Dichloromethylenation of Lactones. 6. Efficient Synthesis of Dichloroolefins from Lactones and Acetates Using Triphenylphosphine and Tetrachloromethane[1]

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Triphenylphosphine and tetrachloromethane react cleanly in refluxing tetrahydrofuran with substituted γ- and δ-lactones and some esters to afford the corresponding dichloroolefins in good yields. This new Wittig-type reaction provides an easy entry to this new class of compounds and tolerates a large variety of protecting groups. Application of this methodology to the dichloroolefination of simple lactones, sugar-derived lactones, and other biologically significant lactones is described.

The dichloromethylenation of ketones and aldehydes is a well known, synthetically useful reaction.[2] It provides *inter alia* entries for the preparation of alkynes from aldehydes in a two-step reaction.[2b] In connection with our program on C-glycoside chemistry, several years ago we began an investigation of olefination reactions at the anomeric center. It was expected that C-glycosylidene compounds should be synthetically useful for subsequent chain extension and modification. In this regard we have explored the dichloroolefination of sugar derivatives, and we demonstrated recently, for the first time, that the dichloromethylenation reaction could be realized on the carbonyl group of some γ-lactones derived from carbohydrates.[3] For this purpose, the reaction of tris(dimethylamino)phosphine tetrachloromethane (TDAP–TCM) performed at −40 °C, gave excellent results. However, the reaction was found to be limited to highly reactive lactones, α-substituted or having a bicyclo[3.3.0] structure **A** (Scheme 1). We have recently shown that the dichloromethylenation reaction using TDAP–TCM proceeds via a nonylide mechanism as generally postulated for this reagent. An ionic mechanism involving the nucleophilic addition of trichloromethylide anion on the lactone carbonyl group followed by oxyphosphonium formation and elimination of HMPA has been proposed.[1] Dichloroolefins **B**, obtained from lactones **A**, are good intermediates for the synthesis of chiral, biologically active tetrahydrofurans such as muscarins[4] and C-glycosides,[5] particularly of 1-methylene sugars.[6] They might be also good candidates for glycosidase inhibition because of the planar geometry at the anomeric center mimicking the oxonium ion, a postulated intermediate of the enzymatic hydrolysis of glycosidic bonds.[7] Subsequent to our work, difluoromethylenation of sugar lactones along the same lines, using tris(dimethylamino)phosphine, dibromodifluoromethane, and zinc has been reported by Motherwell *et al.*[8] The difluoromethylene sugar proved to be a good radical acceptor.[9] More recently, our dichloroolefins derived from sugars have been successfully used for the synthesis of chiral nonracemic acetylenic alcohols on treatment with lithium sand.[10] In an effort to generalize the dichloromethylenation reaction, we have investigated more suitable reagents. We have found that using the combination of triphenylphosphine and tetrachloromethane (TPP–TCM), lactones **C** and, to some extent, esters gave the corresponding dichloroolefins **D** in good to excellent yields. We report here in full the details of this investigation with applications of this methodology to biologically interesting lactones.[11]

Scheme 1

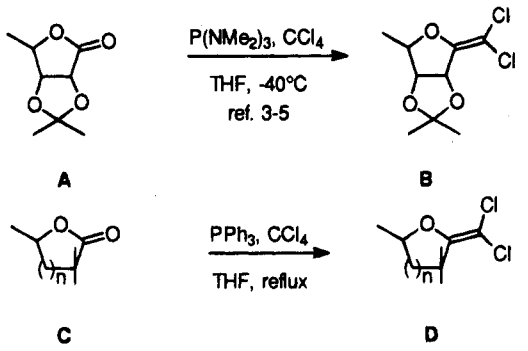

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Table 1. Dichloromethylenation of Lactones

entry	starting compd	PPh_3, equiv	CCl_4, equiv	time (h)	products	yield[a] (%)
1	**1**	4	24	3	**2**	95[b]
2	**3**	4	24	4	**4**	85[b]
3	**5**	4	24	5	**6**	78
4	**7**	4	24	3	**8**	90
5	**9**	8	48	24	**10**	45
6	**11**	8	48	20	**12**	45[c]
7	**13**	4	24	2.5	**14, 15, 16**	87[c]
8	**17**	4	24	8	**18**	74[c]
9	**19**	4	24	3	**20**	81
10	**21**	4	24	3	**22**	38[c,d]
11	**23**	4	24	2.5	**24**	90
12	**25**	4	24	2.5	**26, 27**	77, 4
13	**28**	6	36	22	**29**	68
14	**30**	12	72	18	**31**	84
15	**32**	8	48	24	**33, 34**	19, 25
16	**35**	4	24	16	**36**	71[b]
17	**37**	8	48	18	**38**	20
18	**39**	4	24	2	**40**	75
19	**41**	4	24	4	**42**	92
20	**43**	4	24	3	**44**	59

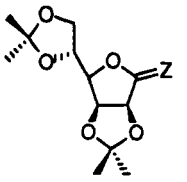
[a] Yields refer to pure isolated compounds. [b] Yields obtained using our previously described method (TDAP–TCM) were, respectively, 92% of **2** from **1**, 85% of **4** from **3**, and 71% of **36** from **35**; see ref 5. [c] No reaction was observed using the TDAP–TCM system. [d] The modest yield could be explained by the low boiling point (114 °C) of the starting compound.

A survey of different reaction conditions was undertaken on the model lactone **1**, which gave excellent results with the TDAP–TCM system. Although acetonitrile was known to be an excellent solvent for the dichloromethylenation of ketones using TPP–TCM,[12] it proved to be completely ineffective in the case of lactone **1**. This compound was found to react slowly in refluxing tetrachloromethane, but at a reasonable rate in refluxing tetrahydrofuran. Using a slow addition of large excess of tetrachloromethane to a solution of TPP and lactone in refluxing tetrahydrofuran, the dichloromethylenation of compound **1** was very efficient, giving **2** in excellent yield (entry 1). These conditions were used with several lactones, and Table 1 summarizes the results obtained.

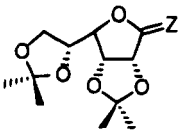
As seen from Table 1, the reaction of TPP–TCM proceeds in good to excellent yields with lactones derived from sugars having a bicyclo[3.3.0] structure (entries 1–5) giving identical or even better results than TDAP–TCM. More interesting were the good results obtained with a series of α-unsubstituted lactones **21**, **23**, and **25** (entries 10–12), with *O*-benzyl-protected lactones **17** and **35** (entries 8 and 16) and the sterically congested lactone **13** (entry 7) which failed to react with the TDAP–TCM system. A modest yield of the expected dichloroolefins was obtained with lactones **9**, **11**, and **37** (entries 5, 6, and 17). This was probably due to side reactions, in particular for lactone **11** and **37**. Although these compounds were not isolated, we felt that reaction of the acetate group with TPP–TCM should be possible. Careful examination of the reaction of the isosaccharino lactone **13** with TPP–TCM revealed that the primary acetate protecting group was also transformed to the corresponding dichloroolefin, and a mixture of compound **14**, **15**, and **16** was isolated in 87% overall yield. Thus, the acetate group is almost as reactive as the sterically hindered carbonyl group of the lactone **13**. The reactivity of ester groups was tested on a simpler model, and acetate **43** was cleanly transformed into olefin **44** in 59% yield (entry 20). However, the olefination reaction seems to be limited to acetate as proved by the inertness of ester protecting groups such as pivaloyl (entries 14 and 15) and 4-phenylbenzoyl esters (entry 14) under our reaction conditions. Benzoyl ester was found to be reactive in a limited extent as seen from the results obtained with lactone **25** (entry 12); only 4% of the bis dichloroolefin was isolated.

This new dichloromethylenation reaction, which seemed to be quite general, was applied to several biologically interesting lactones. We investigated first the reactivity of the Corey lactone[13] derivative **28**. The primary alcohol was first protected as a *tert*-butyldimethylsilyl (TBDMS) group. Upon treatment with TPP–TCM, a dichloro-

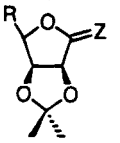
Chart 1



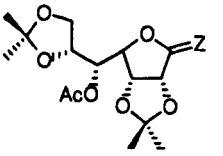
1 Z = O
2 Z = CCl_2



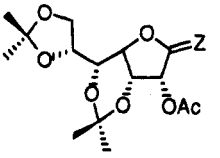
3 Z = O
4 Z = CCl_2



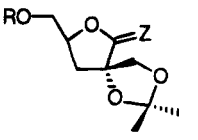
5 Z = O R = CH_2OMOM
6 Z = CCl_2 R = CH_2OMOM
7 Z = O R = H
8 Z = CCl_2 R = H



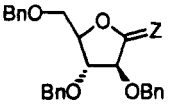
9 Z = O
10 Z = CCl_2



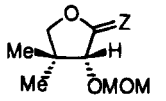
11 Z = O
12 Z = CCl_2



13 Z = O R = CH_3-CO
14 Z = CCl_2 R = CH_3-C(CCl_2)
15 Z = CCl_2 R = CH_3-CO
16 Z = O R = CH_3-C(CCl_2)

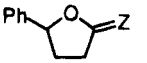


17 Z = O
18 Z = CCl_2



19 Z = O
20 Z = CCl_2

21 Z = O
22 Z = CCl_2



23 Z = O
24 Z = CCl_2

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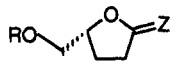
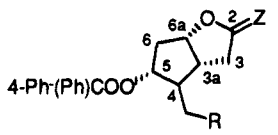
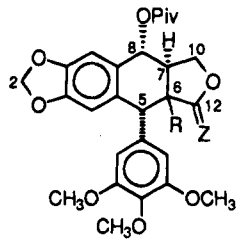
Chart 2



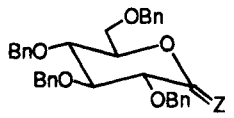
25 Z = O R = PhCO
26 Z = CCl_2 R = PhCO
27 Z = CCl_2 R = $PhC(CCl_2)$



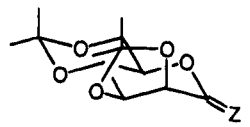
28 Z = O R = $OSiMe_2tBu$
29 Z = CCl_2 R = Cl
30 Z = O R = OCOtBu
31 Z = CCl_2 R = OCOtBu



32 Z = O R = H β
33 Z = CCl_2 R = H β
34 Z = CCl_2 R = H α

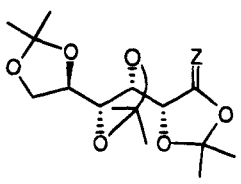


35 Z = O
36 Z = CCl_2

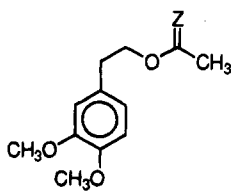


37 Z = O
38 Z = CCl_2

39 Z = O
40 Z = CCl_2



41 Z = O
42 Z = CCl_2



43 Z = O
44 Z = CCl_2

methylenated product was formed as seen from the IR spectrum, but the absence of the TBDMS group in the NMR spectrum and the presence of three chlorine atoms revealed by mass spectrometry supported structure **29**. Thus, the presence of the *tert*-butyldimethylsilyl protective group of the primary alcohol is not compatible with our reaction conditions. An analogous direct bromination of a TBDMS ether derived from a primary alcohol with TPP–tetrabromomethane has been reported by Mattes and Benezra.[14] Alternatively, the primary hydroxyl group was protected as a pivalate ester to produce **30** which was efficiently converted into the dichloroolefin **31** in 84% yield. Compound **31** may be a good starting compound for the synthesis of long-lived prostacyclin (PGI_2) analogues. Another interesting example came from the podophyllotoxin series. Protection of the benzylic alcohol of podophyllotoxin with a pivaloyl group gave lactone **32** which was treated with TPP–TCM. A mixture of the expected dichloroolefin **33** and its *cis* isomer **34** were isolated in a 1/1 ratio (44% overall yield). It was concluded that the *trans* ring junction readily changed for the more stable *cis* one under our reaction conditions which are acidic enough to promote enolization of the lactone. Epimerization of **33** to **34** cannot be excluded, but prolonged reaction time did not change the *trans*/*cis* ratio. Dichloroolefins **33** or **34** are interesting compounds which may be advanced intermediates for the synthesis of potential antitumor agents related to podophyllotoxin.

Interestingly, dioxolanone **41** is also a good substrate for the TPP–TCM reaction. The corresponding dichloroolefin **42** was obtained in 92% yield. This compound should be a good intermediate for the chain elongation of linear sugar. Finally, δ-lactones are also easily transformed into dichloroolefins as demonstrated on several substrates. The presence of acetate at C-2 may be responsible for side reactions during the dichloromethylenation of lactone **37** (entry 17). Lactones **35** and **39** were efficiently converted into dichloroolefins **36** and **40** in 71 and 75% yield, respectively, using TPP–TCM (entry 16 and 18). It is worthy of note that using the TDAP–TCM system compound **36** was formed in only 34% yield, and lactone **39** reacted in a completely different way to give the anomeric vinylic chloride instead of the dichloroolefin.[1]

Conclusion

Although the reaction mechanism of the dichloromethylenation of lactone is not completely elucidated, there is strong evidence for two different pathways depending upon the phosphine.[15] The tris(dimethylamino)phosphine–tetrachloromethane system reacted at −40 °C mainly via an ionic mechanism with highly reactive lactones,[1] whereas the triphenylphosphine–tetrachloromethane system needed high temperature and allowed the transformation of less reactive lactones such as **13**, and even esters such as **43**, probably via a Wittig-type mechanism. This could explain the different reactivities of lactones toward these dichloromethylenating reagents. This is one of the rare cases of Wittig olefination of esters. Most examples of Wittig reaction of esters reported so far concern intramolecular reactions.[16,17] The present method of dichloromethylenation is a good alternative to our previous procedure,[3-5] avoiding the formation of the carcinogenic hexamethylphosphoric triamide (HMPA), the end product of this latter reaction. It tolerates a number of protecting groups such as ethers, acetals, and esters except acetate and silyl ethers. The new conditions are useful for the transformation of lactones and acetates, opening a route to new dichloroolefinic structures such as **31**, **33**, and **34**, the chemistry of which needs to be explored.

Experimental Section

^1H NMR spectra were recorded with a Bruker Aspect 3000 spectrometer operating at 400 MHz and AC250 operating at 250 MHz, using deuteriochloroform as solvent. Assignments were confirmed by double irradiation. Chemical shifts are

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(16) Brennan, J.; Murphy, P. J. *Tetrahedron Lett.* **1988**, *29*, 2063.
(17) Dugan, A. J.; Adams, M. A.; Brynes, P. J.; Meinwald, J. *Tetrahedron Lett.* **1978**, 4323.

reported relative to internal $SiMe_4$, and J values are given in Hz. TLC was performed on silica gel plates (Merk $60F_{254}$). Column chromatography used silica gel (Merck 60 70–23 mesh). Mixtures of ethyl acetate (A) or diethyl ether (E) and hexane (H) were used as eluents. Optical rotations were measured on a Perkin-Elmer 141 polarimeter at 20 °C. Melting points were measured in capillary tubes and are uncorrected. The elementary analyses were performed by the Service Central de Microanalyses du CNRS at Vernaison, France. Mass spectra were obtained on a Nermag R10-10C. Starting lactones were obtained from commercially available lactones which were protected using standard procedures or by oxidation of the corresponding lactols. Tetrahydrofuran was distilled prior to use from sodium–benzophenone. All reactions were performed under nitrogen atmosphere.

General Procedure for Dichloroolefination. In a typical experiment the lactone (1 mmol) and triphenylphosphine (4 mmol) were dissolved in dry tetrahydrofuran (20 mL). To this refluxing solution was slowly added, preferably via a motor-driven syringe, tetrachloromethane (24 mmol) over a period of 2 h or more. If necessary, the reflux was maintained until no starting material was present by TLC. In some cases, a further amount of reagent (TPP and TCM) was added (see Table 1). After cooling, water was added and the products were extracted with dichloromethane (3 × 100 mL). The organic layer was washed with dilute sodium bicarbonate solution and water until neutral and dried over magnesium sulfate. Evaporation of the solvent afforded the crude compound which was purified by silica gel column chromatography using the appropriate eluent. The scale is indicated for each reaction as well as the amount of pure isolated product.

2,5-Anhydro-1-deoxy-1,1-dichloro-3,4:6,7-di-*O*-isopropylidene-D-*manno*-hept-1-enitol (2). Prepared from lactone **1**[18] (258 mg, 1 mmol), 307 mg (95%): R_f = 0.7 (H–A, 2/1); $[\alpha]_D$ +172° (*c* 0.5, $CHCl_3$). Analytical data are given in ref. 5.

2,5-Anhydro-1-deoxy-1,1-dichloro-3,4:6,7-di-*O*-isopropylidene-L-*gluco*-hept-1-enitol (4). Prepared from lactone **3**[19] (258 mg, 1 mmol), 277 mg (85%); R_f = 0.57 (H–A, 1/1); $[\alpha]_D$ −175° (*c* 0.5, $CHCl_3$). Analytical data are given in ref. 5.

2,5-Anhydro-1-deoxy-1,1-dichloro-6-*O*-(methoxymethoxy)-3,4-*O*-isopropylidene-D-*ribo*-hex-1-enitol (6). Prepared from lactone **5**[20,21] (231 mg, 1 mmol), 211 mg (78%): R_f = 0.55 (H–A, 3/1); $[\alpha]_D$ −140° (*c* 0.4, $CHCl_3$); IR 1675 cm^{-1}; ^1H NMR δ 1.40 (s, 3 H), 1.50 (s, 3 H), 3.35 (s, 3 H), 3.65 (dd, 1 H, J = 14, 2.5 Hz), 3.75 (dd, 1 H, J = 14, 3 Hz), 4.58 (s, 2 H), 4.67 (m, 1 H), 4.80 (dd, 1 H, J = 6, 7 Hz), 5.27 (d, 1 H); EIMS *m/z* 298 (M^+), 283, 175, 117, 87, 69, 59, and 45. Anal. Calcd for $C_{11}H_{16}Cl_2O_5$: C, 44.17; H, 5.39; Cl, 23.70. Found: C, 44.40; H, 5.48; Cl, 23.85.

2,5-Anhydro-1-deoxy-1,1-dichloro-3,4-*O*-isopropylidene-D-*erythro*-pent-1-enitol (8). Prepared from lactone **7**[22] (250 mg, 2 mmol), 345 mg (90%): R_f = 0.68 (H–A, 4/1); $[\alpha]_D$ −247° (*c* 0.4, $CHCl_3$); IR 1675 cm^{-1}; ^1H NMR δ 1.40 (s, 3 H), 1.50 (s, 3 H), 4.20 (dd, 1 H, J = 11.5, 5 Hz), 4.43 (d, 1 H, J = 11.5 Hz), 4.91 (m, 1 H), 5.28 (d, 1 H, J = 7 Hz); EIMS *m/z* 224 (M^+), 209, 149, 115, 110, 85, 73, 59, 51, and 43. Anal. Calcd for $C_8H_{10}Cl_2O_3$: C, 42.69; H, 4.48; Cl, 31.50. Found: C, 42.85; H, 4.53; Cl, 31.8.

6-*O*-Acetyl-2,5-anhydro-1-deoxy-1,1-dichloro-3,4:7,8-di-*O*-isopropylidene-D-*glycero*-D-*gluco*-oct-1-enitol (10). Prepared from lactone **9**[23] (330 mg, 1 mmol), 178 mg (45%): mp 77 °C; R_f = 0.55 (H–A, 2/1); $[\alpha]_D$ −85° (*c* 0.5, $CHCl_3$); IR 1745 and 1665 cm^{-1}; ^1H NMR δ 1.30 (s, 3 H), 1.39 (s, 3 H), 1.42 (s, 3 H), 1.45 (s, 3 H), 2.10 (s, 3 H), 3.97 (dd, 1 H, J = 6, 9 Hz), 4.05 (dd, 1 H, J = 9, 6.5 Hz), 4.20 (dd, 1 H, J = 3.5, 7 Hz), 4.30 (dd, 1 H, J = 6.5, 5.5 Hz), 4.80 (dd, 1 H, J = 5.5, 3.5 Hz), 5.30 (d, 1 H), 5.55 (dd, 1 H). Anal. Calcd for $C_{16}H_{22}Cl_2O_7$: C, 48.38; H, 5.58; Cl, 17.85. Found: C, 48.52; H, 5.48; Cl, 17.64.

3-*O*-Acetyl-2,5-anhydro-1-deoxy-1,1-dichloro-4,6:7,8-di-*O*-isopropylidene-D-*glycero*-D-*gluco*-oct-1-enitol (12). Prepared from lactone **11**[23] (330 mg, 1 mmol), 178 mg (45%); R_f = 0.26 (H–A, 3/1); $[\alpha]_D$ −75° (*c* 0.2, $CHCl_3$); IR 1750 and 1675 cm^{-1}; ^1H NMR δ 1.38 (s, 3 H), 1.45 (s, 9 H), 2.19 (s, 3 H), 3.88 (dd, 1 H, J = 8, 3 Hz), 3.99 (dd, 1 H, J = 4.5, 9 Hz), 4.10 (m, 2 H), 4.37 (m, 1 H, J = 8, 6.5, 4.5 Hz), 4.69 (dd, 1 H, J = 4.5, 2 Hz), 5.82 (d, 1 H, J = 4.5 Hz); EIMS *m/z* 396 (M^+), 381, 323, 149, 131, 101, 73, 59, 49, and 43. Anal. Calcd for $C_{16}H_{22}Cl_2O_7$: C, 48.38; H, 5.58; Cl, 17.85. Found: C, 48.50; H, 5.67; Cl, 17.81.

6-(Dichloromethylene)-8-[[(2,2-dichloro-1-methylethenyl)oxy]methyl]-2,2-dimethyl-*trans*-1,3,7-trioxaspiro[4.4]nonane (14). Lactone **13** prepared by standard acetylation of the corresponding alcohol[24] (480 mg, 2 mmol) gave **14**, **15**, and **16**. Compound **14**, 264 mg (35%); R_f = 0.51 (H–A, 5/1); $[\alpha]_D$ −24.9° (*c* 0.9, $CHCl_3$); IR 1655 and 1645 cm^{-1}; ^1H NMR δ 1.20 (s, 3 H), 1.31 (s, 3 H), 2.04 (s, 3 H), 2.46 (dq, 2 H, J = 13.5, 8, 7 Hz), 3.90 (dd, 1 H, J = 11, 3,5 Hz), 4.06 (dd, 1 H, J = 11, 3.5 Hz), 4.12 (d, 1 H, J = 9 Hz), 4.54 (d, 1 H), 4.68 (m, 1 H); EIMS *m/z* 376 (M^+), 361, 195, 117, 99, 83, 72, 65, 55 and 43. Anal. Calcd for $C_{13}H_{16}Cl_4O_4$: C, 41.30; H, 4.27; Cl, 37.51. Found: C, 41.52; H, 4.32; Cl, 37.62.

A 1/1 mixture of compounds **15** and **16** was obtained in 52% yield. Small quantities of analytically pure samples were obtained by careful chromatography on silica gel column.

6-(Dichloromethylene)-8-(acetoxymethyl)-2,2-dimethyl-*trans*-1,3,7-trioxaspiro[4.4]nonane (15): R_f = 0.32 (H–A, 5/1); IR 1755 and 1655 cm^{-1}; ^1H NMR δ 1.40 (s, 3 H); 1.54 (s, 3 H), 2.11 (s, 3 H), 2.50 (m, 2 H), 4.14 (dd, 1 H, J = 12.5, 5 Hz), 4.31 (dd, 1 H, J = 3.5, 12.5 Hz), 4.35 (d, 1 H, J = 9 Hz), 4.57 (d, 1 H, J = 9 Hz), 4.68 (m, 1 H, J = 3.5, 5, 6.5, 9 Hz); EIMS *m/z* 310 (M^+), 295, 235, 192, 175, 152, 82, 72, 52, and 43.

8-[[(2,2-Dichloro-1-methylethenyl)oxy]methyl]-2,2-dimethyl-*trans*-1,3,7-trioxaspiro[4.4]nonan-6-one (16): R_f = 0,32 (H–A, 5/1); IR 1800 and 1645 cm^{-1}; ^1H NMR δ 1.46 (s, 3 H), 1.50 (s, 3 H), 2.03 (s, 3 H), 2.16 (dd, 1 H, J = 9, 6 Hz), 2.50 (m, 1 H), 3.89 (dd, 1 H, J = 11, 3 Hz), 4.06 (m, 2 H), 4.14 (dd, 1 H, J = 9 Hz), 4.80 (m, 1 H, J = 9, 6, 3 Hz); EIMS *m/z* 310 (M^+), 295, 282, 141, 127, 99, 83, 71, 55, and 43.

2,5-Anhydro-1-deoxy-1,1-dichloro-3,4,6-tris(benzyloxy)-*arabino*-hex-1-enitol (18). Prepared from lactone **17**[25] (417 mg, 1 mmol), 358 mg (74%): R_f = 0.49 (H–A, 6/1); $[\alpha]_D$ +33.6° (*c* 0.1, $CHCl_3$); IR 1670 cm^{-1}; ^1H NMR δ 3.58 (dd, 1 H, J = 10, 8 Hz), 3.68 (dd, 1 H, J = 10, 6 Hz), 4.09 (s, 1 H), 4.45–4.60 (m, 7 H), 4.65 (t, 1 H), 7.20–7.40 (m, 15 H); EIMS *m/z* 484 (M^+), 393, 270, 215, 205, 181, 167, 149, 91, and 65. Anal. Calcd for $C_{27}H_{26}Cl_2O_4$: C, 66.81; H, 5.40; Cl, 14.61. Found: C, 67.2; H, 5.37; Cl, 14.48.

3*R*-(−)-Dihydro-4,4-dimethyl-3-[(methoxymethyl)oxy]-2(3*H*)-furanone (19). To a solution of commercial pantolactone (260 mg, 2 mmol) in dichloromethane was added at room temperature diisopropylethylamine (0.84 mL, 4.8 mmol) followed by chloromethyl methyl ether (0.34 mL). The mixture was stirred overnight. Water was added, and the crude lactone **19** was extracted with dichloromethane (3 × 40 mL). The organic phase was washed with 3 N HCl and water until neutral and dried over magnesium sulfate. Column chromatography on silica gel gave pure **19** (260 mg, 75%): R_f = 0.44 (H–A, 3/1); $[\alpha]_D$ +121° (*c* 0.6, $CHCl_3$); IR 1795 cm^{-1}; ^1H NMR δ 1.60 (s, 3 H), 1.81 (s, 3 H), 3.44 (s), 3.93 (d, 1 H, J = 8 Hz), 4.00 (d, 1 H, J = 8 Hz), 4.10 (s, 1 H), 4.73 (d, 1 H, J = 6.5 Hz), 5.03 (d, 1 H, J = 6.5 Hz).

(3*R*)-(−)-2-(Dichloromethylene)-4,4-dimethyl-3-[(methoxymethyl)oxy]-2(3*H*)-tetrahydrofuran (20). Prepared from lactone **19** (173 mg, 1 mmol), 195 mg (81%): R_f = 0.47 (H–A, 10/1); $[\alpha]_D$ +48.9° (*c* 0.5, $CHCl_3$); IR 1665 cm^{-1}; ^1H NMR

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δ 1.25 (s, 3 H), 1.75 (s, 3 H), 3.40 (s, 3 H), 3.89 (d, 1 H, J = 8 Hz), 4.13 (d, 1 H, J = 8 Hz), 4.50 (s, 1 H), 4.62 (d, 1 H, J = 6.5 Hz), 4.93 (d, 1 H, J = 6.5 Hz); EIMS m/z 240 (M^+), 179, 165, 145, 123, 109, 101, 69, 56, and 45. Anal. Calcd for $C_9H_{14}Cl_2O_3$: C, 44.83; H, 5.85; Cl, 29.41. Found: C, 44.58; H, 5.79; Cl, 29.78.

2-(Dichloromethylene)tetrahydrofuran (22). Prepared from commercial lactone **21** (340 mg, 4 mmol), 231 mg (38%): R_f = 0.68 (H–A, 8/1); IR 1670 cm^{-1}; ^1H NMR δ 2.13 (m, 2 H), 2.69 (m, 2 H), 4.31 (m, 2 H); EIMS m/z 152 (M^+), 110, 82, 73, 61, 51, and 42. Anal. Calcd for $C_5H_6Cl_2O$: C, 39.25; H, 3.95; Cl, 46.34. Found: C, 39.43; H, 4.02; Cl, 46.58.

(±)-2-(Dichloromethylene)-5-phenyltetrahydrofuran (24). Prepared from commercial lactone **23** (320 mg, 2 mmol), 410 mg (90%): R_f = 0.62 (H–A, 10/1); IR 1670 cm^{-1}; ^1H NMR δ 2.06 (dq, 1 H, J = 6.5, 5, 13 Hz), 2.50 (m, 1 H), 2.75 (dd, 1 H, J = 17, 9 Hz), 2.83 (dd, 1 H, J = 17, 5 Hz), 5.42 (t, 1 H, J = 6.5, 7 Hz), 7.20–7.40 (m, 5 H); EIMS m/z 228 ($M^{+\cdot}$), 193, 175, 157, 138, 129, 117, 105, 91, 77, 63, and 51. Anal. Calcd for $C_{11}H_{10}Cl_2O$: C, 57.67; H, 4.40; Cl, 30.95. Found: C, 57.84; H, 4.5; Cl, 31.30.

2-(Dichloromethylene)-5(*R*)-[(benzoyloxy)methyl]tetrahydrofuran (26). Lactone **25** (219 mg, 1 mmol) prepared in 89% yield by standard benzoylation of commercially available 5-(hydroxymethyl)furanone, gave 220 mg (77%): R_f = 0.43 (H–A, 6/1); $[\alpha]_D$ +7.5° (c 0.5, $CHCl_3$); IR 1730, 1675, and 1610 cm^{-1}; ^1H NMR δ 2.04 (m, 1 H), 2.30 (m, 1 H), 2.76 (m, 1 H), 2.85 (m, 1 H), 4.42 (dd, 1 H, J = 12, 5 Hz), 4.50 (dd, 1 H, J = 12, 4 Hz), 4.82 (m, 1 H), 7.40–8.00 (m, 5 H); EIMS m/z 286 (M^+), 221, 146, 105, 77, 51, and 41. Anal. Calcd for $C_{13}H_{12}Cl_2O_3$: C, 54.38; H, 4.21; Cl, 24.69. Found: C, 54.49; H, 4.30; Cl, 24.43.

2-(Dichloromethylene)-5-[[(2′,2′-dichloro-1′-phenylethenyl)oxy]methyl]tetrahydrofuran (27): 14 mg (4%); R_f = 0.56 (H–A, 6/1); $[\alpha]_D$ + 4° (c 0.2, $CHCl_3$); IR 1635, 1675, and 1610 cm^{-1}; ^1H NMR δ 2.15 (m, 1 H), 2.25 (m, 1 H), 2.70 (dq, 1 H, J = 9.5, 7 Hz), 2.85 (dq, 1 H, J = 9.5, 6 Hz), 3.67 (dd, 1 H, J = 11, 4.5 Hz), 3.75 (dd, 1 H, J = 11, 4 Hz), 4.65 (m, 1 H), 7.50 (m, 5 H); EIMS m/z 352 (M^+), 315, 281, 269, 209, 188, 172, 165, 136, 129, 115, 105, 81, 65, 51, and 43.

(3a*R*,4*S*,5*R*,6a*R*)-2-(Dichloromethylene)-4-(chloromethyl)hexahydro-2*H*-cyclopenta[*b*]furan-5-yl-1,1′-Biphenyl-4-carboxylate (29). Prepared from lactone **28**[26] (233 mg, 0.5 mmol), 148 mg (68%): R_f = 0.39 (H–A, 7/1); $[\alpha]_D$ −57.6° (c 0.3, $CHCl_3$); IR 1725 and 1670 cm^{-1}; ^1H NMR δ 2.35 (dd, 1 H, J = 15.5, 3 Hz), 2.48 (m, 1 H, J = 11, 6 Hz), 2.54 (m, 1 H, J = 4.5 Hz), 2.86 (d, 1 H, J = 6.5 Hz), 2.92 (dd, 1 H, J = 8.5, 15.5 Hz), 3.03 (dd, 1 H, J = 16.5, 8.5 Hz), 3.72 (s, 1 H), 3.76 (s, 1 H), 5.06 (t, 1 H), 5.35 (m, 1 H, J = 6.5, 4 Hz), 7.40–8.20 (m, 9 H); EIMS m/z 436 (M^+), 181, 167, 152, 91, 79, 53, and 41. Anal. Calcd for $C_{22}H_{19}Cl_3O_3$: C, 60.36; H, 4.37; Cl, 24.30. Found: C, 60.54; H, 4.48; Cl, 24.5.

(3a*R*,4*S*,5*R*,6a*R*)-[4-[(2,2-Dimethyl-1-oxopropoxy)methyl]-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-yl 1,1′-Biphenyl-4-carboxylate (30). To a solution of Corey lactone (352 mg, 1 mmol) dissolved in pyridine (10 mL) containing DMAP (20 mg) was added pivaloyl chloride (1.23 mL, 10 mmol). This solution was stirred at room temperature overnight. Standard workup and purification on silica gel chromatography gave lactone **30** (420 mg, 97%): R_f = 0.44 (H–A, 2/1); $[\alpha]_D$ −14.7° (c 0.2, $CHCl_3$); mp 114 °C; IR 1775, 1725, and 1610 cm^{-1}; ^1H NMR δ 1.20 (s, 9H), 2.40 (dd, 1 H, J = 3.5, 16.5 Hz), 2.50 (dd, 1 H, J = 6, 7 Hz), 2.55 (m, 1 H), 2.60 (dd, 1 H, J = 2, 18 Hz), 2.80 (m, 1 H, J = 10, 2, 2.5 Hz), 2.95 (dd, 1 H, J = 10, 18 Hz), 4.14 (d, 2 H), 5.13 (t, 1 H, J = 6 Hz), 5.40 (m, 1 H), 7.40–8.20 (m, 9 H).

(3a*R*,4*S*,5*R*,6a*R*)-[2-(Dichloromethylene)-4-[(2,2-dimethyl-1-oxopropoxy)methyl]hexahydro-2*H*-cyclopenta-[*b*]furan-5-yl 1,1′-Biphenyl-4-carboxylate (31). Prepared from lactone **30** (210 mg, 0.5 mmol), 211 mg (84%): R_f = 0.46 (H–A, 4/1); mp 120 °C; $[\alpha]_D$ −56° (c 0.3, $CHCl_3$); IR 1725, 1670 and 1610 cm^{-1}; ^1H NMR δ 1.20 (s, 9H), 2.39 (dd, 1 H, J = 3.5, 16.5 Hz), 2.48 (m, 2 H, J = 5 Hz), 2.73 (m, 1 H, J = 6 Hz), 2.89 (dd, 1 H, J = 10, 18 Hz), 3.02 (dd, 1 H, J = 18, 2 Hz, H-3), 4.15 (dq, 2 H), 5.08 (dd, 1 H, J = 5, 2 Hz), 5.33 (m, 1 H), 7.40–8.20 (m, 9 H); EIMS m/z 502 (M^+), 304, 181,167, 152, 78, 69, 57, and 41. Anal. Calcd for $C_{27}H_{28}Cl_2O_5$: C, 64.42; H, 5.61; Cl, 14.08. Found: C, 64.55; H, 5.7; Cl, 14.2.

(6*S*,7*S*)-5,6,7,8-Tetrahydro-7-(hydroxymethyl)-8-[(2,2-dimethyl-1-propyl)oxy]-5-(3,4,5-trimethoxyphenyl)naphtho[2,3-*d*]-1,3-dioxole-6-carboxylic Acid γ-Lactone (32). Standard pivaloylation (see Compound **30**) of podophyllotoxin (200 mg, 0.5 mmol) gave ester **32** (140 mg, 56%): R_f = 0.39 (H–A, 2/1); $[\alpha]_D$ −142.5° (c 0.2, $CHCl_3$); IR 1790, 1740, and 1710 cm^{-1}; ^1H NMR δ 1.22 (s, 3 H), 1.25 (s, 6 H), 2.82 (m, 1 H), 2.94 (dd, 1 H, J = 9, 15 Hz), 3.78 (s, 6 H), 3.82 (s, 3 H), 4.24 (t, 1 H, J = 10 Hz), 4.34 (dd, 1 H, J = 9, 7 Hz), 4.62 (d, 1 H, J = 9 Hz), 5.86 (d, 1H, J = 9 Hz), 5.98 (d, 1 H, J = 12 Hz), 6.00 (d, 1 H, J = 12 Hz), 6.40 (s, 2 H), 6.58 (s, 1 H), 6.77 (s, 1 H).

(6*S*,7*S*)-5,6,7,8,10,12-Hexahydro-11-(dichloromethylene)-8-[(2,2-dimethyl-1-propyl)oxy]-5-(3,4,5-trimethoxyphenyl)-naphtho-[2,3-*d*]-1,3-dioxolo-[6,7-*c*]furan (33). Prepared from lactone **32** (140 mg, 0.3 mmol), 32 mg (19%): R_f = 0.29 (H–A, 6/1); $[\alpha]_D$ −56° (c 0.1, $CHCl_3$); IR 1735 and 1665 cm^{-1}. ^1H NMR δ 1.25 (s, 9 H), 2.78 (m, 1 H), 3.24 (dd, 1 H, J = 4, 13 Hz), 3.73 (s, 6 H), 3.85 (s, 3 H), 3.93 (dd, 1 H, J = 8.5, 11 Hz), 4.18 (dd, 1 H, J = 8.5, 7 Hz), 4.88 (d, 1 H, J = 4 Hz), 5.87 (d, 1 H, J = 10 Hz), 5.97 (d, 1H, J = 8 Hz), 5.99 (d, 1 H, J = 8 Hz), 6.40 (s, 2 H), 6.55 (s, 1 H), 6.72 (s, 1 H); EIMS m/z 564 (M^+), 529, 427, 391, 363, 312, 297, 259, 185, 168, 57, and 41. Anal. Calcd for $C_{28}H_{30}Cl_2O_8$: C, 59.48; H, 5.80; Cl, 12.54. Found: C, 59.61; H, 5.88; Cl, 12.32.

(6*R*,7*S*)-5,6,7,8,10,12-Hexahydro-11-(dichloromethylene)-8-[(2,2-dimethyl-1-propyl)oxy]-5-(3,4,5-trimethoxyphenyl)-naphtho[2,3-*d*]-1,3-dioxolo-[6,7-*c*]furan (34): 42 mg (25%); R_f = 0.22 (H–A, 6/1); $[\alpha]_D$ +62.6° (c 0.1, $CHCl_3$); IR 1730 and 1665 cm^{-1}; ^1H NMR δ 1.15 (s, 9 H), 2.99 (m, 1 H), 3.56 (t, 1 H, J = 7 Hz), 3.80 (s, 6 H), 3.82 (s, 3 H), 3.91 (dd, 1 H, J = 8, 10.5 Hz), 4.02 (d, 1 H, J = 7.5 Hz), 4.50 (t, 1 H, J = 8 Hz), 5.80 (d, 1 H, J = 2.5 Hz), 5.94 (d, 1 H, J = 1 Hz), 5.98 (d, 1 H, J = 1 Hz), 6.40 (s, 2 H), 6.58 (s, 1 H), 6.77 (s, 1 H, Ar); EIMS m/z 564 (M^+), 529, 462, 351, 338, 313, 282, 255, 57, and 41.

2,6-Anhydro-1-deoxy-1,1-dichloro-3,4,5,7-tetrakis-*O*-(phenylmethyl)-D-*gluco*-hept-1-enitol (36). Prepared from lactone **35**[27] (537 mg, 1 mmol), 428 mg (71%): R_f = 0.47 (H–A, 6/1); $[\alpha]_D$ +17.2° (c 0.5, $CHCl_3$); IR 1635 cm^{-1}; ^1H NMR δ 3.70 (dd, 1 H, J = 4.5, 10 Hz), 3.74 (dd, 1 H, J = 4, 11 Hz), 3.78 (dd, 1 H, J = 11, 2 Hz), 3.92 (dd, 1 H, J = 4.5, 1.5 Hz), 4.51 (m, 1 H), 4.70 (d, 1 H, J = 1.5 Hz), 4.35–4.70 (m, 8 H), 7.15–7.40 (m, 20 H); EIMS m/z 604 (M^+), 569, 405, 390, 229, 281, 271, 253, 181, 91, 65, and 51. Anal. Calcd for $C_{35}H_{34}Cl_2O_4$: C, 71.31; H, 5.81; Cl, 12.03. Found: C, 71.64; H, 5.92; Cl, 12.12.

2,6-Anhydro-3-*O*-acetyl-1-deoxy-1,1-dichloro-4,5-*O*-isopropylidene-D-*ribo*-hex-1-enitol (38). Prepared from lactone **37**[28,29] (277 mg, 1 mmol), 68 mg, (20%): R_f = 0.68 (H–A, 1/1); $[\alpha]_D$ +2.3° (c 1.5, $CHCl_3$); IR 1730 and 1665 cm^{-1}; ^1H NMR δ 1.80 (s, 3 H), 4.25 (m, 2 H), 4.60 (m, 2 H), 5.50 (d, 1 H, J = 5 Hz), 5.90 (s, 1 H), 7.40–7.60 (m, 5 H); EIMS m/z 344 (M^+), 196, 162, 115, 105, 99, 91, 77, 55, and 43. Anal. Calcd for $C_{15}H_{14}Cl_2O_5$: C, 52.19; H, 4.09; Cl, 20.54. Found: C, 52.51; H, 4.21; Cl, 20.32.

2,6-Anhydro-1,1-dichloro-3,4:5,7-di-*O*-isopropylidene-D-*manno*-hept-1-enitol (40). Lactone **39** was prepared from the corresponding lactol[30] (520 mg, 2 mmol). The lactol dissolved in dichloromethane (7 mL) was added to a preformed solution of the reagent (CO_2Cl_2 2.2 mmol, DMSO, 4.4 mmol in dichloromethane, 3.5 mL) at −60 °C. After 20 min triethylamine was added (1.27 mL, 9 mmol), and the mixture was stirred at room temperature for another 20 min. Standard workup and column chromatography gave lactone **39** (428 mg,

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83%). From lactone **39** (257 mg, 1 mmol), 243 mg (75%) of **40** was obtained: R_f = 0,61 (H–A, 4/1); $[\alpha]_D$ +109° (*c* 0.3, $CHCl_3$); IR 1631 cm^{-1}; ^1H NMR δ 1.45 (s, 3H), 1.50 (s, 3H), 1.56 (s, 3H), 1.60 (s, 3H), 3.40 (dt, 1H, J = 10, 6 Hz), 3.70 (m, 2H), 4.07 (dd, 1H, J = 6, 11 Hz), 4.15 (dd, 1H, J = 6, 8 Hz), 5.10 (d, 1H, J = 6 Hz); EIMS *m/z* 324 (M^+), 309, 262, 183, 101, 85, 62, 59, 51, and 43. Anal. Calcd for $C_{13}H_{18}Cl_2O_5$: C, 48.02; H, 5.58; Cl, 21.80. Found: C, 48.32; H, 5.63; Cl, 21.71.

1-Deoxy-1,1-dichloro-2,3:4,5:6,7-tri-*O*-isopropylidene-D-*gluco*-hept-1-enitol (42). Prepared from dioxolan **41**[31] (315 mg, 1 mmol), 351 mg (92%): mp 155–160 °C; R_f = 0.76 (H–A, 3/1); $[\alpha]_D$ +108.6° (*c* 1, $CHCl_3$); IR 1765 cm^{-1}; ^1H NMR δ 1.34 (s, 3H), 1.38 (s, 3H), 1.41 (s, 3H), 1.42 (s, 3H), 1.46 (s, 3H), 1.62 (s, 3H), 3.97 (m, 2H), 4.09 (m, 2H), 4.45 (dd, 1H, J = 8, 2 Hz), 4.99 (d, 1H, J = 2 Hz); EIMS *m/z* 382 (M^+), 367, 249, 223, 181, 143, 101, 85, 73, 59, and 43. Anal. Calcd for $C_{16}H_{24}Cl_2O_5$: C, 50.14; H, 6.31; Cl, 18.5. Found: C, 50.39; H, 6.29; Cl, 18.24.

4-[2-[(2,2-Dichloro-1-methylethenyl)oxy]ethyl]-1,2-dimethoxybenzene (44). Ester **43** was prepared by acetylation of the corresponding alcohol (364 mg, 2 mmol) with acetic anhydride (0.38 mL, 4 mmol) in pyridine (10 mL) overnight at room temperature. Standard workup and column chromatography gave **43** (444 mg, 98%). Compound **43** (220 mg, 1 mmol) gave **44** (174 mg, 59%): R_f = 0.42 (H–A, 5/1); IR 1645 cm^{-1}; ^1H NMR δ 2.00 (s, 3 H), 2.90 (t, 2 H, J = 7 Hz), 3.88 (s, 3 H), 3.92 (s, 3 H), 4.00 (t, 2 H, J = 7 Hz), 6.80 (m, 3 H); EIMS *m/z* 290 (M^+), 165, 150, 134, 121, 105, 91, 77, 65, 51, and 43.

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