m, 1H), 4.49 (ddd, *J*=10.0, 4.7, 1.8 Hz, 1H), 3.17 (dd, *J*=4.7, 1.8 Hz, 1H), 2.56 (ddt, *J*=14.0, 9.5, 1.8 Hz, 1H), 2.48 (dd, *J*=5.2, 0.9 Hz, 1H), 2.24–2.16 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ ppm: 147.5, 126.9, 124.8, 123.7, 103.5, 79.6, 66.9, 40.1; FTIR:

3417 (s), 3055 (s), 2987 (s), 1423 (m) cm^{-1}; HRMS *m*/*z* calcd for $C_8H_9Cl_3O_2S$ 273.9389; found 273.9387.

*4.5.4. (2R,4S)-1,1,1-Trichlorohept-6-ene-2,4-diol (**16d**).* The crude material was purified by silica gel flash chromatography using 6:4 hexane/Et_2O as the eluent. The indicated compound was obtained as a white solid (184 mg, 79% yield), mp 102–10 °C, $[\alpha]_D^{20}$ −40.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$) δ ppm: 5.89–5.78 (m, 1H), 5.22–5.16 (m, 2H), 4.43 (d, *J*=10.0 Hz, 1H), 4.08–4.02 (m, 1H), 3.34 (br s, 1H), 2.42–2.23 (m, 2H), 2.15–2.08 (m, 1H), 1.95 (s, 1H), 1.90–1.83 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ ppm: 133.8, 119.1, 103.9, 79.6, 67.3, 42.0, 37.8; FTIR: 3581 (m), 3055 (s), 2985 (s), 1423 (s) cm^{-1}; HRMS *m*/*z* calcd for $C_7H_{11}Cl_3O_2$ 231.9825; found 115.0757, which corresponds to $[M-CCl_3]^+$.

*4.5.5. (2R,4R)-1,1,1-Trichlorohex-5-ene-2,4-diol (**16e**).* The crude material was purified by silica gel flash chromatography using 6:4 hexane/Et_2O as the eluent. The indicated compound was obtained as a white solid (169 mg, 77% yield), mp 103–104 °C, $[\alpha]_D^{20}$ +22.0 (*c* 1.0, CH_2Cl_2).. ^1H NMR (360 MHz, $CDCl_3$) δ ppm: 5.96 (ddd, *J*=17.2, 10.5, 5.4 Hz, 1H), 5.36 (dt, *J*=17.2, 1.4 Hz, 1H), 5.21 (dt, 10.51, 1.4 Hz, 1H), 4.54 (s, 1H), 4.43–4.39 (m, 1H), 3.48 (d, *J*=4.2 Hz, 1H), 2.23–2.16 (m, 2H), 2.01–1.93 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ ppm: 139.8, 115.3, 103.6, 79.7, 69.6, 37.7; FTIR: 3415 (m), 3054 (m), 2987 (m), 1421 (m) cm^{-1}; HRMS *m*/*z* calcd for $C_6H_9Cl_3O_2$ 217.9668; found 217.9666.

*4.5.6. (2R,4S)-1,1,1-Trichlorodecane-2,4-diol (**16f**).* The crude material was purified by silica gel flash chromatography using 6:4 hexane/Et_2O as the eluent. The indicated compound was obtained as a white solid (255 mg, 92% yield), mp 107–108 °C, $[\alpha]_D^{20}$ +26.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$) δ ppm: 4.39 (dd, *J*=8.3, 1.8 Hz, 1H), 4.02–3.95 (m, 2H), 2.25 (br s, 1H), 2.10–2.05 (m, 1H), 1.89–1.83 (m, 1H), 1.58–1.53 (m, 2H), 1.33–1.30 (m, 8H), 0.88 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ ppm: 104.0, 79.7, 68.8, 38.2, 37.7, 31.7, 29.2, 25.6, 22.6, 14.0; FTIR: 3421 (m), 3055 (m), 2987 (m), 1421 (m) cm^{-1}; HRMS *m*/*z* calcd for $C_{10}H_{19}Cl_3O_2$ 276.0451; found 258.0338, which corresponds to $[M-H_2O]^+$.

4.6. General procedure for the synthesis of *cis*-3-azidodihydro-5-alkylfuran-2(3*H*)-ones and 3-azidodihydro-5-arylfuran-2(3*H*)-ones (17)

The trichloromethyl carbinol **15** (0.25 mmol) in DME/water (0.5:2.0 mL/mL) was placed in a 4-dram vial, and then sodium azide (32 mg, 0.5 mmol) (CAUTION: may explode if ground or contacted by some metal surfaces) and powdered NaOH (40 mg, 1.0 mmol) were added at once. The reaction mixture was vigorously stirred at room temperature until judged complete by TLC analysis (12–24 h), then it was cooled to 0 °C and the pH was adjusted to pH=2 with 0.5 N HCl (or an aqueous solution of KH_2PO_4 with **17c**). This mixture was stirred vigorously for 1–4 h to promote lactonization. The aqueous phase was extracted with EtOAc (5×5 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography using hexane/EtOAc as eluent as outlined below.

4.7. General procedure for the synthesis of *cis*-3-hydroxydihydro-5-alkylfuran-2(3*H*)-ones and 3-hydroxydihydro-5-arylfuran-2(3*H*)-ones (17)

The trichloromethyl carbinol (0.25 mmol) in DME/water (0.5:2 mL/mL) was placed in a 4-dram vial, and then powdered NaOH (40 mg, 1.0 mmol) was added. The reaction mixture was stirred at room temperature until judged complete by TLC analysis (12–24 h), then it was cooled to 0 °C and the pH was adjusted to pH=2 with 0.5 N HCl (or an aqueous solution of KH_2PO_4 with **17d**). This mixture was stirred vigorously for 1–4 h to promote lactonization. The aqueous phase was extracted with EtOAc (5×5 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography using hexane/EtOAc as eluent as outlined below.

*4.7.1. (3S,5S)-3-Azidodihydro-5-phenylfuran-2(3H)-one (**17a**).* The crude material was purified by silica gel flash chromatography using 8:2 hexane/EtOAc as the eluent. The indicated compound was obtained as yellow oil (50 mg, 98% yield), $[\alpha]_D^{20}$ −207.7 (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.42–7.34 (m, 5H), 5.40 (dd, J=10.4, 5.6 Hz, 1H), 4.50 (dd, J=11.1, 8.6 Hz, 1H), 2.98–2.92 (m, 1H), 2.14 (dt, J=12.9, 11.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 172.9, 137.2, 129.1, 128.9, 125.7, 78.4, 58.1, 37.3; FTIR: 2927 (w), 2848 (w), 1780 (s), 1456 (w) cm^{-1}; HRMS *m*/*z* calcd for $C_{10}H_9N_3O_2$ 203.0695; found 175.0628, which corresponds to $[M-N_2]^+$.

*4.7.2. (3S,5S)-Dihydro-3-hydroxy-5-phenylfuran-2(3H)-one (**17b**).* The crude material was purified by silica gel flash chromatography using 59:40:1 hexane/EtOAc/triethylamine as the eluent. The indicated compound was obtained as a yellow oil (41 mg, 93% yield), $[\alpha]_D^{20}$ −32.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.43–7.36 (m, 5H), 5.43 (dd, *J*=10.2, 5.7 Hz, 1H), 4.70 (dd, *J*=11.0, 8.3 Hz, 1H), 3.74 (t, *J*=3 Hz, 1H), 3.25–3.18 (m, 1H), 2.53–2.46 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 176.9, 137.7, 129.0, 128.8, 125.8, 77.7, 69.0, 39.6; FTIR: 3435 (s), 3086 (m), 2933 (m), 2852 (m), 1776 (s), 1637 (m), 1442 (w) cm^{-1}; HRMS *m*/*z* calcd for $C_{10}H_{10}O_3$ 178.0630; found 178.0628.

*4.7.3. (3S,5S)-3-Azidodihydro-5-(furan-2-yl)dihydrofuran-2(3H)-one (**17c**).* The crude material was purified by silica gel flash chromatography using 6:4 hexane/EtOAc as the eluent. The indicated compound was obtained as a yellow oil (35 mg, 72% yield), $[\alpha]_D^{20}$ −109.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.47 (d, *J*=1.1 Hz, 1H), 6.51 (d, *J*=3.3 Hz, 1H), 6.40 (dd, *J*=3.3, 1.8 Hz, 1H), 5.40 (dd, *J*=10.5, 5.9 Hz, 1H), 4.45 (dd, *J*=11.1, 8.7 Hz, 1H), 2.82 (ddd, *J*=13.1, 8.7, 5.9 Hz, 1H), 2.50 (dt, *J*=13.1, 10.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 172.1, 148.7, 144.2, 110.9, 110.7, 71.4, 57.5, 32.8; FTIR: 3057 (m), 2989 (m), 1644 (m) cm^{-1}; HRMS *m*/*z* calcd for $C_8H_7N_3O_3$ 193.0487; found 193.0490.

*4.7.4. (3S,5S)-5-(Furan-2-yl)dihydro-3-hydroxyfuran-2(3H)-one (**17d**).* The crude material was purified by silica gel flash chromatography using 59:40:1 hexane/EtOAc/triethylamine as the eluent. The indicated compound was obtained as a yellow oil (28 mg, 66% yield), $[\alpha]_D^{20}$ −42.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.43 (d, *J*=1.1 Hz, 1H), 6.42 (d, *J*=3.2 Hz, 1H), 6.37 (dd, *J*=3.2, 1.8 Hz, 1H), 5.60 (dd, *J*=8.6, 2.8 Hz, 1H), 4.85 (t, *J*=8.6 Hz, 1H), 3.05 (br s, 1H), 2.83 (ddd, *J*=13.1, 8.2, 2.8 Hz, 1H), 2.59 (dt, *J*=13.1, 8.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 177.0, 150.6, 143.7, 110.6, 109.8, 71.7, 67.3, 34.7; FTIR: 3429 (m), 3055 (m), 2987 (m), 1639 (m), 1421 (m) cm^{-1}; HRMS *m*/*z* calcd for $C_8H_8O_4$ 168.0423; found 168.0423.

*4.7.5. (3S,5S)-3-Azidodihydro-5-(thiophen-2-yl)furan-2(3H)-one (**17e**).* The crude material was purified by silica gel flash chromatography using 8:2 hexane/EtOAc as the eluent. The indicated compound was obtained as a yellow oil (50 mg, 98% yield), $[\alpha]_D^{20}$ −109.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$) δ ppm: 7.40 (dd, *J*=5.1, 1.1 Hz, 1H), 7.14 (d, *J*=3.6 Hz, 1H), 7.03 (dd, *J*=5.1, 3.6 Hz, 1H), 5.63 (dd, *J*=10.5, 5.6 Hz, 1H), 4.48 (dd, *J*=11.2, 8.5 Hz, 1H), 2.99 (ddd, *J*=13.0, 8.5, 5.6 Hz, 1H), 2.31 (ddd, *J*=13.0, 11.2, 10.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 172.0, 139.4, 127.3, 127.2, 127.1, 74.2,

57.9, 37.2; FTIR: 2925 (s), 2858 (m), 1780 (s), 1437 (m) cm^{-1}; HRMS *m/z* calcd for $C_8H_7N_3O_2S$ 209.0259; found 209.0260.

*4.7.6. (3S,5S)-Dihydro-3-hydroxy-5-(thiophen-2-yl)furan-2(3H)-one (**17f**).* The crude material was purified by silica gel flash chromatography using 59:40:1 hexane/EtOAc/triethylamine as the eluent. The indicated compound was obtained as yellow oil (43 mg, 94% yield), $[\alpha]_D^{20}$ +23.0 (*c* 0.5, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$) δ ppm: 7.40 (dd, *J*=5.0, 1.2 Hz, 1H), 7.21–7.11 (m, 1H), 7.04 (dd, *J*=5.0, 3.6 Hz, 1H), 5.60 (dd, J=11.0, 5.2 Hz, 1H), 4.67 (dd, *J*=11.2, 8.2 Hz, 1H), 3.05 (ddd, *J*=12.7, 8.2, 5.2 Hz, 1H), 2.88 (br s, 1H), 2.44 (dt, *J*=12.7, 11.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 176.2, 139.9, 127.2, 127.1, 127.0, 73.5, 68.8, 39.3; FTIR: 3695 (m), 3055 (m), 2987 (m), 1778 (m), 1423 (m) cm^{-1}; HRMS *m/z* calcd for $C_8H_8O_3S$ 184.0194; found 184.0199.

*4.7.7. (3S,5R)-5-Allyl-3-azidodihydrofuran-2(3H)-one (**17g**).* The crude material was purified by silica gel flash chromatography using 6:4 hexane/EtOAc as the eluent. The indicated compound was obtained as a yellow oil (39 mg, 93% yield), $[\alpha]_D^{20}$ −197.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 5.78–5.71 (m, 1H), 5.20–5.16 (m, 2H), 4.50–4.44 (m, 1H), 4.35 (dd, *J*=10.9, 8.8 Hz, 1H), 2.61 (ddd, *J*=13.0, 8.8, 5.5 Hz, 1H), 2.56–2.51 (m, 1H), 2.47–2.41 (m, 1H), 1.86–1.80 (m, 1H); ^{13}C NMR (125 MHz, CDCl3) δ ppm: 172.8, 131.1, 119.6, 76.8, 57.6, 39.0, 34.1; FTIR: 3032 (m), 2850 (w), 1780 (s), 1626 (m), 1450 (m) cm^{-1}; HRMS *m/z* calcd for $C_7H_9N_3O_2$ 167.0695; found 139.0630, which corresponds to $[M-N_2]^+$.

*4.7.8. (3S,5R)-5-Allyl-3-hydroxydihydrofuran-2(3H)-one (**17h**).* The crude material was purified by silica gel flash chromatography using 59:40:1 hexane/EtOAc/triethylamine as the eluent. The indicated compound was obtained as a yellow oil (34 mg, 95% yield), $[\alpha]_D^{20}$ −72.0 (*c* 0.5, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 5.83–5.74 (m, 1H), 5.21–5.18 (m, 2H), 4.53 (dd, *J*=11.0, 8.4 Hz, 1H), 4.44 (dt, *J*=11.0, 6.1 Hz, 1H), 2.71–2.65 (m, 2H), 2.59–2.56 (m, 1H), 2.50–2.46 (m, 1H), 1.95 (dt, *J*=12.5, 10.8 Hz, 1H); ^{13}C NMR (125 MHz, CDCl3) δ ppm: 177.2, 131.6, 119.6, 76.3, 68.8, 39.4, 36.6; FTIR: 3464 (m), 3062 (m), 2989 (m), 1775 (m), 1426 (m) cm^{-1}; HRMS *m/z* calcd for $C_7H_{10}O_3$ 142.0630; found 142.0630.

*4.7.9. (3S,5S)-3-Azidodihydro-5-vinylfuran-2(3H)-one (**17i**).* The crude material was purified by silica gel flash chromatography using 6:4 hexane/EtOAc as the eluent. The indicated compound was obtained as a yellow oil (26 mg, 69% yield), $[\alpha]_D^{20}$ −152.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 5.87 (ddd, *J*=17.1, 10.4, 6.7 Hz, 1H), 5.42 (d, *J*=17.1 Hz, 1H), 5.34 (d, *J*=10.4 Hz, 1H), 4.86–4.81 (m, 1H), 4.36 (dd, *J*=10.8, 8.6 Hz, 1H), 2.72 (ddd, *J*=13.0, 8.5, 5.8 Hz, 1H), 1.92 (dt, *J*=13.0, 10.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 172.6, 134.2, 119.4, 77.8, 57.5, 35.1; FTIR 3057 (m), 2989 (m), 1791 (m), 1432 (m) cm^{-1}; HRMS *m/z* calcd for $C_6H_7N_3O_2$ 153.0538; found 111.0445, which corresponds to $[M-N_3]^+$.

*4.7.10. (3S,5S)-Dihydro-3-hydroxy-5-vinylfuran-2(3H)-one (**17j**).* The crude material was purified by silica gel flash chromatography using 59:40:1 hexane/EtOAc/triethylamine as the eluent. The indicated compound was obtained as a yellow oil (22 mg, 69% yield), $[\alpha]_D^{20}$ −20.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 5.90 (ddd, *J*=17.1, 10.4, 6.7 Hz, 1H), 5.43 (d, *J*=17.1 Hz, 1H), 5.34 (d, *J*=10.4 Hz, 1H), 4.83–4.78 (m, 1H), 4.57–4.54 (m, 1H), 2.81–2.75 (m, 2H), 2.07–2.00 (m, 1H); ^{13}C NMR (125 MHz, CDCl3) δ ppm: 176.6, 134.6, 119.1, 77.2, 68.5, 37.3; FTIR: 3454 (m), 3048 (m), 2983 (m), 1770 (m), 1423 (m) cm^{-1}; HRMS *m/z* calcd for $C_6H_8O_3$ 128.0473; found 111.0447, which corresponds to $[M-OH]^+$.

*4.7.11. (3S,5R)-3-Azido-5-hexyldihydrofuran-2-one (**17k**).* The crude material was purified by silica gel flash chromatography using 6:4 hexane/EtOAc as the eluent. The indicated compound was obtained as a yellow oil (48 mg, 90% yield), $[\alpha]_D^{20}$ −117.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$) δ ppm: 4.42–4.37 (m, 1H), 4.32 (dd, *J*=11.0, 8.7 Hz, 1H), 2.63 (ddd, *J*=12.9, 8.7, 5.4 Hz, 1H), 1.80–1.73 (m, 1H), 1.68–1.58 (m, 1H), 1.51–1.41 (m, 1H), 1.29–1.27 (m, 8H), 0.88 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ ppm: 173.0, 77.9, 57.8, 35.2, 34.9, 31.5, 28.8, 24.8, 22.4, 13.9; FTIR: 3055 (m), 2986 (m), 1641 (m), 1421 (m) cm^{-1}; HRMS *m/z* calcd for $C_{10}H_{17}N_3O_2$ 211.1321; found 211.1314.

*4.7.12. (3S,5R)-3-Hydroxy-5-hexyldihydrofuran-2-one (**17l**).* The crude material was purified by silica gel flash chromatography using 59:40:1 hexane/EtOAc/triethylamine as the eluent. The indicated compound was obtained as a yellow oil (44 mg, 95% yield), $[\alpha]_D^{20}$ −120.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 4.52 (dd, *J*=11.1, 8.4 Hz, 1H), 4.40–4.34 (m, 1H), 2.72–2.67 (m, 1H), 1.88 (dt, *J*=12.4, 10.9 Hz, 1H), 1.84–1.76 (m, 1H), 1.70–1.62 (m, 1H), 1.57 (br s, 1H), 1.50–1.44 (m, 1H), 1.34–1.27 (m, 7H), 0.89 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 177.4, 77.4, 68.7, 37.1, 35.3, 31.6, 28.9, 24.9, 22.5, 14.0; FTIR: 3425 (m), 3054 (m), 2986 (m), 1774 (m), 1642 (m), 1421 (s) cm^{-1}. HRMS *m/z* calcd for $C_{10}H_{18}O_3$ 186.1256; found 186.1250.

4.8. General procedure for the synthesis of *trans*-3-azidodihydro-5-alkylfuran-2(3*H*)-ones and 3-azidodihydro-5-arylfuran-2(3*H*)-ones (18)

The trichloromethyl carbinol (0.25 mmol) in DME/water (1:4 mL/mL) was placed in a 4-dram vial, and then sodium azide (32 mg, 0.5 mmol) (CAUTION: may explode if ground or contacted by some metal surfaces) and powdered NaOH (40 mg, 1.0 mmol) were added at once. The reaction mixture was vigorously stirred at room temperature until judged complete by TLC analysis (12–24 h), then it was cooled to 0 °C and the pH was adjusted to pH=2 with 0.5 N HCl (or an aqueous solution of KH_2PO_4 with **18c**). This mixture was stirred vigorously for 1–4 h to promote lactonization. The aqueous phase was extracted with EtOAc (5×5 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography using hexane/EtOAc as eluent as outlined below.

4.9. General procedure for the synthesis of *trans*-3-hydroxydihydro-5-alkylfuran-2(3*H*)-ones and 3-hydroxydihydro-5-arylfuran-2(3*H*)-ones (18)

The trichloromethyl carbinol (0.25 mmol) in DME/water (1:4 mL/mL) was placed in a 4-dram vial, and then powdered NaOH (40 mg, 1.0 mmol) was added. The reaction mixture was stirred at room temperature until judged complete by TLC analysis (12–24 h), then it was cooled to 0 °C and the pH was adjusted to pH=2 with 0.5 N HCl (or an aqueous solution of KH_2PO_4 with **18d**). This mixture was stirred vigorously for 1–4 h to promote lactonization. The aqueous phase was extracted with EtOAc (5×5 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography using hexane/EtOAc as eluent as outlined below.

*4.9.1. (3S,5R)-3-Azidodihydro-5-phenylfuran-2(3H)-one (**18a**).* The crude material was purified by silica gel flash chromatography using 6:4 hexane/EtOAc as the eluent. The indicated compound was obtained as a yellow oil (36 mg, 70% yield), $[\alpha]_D^{20}$ −175.6 (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.42–7.36 (m, 3H), 7.30–7.28 (m, 2H), 5.64 (t, *J*=6.5 Hz, 1H), 4.36 (dd, *J*=7.8, 6.1 Hz, 1H), 2.59–2.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 172.7, 138.1, 129.0, 128.8, 125.1, 79.2, 57.1, 36.8; FTIR: 2927 (s), 2854 (m), 1776 (s),

1452 (m) cm^{-1}; HRMS *m*/*z* calcd for $C_{10}H_9N_3O_2$ 203.0695; found 161.0628, which corresponds to $[M-N_2]^+$.

*4.9.2. (3S,5R)-Dihydro-3-hydroxy-5-phenylfuran-2(3H)-one (**18b**).* The crude material was purified by silica gel flash chromatography using 59:40:1 hexane/EtOAc/triethylamine as the eluent. The indicated compound was obtained as a yellow oil (31 mg, 69% yield), $[\alpha]_D^{20}$ −19.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.41–7.35 (m, 3H), 7.30–7.28 (m, 2H), 5.72 (dd, *J*=7.8, 4.2 Hz, 1H), 4.56 (t, *J*=7.7 Hz, 1H), 3.01 (br s, 1H), 2.73–2.67 (m, 1H), 2.64–2.57 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 177.0, 138.8, 128.9, 128.5, 125.0, 78.5, 67.2, 38.2; FTIR: 3435 (s), 2933 (m), 2849 (w), 1776 (s), 1637 (m), 1439 (w) cm^{-1}; HRMS *m*/*z* calcd for $C_{10}H_{10}O_3$ 178.0630; found 178.0637.

*4.9.3. (3S,5R)-3-Azidodihydro-5-(furan-2-yl)dihydrofuran-2(3H)-one (**18c**).* The crude material was purified by silica gel flash chromatography using 6:4 hexane/EtOAc as the eluent. The indicated compound was obtained as a yellow oil (29 mg, 60% yield), $[\alpha]_D^{20}$ −177.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$) δ ppm: 7.44 (dd, *J*=1.8, 0.7 Hz, 1H), 6.45–6.44 (m, 1H), 6.38 (dd, *J*=3.3, 1.9 Hz, 1H), 5.57 (dd, *J*=8.1, 4.0 Hz, 1H), 4.64 (t, *J*=8.1 Hz, 1H), 2.77 (ddd, *J*=13.4, 8.1, 4.0 Hz, 1H), 2.44 (dt, *J*=13.4, 8.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 172.6, 149.9, 143.8, 110.7, 110.2, 72.1, 56.9, 33.0; FTIR: 3055 (m), 2986 (m), 1788 (m), 1421 (m) cm^{-1}; HRMS *m*/*z* calcd for $C_8H_7N_3O_3$ 193.0487; found 193.0490.

*4.9.4. (3S,5R)-Dihydro-3-hydroxy-5-(furan-2-yl)furan-2-(3H)-one (**18d**).* The crude material was purified by silica gel flash chromatography using 59:40:1 hexane/EtOAc/triethylamine as the eluent. The indicated compound was obtained as a yellow oil (29 mg, 52% yield), $[\alpha]_D^{20}$ +28.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.48 (d, *J*=1.1 Hz, 1H), 6.52 (d, *J*=3.3 Hz, 1H), 6.41 (dd, *J*=3.3, 1.8 Hz, 1H), 5.37 (dd, *J*=11.0, 5.5 Hz, 1H), 4.68–4.63 (m, 1H), 3.07 (d, *J*=2.5 Hz, 1H), 2.88 (ddd, *J*=12.7, 8.3, 5.5 Hz, 1H), 2.61 (dt, *J*=12.7, 11.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 176.3, 149.2, 144.0, 110.8, 110.7, 70.7, 68.4, 34.9; FTIR: 3428 (m), 3055 (m), 2987 (m), 1639 (m) cm^{-1}; HRMS *m*/*z* calcd for $C_8H_8O_4$ 168.0423; found 168.0422.

*4.9.5. (3S,5R)-3-Azidodihydro-5-(thiophen-2-yl)furan-2(3H)-one (**18e**).* The crude material was purified by silica gel flash chromatography using 6:4 hexane/EtOAc as the eluent. The indicated compound was obtained as a yellow oil (43 mg, 83% yield), $[\alpha]_D^{20}$ −215.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$) δ ppm: 7.37 (dd, *J*=5.1, 1.2 Hz, 1H), 7.10–7.09 (m, 1H), 7.02 (dd, *J*=5.1, 3.6 Hz, 1H), 5.87–5.83 (m, 1H), 4.45 (dd, *J*=7.8, 6.7 Hz, 1H), 2.71–2.64 (m, 1H), 2.60–2.53 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 172.2, 140.4, 127.2, 126.8, 126.3, 75.5, 57.1, 36.6; FTIR: 3054 (m), 2986 (m), 1765 (s), 1421 (m) cm^{-1}. HRMS *m*/*z* calcd for $C_8H_7N_3O_2S$ 209.0259; found 209.0260.

*4.9.6. (3S,5S)-3-Hydroxydihydro-5-(thiophen-2-yl)furan-2(3H)-one (**18f**).* The crude material was purified by silica gel flash chromatography using 59:40:1 hexane/EtOAc/triethylamine as the eluent. The indicated compound was obtained as a yellow oil (33 mg, 71% yield), $[\alpha]_D^{20}$ −30.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$) δ ppm: 7.40 (dd, *J*=5.1, 1.2 Hz, 1H), 7.17–7.16 (m, 1H), 7.03 (dd, *J*=5.1, 3.6 Hz, 1H), 5.60 (dd, *J*=11.0, 5.2 Hz, 1H), 4.69 (dd, *J*=11.2, 8.1 Hz, 1H), 3.16 (br s, 1H), 3.05 (ddd, *J*=12.7, 8.1, 5.2 Hz, 1H), 2.45 (dt, *J*=12.7, 11.2 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ ppm: 176.3, 139.8, 127.2, 127.1, 127.0, 73.5, 68.8, 39.3; FTIR: 3665 (m), 3045 (m), 2982 (m), 1765 (m), 1423 (m) cm^{-1}; HRMS *m*/*z* calcd for $C_8H_8O_3S$ 184.0194; found 184.0191.

*4.9.7. (3S,5S)-5-Allyl-3-azidodihydrofuran-2(3H)-one (**18g**).* The crude material was purified by silica gel flash chromatography using 8:2 hexane/EtOAc as the eluent. The indicated compound was obtained as a yellow oil (39 mg, 93% yield), $[\alpha]_D^{20}$ −197.0 (*c* 1.0, in CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$) δ ppm: 5.77–5.72 (m, 1H), 5.22 (s, 1H), 5.19–5.18 (m, 1H), 4.70–4.65 (m, 1H), 4.29 (dd, *J*=8.5, 4.7 Hz, 1H), 2.50–2.39 (m, 2H), 2.26–2.16 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 172.9, 131.1, 119.9, 76.7, 57.1, 39.1, 33.0; FTIR: 3032 (m), 2927 (m), 2858 (w), 2116 (s), 1780 (s), 1628 (m), 1456 (m) cm^{-1}; HRMS *m*/*z* calcd for $C_7H_9N_3O_2$ 167.0695; found 139.0630, which corresponds to $[M-N_2]^+$.

*4.9.8. (3S,5S)-5-Allyl-3-hydroxydihydrofuran-2(3H)-one (**18h**).* The crude material was purified by silica gel flash chromatography using 8:2 hexane/EtOAc as the eluent. The indicated compound was obtained as a yellow oil (28 mg, 78% yield), 88:12 de. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 5.81–5.72 (m, 1H), 5.24–5.16 (m, 1H), 4.58–4.47 (m, 2H), 2.88 (ddd, *J*=13.5, 8.6, 5.8 Hz, 1H), 2.64–2.58 (m, 1H), 2.52–2.46 (m, 1H), 2.22–2.16 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 171.8, 131.0, 119.6, 77.1, 51.0, 39.1, 38.0. Material contained a minor impurity that could not be completely removed. As such, compound was not characterized further.

*4.9.9. (3S,5R)-5-Vinyl-3-azidodihydrofuran-2(3H)-one (**18i**).* The crude material was purified by silica gel flash chromatography using 6:4 hexane/EtOAc as the eluent. The indicated compound was obtained as a yellow oil (21 mg, 55% yield), $[\alpha]_D^{20}$ −123.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$) δ ppm: 5.91–5.81 (m, 1H), 5.42–5.30 (m, 2H), 5.08–5.03 (m, 1H), 4.29 (t, *J*=7.6 Hz, 1H), 2.31 (dd, *J*=7.6, 6.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 172.7, 134.5, 118.2, 78.2, 56.6, 34.3; FTIR: 3055 (m), 2987 (m), 1780 (m), 1423 (m) cm^{-1}; HRMS *m*/*z* calcd for $C_6H_7N_3O_2$ 153.0538; found 153.0532.

*4.9.10. (3S,5S)-3-Azido-5-hexyldihydrofuran-2-one (**18k**).* The crude material was purified by silica gel flash chromatography using 6:4 hexane/EtOAc as the eluent. The indicated compound was obtained as a yellow oil (44 mg, 84% yield), $[\alpha]_D^{20}$ −190.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$) δ ppm: 4.62–4.57 (m, 1H), 4.27 (dd, *J*=8.1, 5.8 Hz, 1H), 2.24–2.19 (m, 1H), 2.16–2.11 (m, 1H), 1.72–1.68 (m, 1H), 1.60–1.57 (m, 1H), 1.43 (m, 1H), 1.31–1.28 (m, 7H), 0.88 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 173.0, 79.4, 57.3, 35.4, 34.2, 31.6, 28.9, 25.1, 22.5, 14.0; FTIR: 3055 (m), 2931 (m), 2859 (m), 1779 (m), 1641 (m), 1421 (m) cm^{-1}; HRMS *m*/*z* calcd for $C_{10}H_{17}N_3O_2$ 211.1321; found 211.1324.

*4.9.11. (3S,5S)-3-Hydroxy-5-hexyldihydrofuran-2-one (**18l**).* The crude material was purified by silica gel flash chromatography using 59:40:1 hexane/EtOAc/triethylamine as the eluent. The indicated compound was obtained as a yellow oil (36 mg, 78% yield), $[\alpha]_D^{20}$ −49.0 (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 4.66–4.62 (m, 1H), 4.50 (t, *J*=7.8 Hz, 1H), 2.77 (br s, 1H), 2.37–2.31 (m, 1H), 2.28–2.23 (m, 1H), 1.73–1.65 (m, 1H), 1.61–1.54 (m, 1H), 1.37–1.24 (m, 8H), 0.88 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 177.2, 78.7, 67.5, 35.7, 35.5, 31.6, 28.9, 25.3, 22.5, 14.0; FTIR: 3403 (m), 3054 (m), 2986 (m), 1777 (m), 1421 (m) cm^{-1}; HRMS *m*/*z* calcd for $C_{10}H_{18}O_3$ 187.1334; found 187.1338.

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Supplementary data

^1H and ^{13}C NMR spectra of all reported compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.04.107.

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