D-RIBONOLACTONE IN ORGANIC SYNTHESIS - A REVIEW

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ABSTRACT - The use of D-ribonolactone, an inexpensive, commercially available sugar, as a chiral template in organic synthesis is described. The versatility of this compound is illustrated with selected examples from the literature. The regio- and stereoselective functionalization of D- ribonolactone and its use in the synthesis of precursors for many natural products demonstrate that D-ribonolactone is a valuable alternative to other sugars.

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INTRODUCTION

Carbohydrates are convenient chiral sources available in cyclic or acyclic forms, varying chain lengths and different oxidation or reduction states. Therefore, they have been used extensively as chiral precursors in the synthesis of natural products.[1,2] Simple sugars such as D-glucose, D-arabinose or D-ribose are employed routinely in organic syntheses.

A problem frequently associated with the utilization of carbohydrates in synthesis is the need for protection and deprotection protocols especially at the anomeric center. This shortcoming may be circumvented by having the anomeric center in its higher oxidation state as the lactone function. Commercially available D-ribonolactone thus provided an interesting alternative to simple sugars for the synthesis of other chiral γ-lactones.

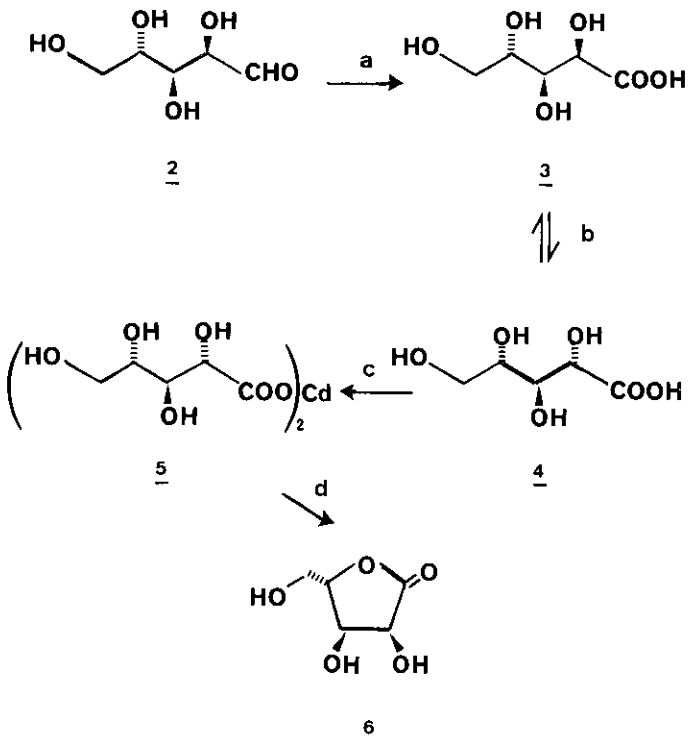
The chemistry of D-ribonolactone has not been extensively investigated, and its utilization in organic synthesis has therefore been fairly limited. Our interest[3] in the development of methodology to transform inexpensive, abundant carbohydrates into versatile intermediates, or "chirons",[1] to be used in natural product synthesis, led us to examine the use of commercially available D-ribonolactone as a chiral precursor.[4,5] As the utilization of D-ribonolactone is rapidly growing,[6-9] a literature review of the synthesis, properties, and uses of this compound appears timely.

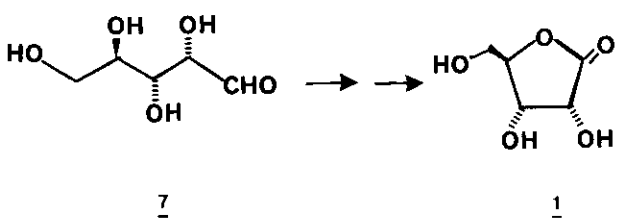
1. Synthesis and Properties of D-Ribonolactone

1.1. Synthesis of D-Ribonolactone and Derivatives

Ribonolactone was first prepared by E. Fischer[10] in 1891 during his historical study of the configuration of monosaccharides. Electrolytic oxidation of L-arabinose (2) (Scheme 1) with

Scheme 1





[a] $CaBr_2$, H_2O; [b] Py, Δ; [c] $Cd(OH)_2$; [d] H_2SO_4.

calcium bromide in aqueous solution afforded L-arabonic acid (3). Epimerization of 3 with pyridine at 130°C gave an equilibrium mixture of 3 and L-ribonic acid (4). Subsequent conversion of 4 into its cadmium salt (5), followed by lactonization with sulfuric acid, yielded L-ribonolactone (6) as a crystalline product, mp 72-76°C, $[\alpha]_D^{20}$ -18.0. Using Fischer's procedure, Steiger[11] converted D-arabinose (7) into D-ribonolactone (1), mp 77°C.

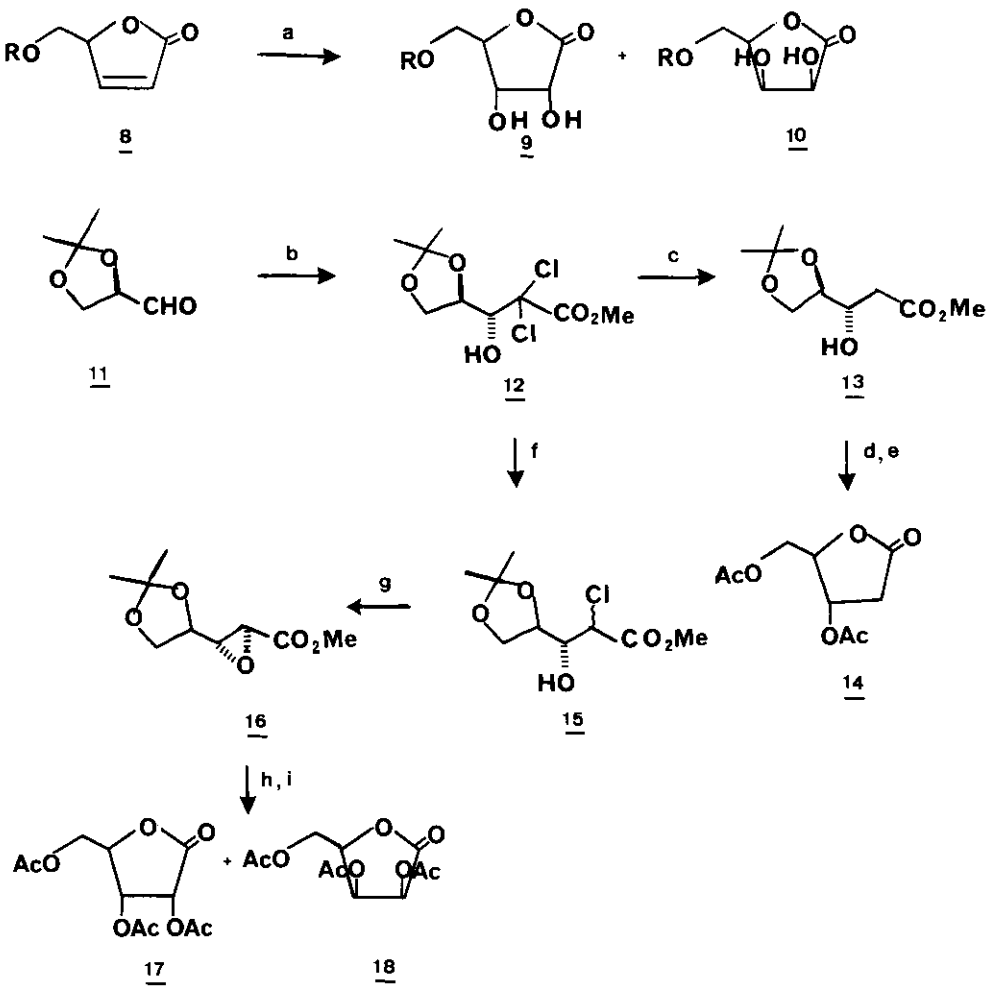
Subsequently D-ribonolactone was prepared by the acid catalyzed lactonization of D-ribonic acid,[12] calcium D-ribonate or alkyl D-ribonates.[13-15] It has also been obtained by the oxidation of D-ribose with an enzyme from the growing and resting cells of Pseudomonas fragi[16] or with silver carbonate on Celite.[17] Interestingly, D-ribonolactone has been reported to inhibit α- and β-glycosidases from rumen liquor, lucerne seed, limpet visceral hump and mouse liver.[18]

The synthesis of several derivatives of D-ribonolactone by oxidation of some γ-butenolides (8, Scheme 2) has been achieved by Mukaiyama and co-workers.[19] After investigating the efficiency of several oxidants, the combination of potassium permanganate with dicyclohexano-18-crown-6-ether (DCH-18-6C) gave the best yields of cis-2,3-dihydroxy-γ-butyrolactones (9 and 10). Examination of the effects of substituents at the γ-position of the butenolides revealed high stereoselectivity when bulky groups such as diphenylsilyl or trityl were present. The effects of substituents on the stereoselectivity of the reaction, as applicable to the synthesis of D-ribonolactone derivatives, are shown in Table 1.

Although the stereoselective incorporation of oxygenated functionalities onto the double bonds could be useful in the synthesis of polyoxygenated natural products such as macrolides and carbohydrates, this methodology offers no special advantages for the synthesis of D-ribonolactone derivatives as the chiral butenolide precursors are prepared from L-glutamic acid[20] via multiple steps.

A stereoselective synthesis of di-O-acetyl-2-deoxy-D-ribonolactone (14) and tri-O-acetyl-D-ribonolactone (17) has been accomplished by Shono and co-workers[21] during investigations of the diastereoselective addition of electrogenerated trichloromethyl and dichloro(methoxycarbonyl) methyl anions to α-branched aldehydes. Thus, the addition of electrogenerated dichloro(methoxycarbonyl) methyl anion to 2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde (11) resulted in almost exclusive formation of the "anti" isomer (12). The words "syn" and "anti" follow the definitions of Masamune[22] in which the main chain is drawn in a zig-zag fashion and the two substituents on the same side are designated as "syn" while those on opposite sides are designated as "anti". Isomer 12 was elaborated to di-O-acetyl-2-deoxy-D-ribonolactone (14) and tri-O-acetyl-D- ribonolactone (17) as shown in Scheme 2. The easy electroreductive generation of dichloro(methoxycarbonyl)methyl anions and the high stereoselectivity observed in their addition to α-branched aldehydes makes this reaction a promising route for the synthesis of

Scheme 2



[a]$KMnO_4$, DCH-18-C-6, CH_2Cl_2; [b]Aldehyde:CCl_3COOMe:$CHCl_2COOMe$ = 1:1:2; [c]+e, 0.3A, 6F/mol, 0.2M Me_4NCl, 90% MeOH; [d]TFA, RT, 2 hrs; [e]Ac_2O, Py, RT, 3 hrs; [f]+e, 0.3A, 3F/mol, 0.2M NH_4NO_3, 90% MeOH; [g]NaOMe, MeOH, RT, 2 hrs; [h]KOH, H_2O-Dioxane, Δ, 6h; [i]HCl, RT, 2 hrs.

Table 1. Effect of Substituents on the Stereoselectivity of Oxidation of 8.[19]

Compound	R	Yield (%)[i]	Selectivity (9:10)[ii]
a	CPh_3	61	>50:1[iii]
b	$Si(Me)Ph_2$	51	>30:1[iii]
c	CH_2Ph	66	12.1[iii]
d	COPh	60	7:1[iv]
e	$COCH_2Ph$	27	5:1[iv]

[i]Yields of isolated diacetates; [ii]Ratio of stereoisomeric diacetates; [iii]Determined by HPLC analysis; [iv]Determined by ^1H NMR integration.

carbohydrates.

1.2 Physical Properties of D-Ribonolactone

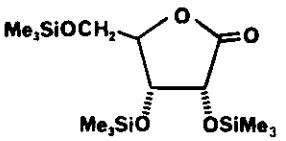
The commercially available D-ribonolactone is a white solid with mp 83-85°C, $[\alpha]_D^{23}$ +18.3° (c=5, H_2O). Its infrared spectrum[23] in Nujol mull displayed the following absorptions: 3330 (vs), 3200 (s), 2930 (s), 2860 (m), 1782 (vs), 1460 (m), 1410 (w), 1330 (m), 1300 (w), 1270 (vw), 1245 (vw), 1215 (w), 1180 (m), 1160 (s), 1096 (w), 1080 (s), 1040 (m, sh), 1015 (s), 950 (m), 897 (m), 850 (w), 767 (m), 707 (m, br) and 676 (m, br) cm^{-1}. The high frequency of the lactone carbonyl group ($1782cm^{-1}$) is noteworthy.

The mass spectrum of 2,3,5-tri-O-trimethylsilyl-D-ribonolactone (19) has been reported.[24,25] The m/e values and relative abundances of the observed peaks are reported in Table 2. The molecular ion (M^+) was recorded as a significant peak at mass 364. Other major fragments were identified as shown in Table 3. The ions with masses 45, 59, 73, 75, 89 and 103 are known to be characteristic of a trimethylsilyl ether.[24,26]

The X-ray crystal structure of D-ribonolactone was determined at -150°C.[27] The X-ray analysis indicated that this compound is orthorhombic and that the γ-lactone ring has a conformation midway between an envelope form (E_3) and a twist form ($^2T_3$) with puckering comparable to that observed in the furanose rings of nucleosides. The C-O-C=O group has bond lengths of 1.467, 1.354, and 1.203 Å, respectively, and a slight deviation from planarity with a C-O-C=O torsion angle of 172.7°. The molecules are believed to be linked by hydrogen bonds and form chains. The carbonyl oxygen is involved in a weak, bifurcated hydrogen-bond interaction with the 3-hydroxyl group. The ring oxygen is not involved in the hydrogen bonding. The orientation of the primary hydroxy group was shown to be gauche-trans.

The conformation of D-ribonolactone in solution has been investigated using its chiroptical properties.[28-30] The sign of the ORD curve in 1,4-lactones derived from carbohydrates was found to depend exclusively on the absolute configuration at the C(2) carbon atom. In the D-series, the first extremum value of lactones with the hydroxylic function in the R-configuration is negative while a positive value corresponds to the S-configuration. An analogous dependence was found by Beecham[31] for the sign of CD curves. Based on these studies, an envelope form was proposed for D-ribonolactone in which the hydroxyl group at position 2 tends to occupy a pseudoequatorial orientation (E_3) (Figure 1). Consequently, the ring is deformed and the C_3 carbon atom projects below the plane of the lactone ring formed by the -C-CO-O-C atoms when the 2-hydroxylic function is in the R-configuration, or above this plane in the case of the 2-hydroxylic function in the S-configuration. Therefore, a negative or positive sign of the ORD and CD curves corresponds respectively, to these two conformations of the lactone ring.

The existence of the conformational equilibria between the two envelope forms (^3E and E_3)



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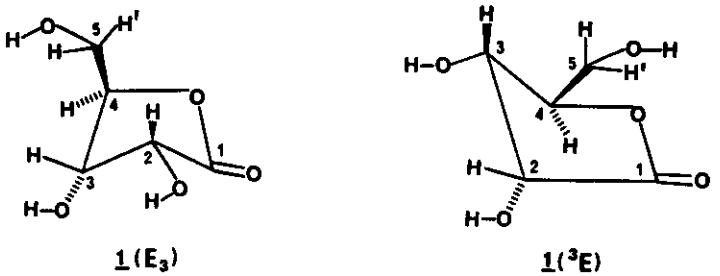


Figure 1

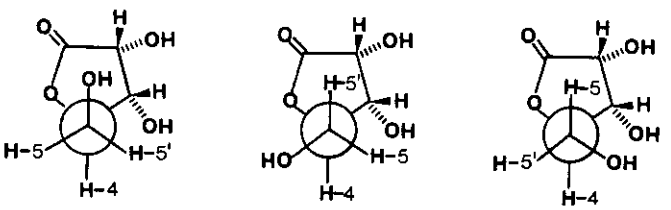


Figure 2

Table 2. Mass Spectrum of 2,3,5-tri-O-trimethylsilyl-D-ribonolactone (19).[25]

m/e	Relative Abundance	m/e	Relative Abundance	m/e	Relative Abundance	m/e	Relative Abundance
41	10	129	30	232	20	307	3
43	10	130	70	233	10	319	7
44	20	131	30	243	2	320	3
45	80	133	60	244	35	321	3
55	20	143	10	245	9	322	1
59	50	147	240	246	58	331	1
61	10	148	40	247	12	332	1
69	20	149	50	248	6	349	56
72	20	189	70	249	2	350	16
73	1000	190	10	257	2	351	8
74	90	191	20	259	55	352	2
75	100	203	20	260	11	353	1
89	30	204	70	261	6	364	52
101	20	205	30	262	1	365	19
102	70	215	70	274	2	366	8
103	90	216	20	291	19	367	2
104	10	217	110	292	6		
117	190	218	30	293	3		
118	20	219	10	305	6		
119	10	231	70	306	2		

Table 3. Major Fragments in the Mass Spectrum of 19.

m/e	Structure
147	CH_2-CH(OH)-CH_2-$OSiMe_3$
130	CH_2=CH-CH_2-$OSiMe_3$
117	CH_2-CH_2-$OSiMe_3$
103	CH_2-$OSiMe_3$
89	O-$SiMe_3$
75	O-$SiMe_2H$
73	$SiMe_3$
59	$SiMe_2H$
45	$SiMeH_2$

was demonstrated by Horton and Walaszek[32] using ^{1}H NMR and ^{13}C NMR spectroscopy. The ^{1}H NMR of D-ribonolactone was measured at 100 MHz in various solvents. The coupling constants and proton chemical shifts were used to provide evidence for the conformational equilibria (Table 4).

A relatively small value of $^{3}J_{3,4}$ (0.8 Hz in methanol-d_4 and in dimethylsulfoxide-d_6, and 0.5 Hz in pyridine-d_5) and also the small values of $^{3}J_{4,5}$ and $^{3}J_{4,5'}$, strongly support a conformational equilibrium in solution between the conformations ^{3}E and E_3. A relatively large value of $^{3}J_{2,3}$ (5.7 Hz in methanol-d_4) was explained in terms of the influence of electronegative substituents bonded to C-1, C-2 and C-3.

The conformational equilibrium is quantitatively defined by data obtained using equations derived for ribonucleosides (Table 5). The possible conformer populations for the 5-CH_2OH group are shown in Figure 2 and have been described as gauche-gauche (gg), gauche-trans (gt), and trans-gauche (tg) according to the relationship of H-4 with respect to H-5 and H-5'. The E_3 conformation, which has the 5-OH group over the lactone ring, and the exocyclic, CH_2OH group in a gauche-gauche disposition, appears to be the favored form in the equilibrium.

1.3. Functional Group Transformations of D-Ribonolactone

Early investigations on D-ribonolactone concerned with the preparation of derivatives, via suitable functionalization, to be used as intermediates in the synthesis of natural products. In 1968, Zinner and co-workers[33] prepared a benzylidene derivative of D-ribonolactone by treatment of 1 with benzaldehyde and concentrated hydrochloric acid. The structure of the product was confirmed to be 3,5-O-benzylidene-D-ribonolactone (20) (Scheme 3) by Chen and Joullié,[4,34] based on ^{1}H NMR studies. Chen and Joullié[35] have also observed that when zinc chloride was used instead of concentrated hydrochloric acid, 2,3-O-benzylidene-D-ribonolactone (21) was isolated as the major product (40%) along with small amounts of 20. Similar results were obtained by Garegg and co-workers[36] during their synthesis of O-benzylidene acetals of carbohydrates. These authors observed the formation of only one isomer (21) when D-ribonolactone was treated with benzal chloride in refluxing pyridine, although no prediction of the configuration at the acetalic carbon atom was made. The 2,3-O-cyclohexylidene-D-ribonic-γ-lactone (22) was prepared by treatment of 1 with cyclohexanone in benzene using Amberlite IR 120(H^+)[37] or ferric chloride[38] as catalyst. In an effort to develop new methodology for a mild, nonaqueous 1,2- and 1,3-diol protection-deprotection sequence, Lipshutz and Morey[39] converted 1 into derivative 23 by reaction with p-methoxyacetophenone dimethyl ketal in methylene chloride using pyridinium p-toluene sulfonate (PPTS) as catalyst. Although this protecting group introduces a new chiral center, in many instances, a preference for the formation of a major isomer was noted. For unexplainable reasons, deprotection of derivative 23 (protected either as its tert-butyl diphenyl silyl ether or

Table 4. ^1H NMR Spectra data for *D*-ribonolactone[32]

Solvent	Chemical shifts in δ values[a]					Coupling constants in Hz				
	H-2	H-3	H-4	H-5	H-5'	$^3J_{2,3}$	$^3J_{3,4}$	$^3J_{4,5}$	$^3J_{4,5'}$	$^3J_{5,5'}$
CD_3OD	4.61d	4.32q	4.39o	3.81q	3.73q	5.7	0.8	3.2	3.2	-13.0
Me_2SO-d_6[b]	4.89d	4.59q	4.70q	4.09m	4.01m	5.3	0.8	3.6	3.6	-12.3
C_5D_5N	5.78d	5.11q	5.09q	4.11q	4.04q	5.5	0.5	3.2	3.2	-12.3

[a]Signal multiplicities: d, doublet; m, complex multiplet; o, octet; q, quartet. [b]In the presence of CF_3CO_2H.

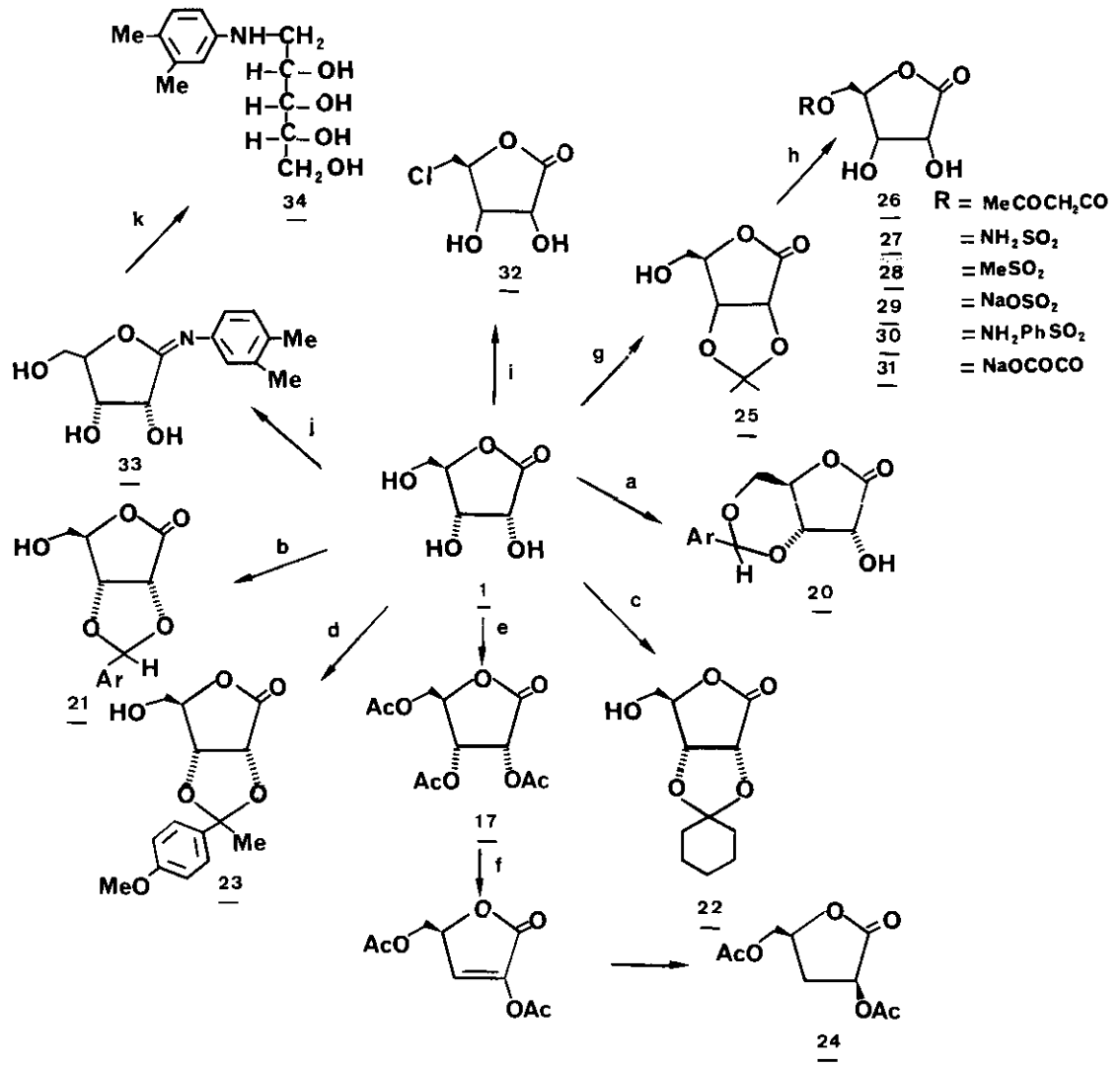
Table 5. Conformer Populations for D-Ribonolactone in Solution.[32]

Solvent	Lactone-ring (%)[a]		CH_2OH Group (%)[b]		
	^3E	E_3	*gauche*-gauche	*gauche*-trans	*trans*-gauche
CD_3OD	10	90	66	17	17
Me_2SO-d_6	10	90	60	20	20
C_5D_5N	5	95	66	17	17

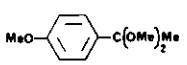
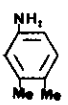
[a]Estimated from experimentally observed interdependence of the ring proton coupling constants in ribonucleosides.

[b]*Estimated from the Karplus equation, with* $J_{60°}$ = 1.5 and $J_{180°}$ = 11.5 Hz.

Scheme 3



[a] C_6H_5CHO, HCl; [b] C_6H_5CHO, $ZnCl_2$ or $C_6H_5CHCl_2$, py; [c]  , Amberlite IR 120 or $FeCl_3$;

[d]  , PPTS, CH_2Cl_2; [e] Ac_2O, py; [f] H_2, Pd-C, NEt_3; [g] CH_3COCH_3, HCl; [h] 1. RX, py or NEt_3, CH_2Cl_2, 2. H_3O^+; [i] 1. MsCl, Py, 2. H_3O^+; [j]  ; [k] H_2, $CuO-Cr_2O_3$.

phenyl carbonate) using tin tetrachloride met with little success.

D-Ribonolactone, on treatment with acetic anhydride in pyridine, afforded a triacetate (17) in 75% yield.[40] In 1981, Bock and co-workers[41] reported that triacetate 17, on treatment with hydrogen, in the presence of triethylamine and palladium on carbon, afforded diacetate 24, presumably via elimination of the 3-acetoxy group and subsequent stereoselective hydrogenation of the corresponding unsaturated intermediate.

Recently, Bigham and co-workers[42] have prepared a series of 5-O-substituted ribonolactones (26-31), to be tested as inhibitors of arabinose 5-phosphate (A5P) isomerase, a key enzyme in the biosynthesis of lipopolysaccharide, an essential component of the outer membrane of Gram-negative bacteria.

2,3-O-*Isopropylidene*-D-*ribonolactone* (25), prepared as described by Hough et al[43] was allowed to react with a variety of reagents under basic conditions (pyridine or triethylamine in methylene chloride) at or below 0°C. Acid removal of the 1,3-dioxolane protecting group gave the desired compounds (26-31) *in fair to good yields. An interesting observation was* the formation of the 5-chloro derivative (32) rather than the expected 5-mesylate or 5-tosylate during attempted sulfonylation in pyridine at room temperature. A recent communication[44] describes a similar transformation using tosyl chloride-dimethylaminopyridine. *In this case, aliphatic primary* alcohols reacted more slowly than allylic or propargylic primary alcohols.

Scholz[45,46] has utilized the functionalization of the lactone carbonyl of D-ribonolactone (1) in the preparation of N-[3,4-dimethylphenyl]-D-ribamine (34). The reaction of D-ribonolactone (1) with 3,4-dimethyl aniline gave the corresponding anilide. The hydrogenation of the anilide over a prereduced $CuO-Cr_2O_3$ catalyst afforded the desired product. The overall yield for this two-step sequence was 62%.

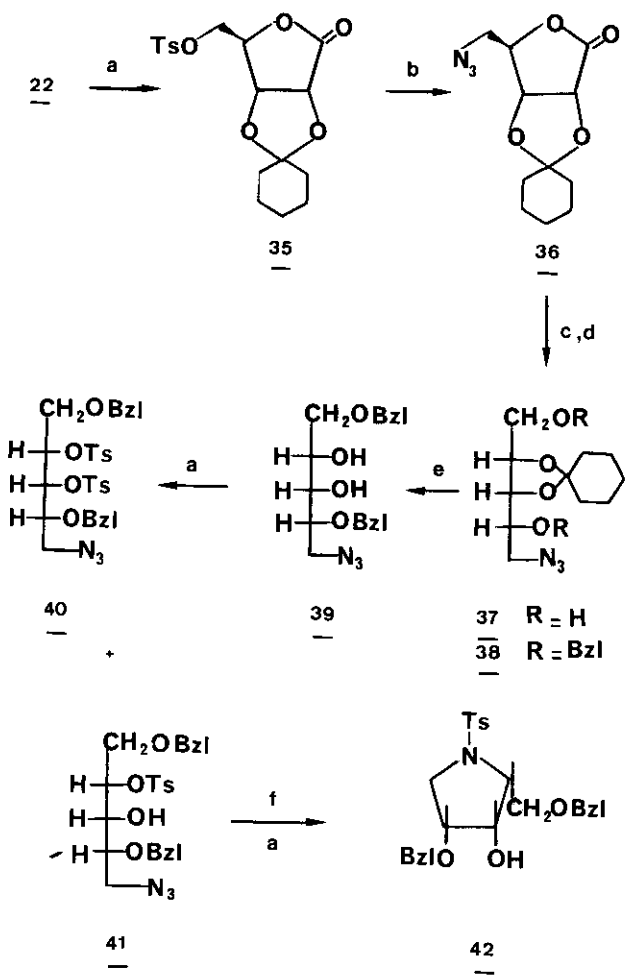
The electrochemical reduction of D-ribonolactone to D-ribose has been the subject of much study.[47,48] Electrolysis of 1 in ammonium sulfate solution on mercury cathode at 40% current efficiencies afforded D-ribose in 60-65% yield. Some of the technical parameters of this reduction on a pilot plant scale in a membrane electrolytic cell equipped with a Hg plate cathode have also been addressed.

2. Use of D-Ribonolactone in Organic Synthesis

2.1. Studies Related to the Synthesis of Anisomycin

Gero and co-workers[49] have carried out a nine-step synthesis of (2R,3S,4R)-4-benzyloxy-2-benzyloxymethyl-3-hydroxy-N-toluene-p-sulfonyl pyrrolidine (42) from D-ribonolactone (1) using an intramolecular reductive cyclization as the key step. This pyrrolidine derivative and related

Scheme 4



[a] $H_3C\ C_6H_4SO_2Cl$, py; [b] NaN_3, DMF; [c] $NaBH_4$, $\rangle$—OH; [d] NaH, $C_6H_5CH_2Cl$, DMSO; [e] Amberlite IR 120 (H^+); [f] H_2, PtO_2.

diastereomeric heterocyclic derivatives are of interest as skeletal analogues of the antitumor antibiotic, anisomycin.

Treatment of 2,3-O-cyclohexylidene-D-ribonolactone (22) with p-toluenesulfonyl chloride in pyridine gave the corresponding tosylate (35) (Scheme 4). Nucleophilic displacement of the tosylate with sodium azide in dimethylformamide afforded the azide 36 in 78% yield. Selective reduction of 36 using sodium borohydride in isopropanol at 0° yielded 5-azido-2,3-O-cyclohexylidene-5-deoxy-D-ribitol (37). Benzylation of 37 with benzyl chloride using sodium hydride in dimethyl sulfoxide, followed by mild acidic hydrolysis of the cyclohexylidene group using Amberlite IR 120 (H^+), afforded 5-azido-1,4-di-O-benzyl-5-deoxy-D-ribitol (39). The leaving group at C-2 in diol 39 was introduced next. Reaction of 39 with three molar equivalents of p-toluenesulfonyl chloride in pyridine gave a mixture of ditosylate (40) and monotosylate (41) in a ratio of 1:9. Hydrogenation of the azide function in 41 using Adam's catalyst followed by p-toluenesulfonylation afforded the desired compound by an intramolecular nucleophilic displacement. The methodology used to construct the pyrrolidine ring presents some advantages over the one used by Moffatt and co-workers[50] in their synthesis of (-) anisomycin from D-glucose as it reduces the number of steps needed and eliminates protection-deprotection protocols at the anomeric center.

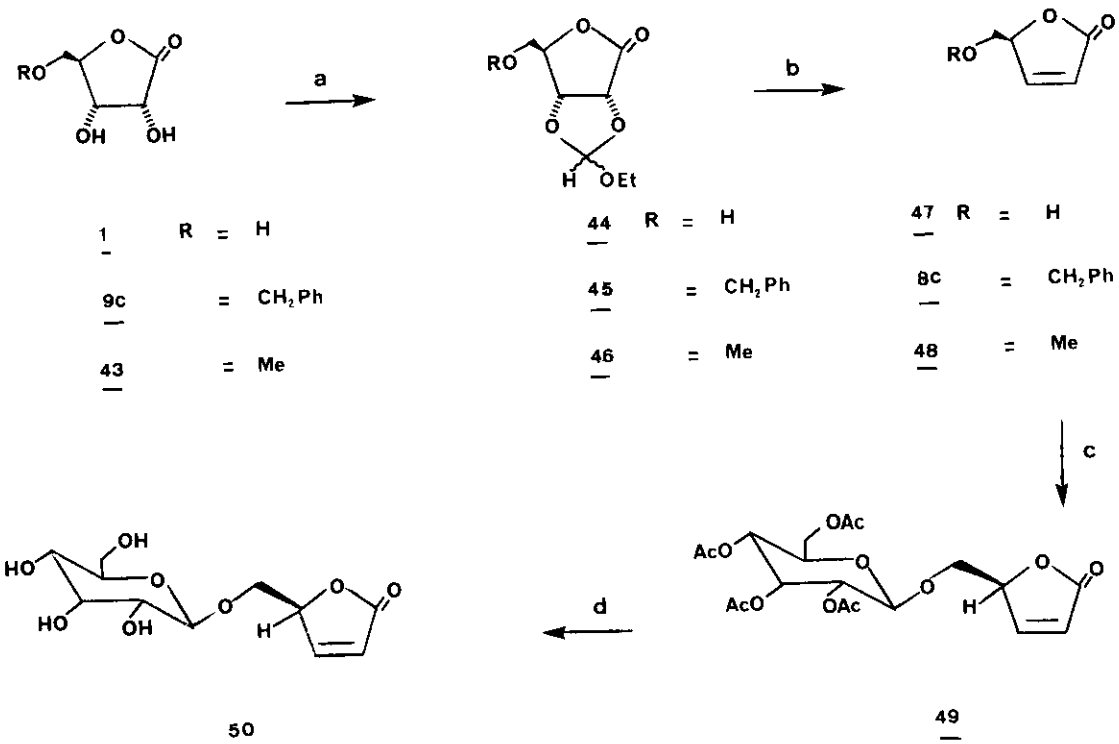
2.2. Synthesis of (S)-5-Hydroxymethyl-(5H)-furan-2-one and Glycoside (-)Ranunculin

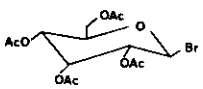
Font and co-workers[51] have utilized the chirality at C-4 of D-ribonolactone in a short synthesis of (S)-5-hydroxymethyl-(5H)-furan-2-one and several derivatives. These derivatives, in turn, are not only potential chiral synthons for the asymmetric total synthesis of several antileukemic lignan lactones but also served as intermediates in the synthesis of (-)Ranunculin,[52] a glycoside present in Ranunculaceae. The required transformations were: (a) conversion of the vic-diol function into a C=C and (b) etherification of the hydroxyl group at C-5. Thus, treatment of D-ribonolactone with one equivalent of triethyl orthoformate in refluxing tetrahydrofuran gave a mixture of stereoisomeric cyclic orthoformates (44) (Scheme 5) in quantitative yield. Pyrolysis at 220°C afforded the butenolide (47) in good yield. The reaction sequence was conveniently extended to O-benzyl-(9c) and O-methyl-(43) D-ribonolactone as well. Reaction of 47 with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide and silver oxide, in anhydrous ethanol, gave ranunculin acetate (49) in 88% yield. Further acid hydrolysis afforded the natural product (50).

2.3. Studies Related to the Synthesis of Maytansinoids

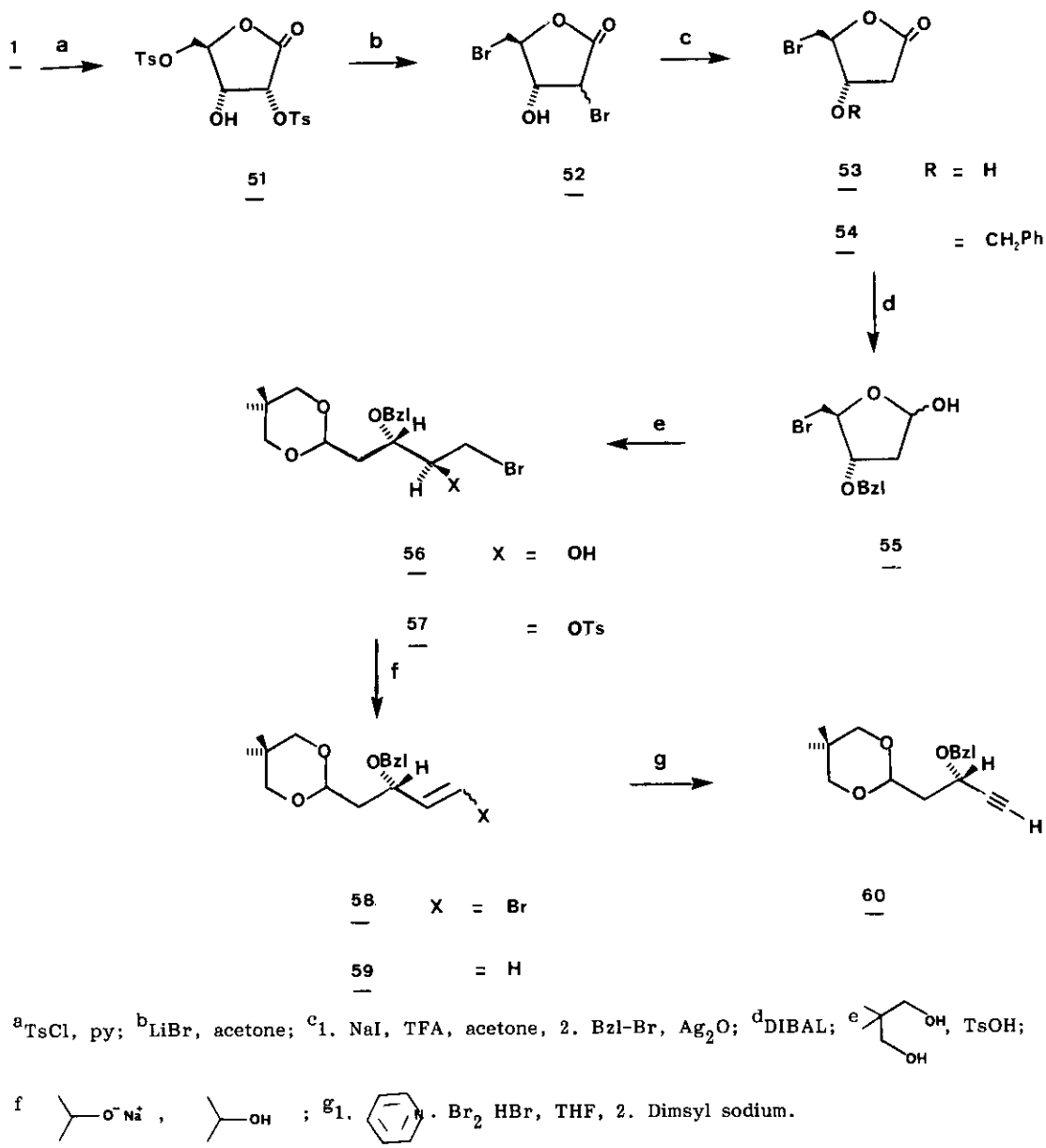
In a study related to the partial synthesis of C_1-C_5 of a bis-nor-maytansinoid, Barton and co-workers[7] selectively tosylated the hydroxyl groups at the 2- and 5-positions of D-ribonolactone to afford a ditosylate 51 (Scheme 6) in moderate yields. Compound 51 was transformed

Scheme 5



$^{a}HC(OEt)_3$; $^{b}\Delta$; ^{c}  , Ag_2O; $^{d}H^{+}$.

Scheme 6



[a]TsCl, py; [b]LiBr, acetone; [c]1. NaI, TFA, acetone, 2. Bzl-Br, Ag_2O; [d]DIBAL; [e] , TsOH;

f , ; [g]1. . Br_2 HBr, THF, 2. Dimsyl sodium.

quantitatively to the dibromide 52 which was then reduced to the 5-bromo compound 53. Treatment of 53 with benzyl bromide and silver oxide in ethyl acetate gave the corresponding O-benzyl derivative 54 in high yields. Reduction of the lactone with DIBAL, followed by acetal formation, afforded 56 in 52% yield. Tosylation of 56 gave 57 which when treated with sodium isopropylate in refluxing isopropanol, gave a low yield of vinyl bromides (58). However, reaction of tosylate 57 with sodium iodide in acetone produced the olefin (59) in good yield. Subsequent bromination and debromination gave the desired compound (60).

2.4. Total Synthesis of (-) Neplanocin A

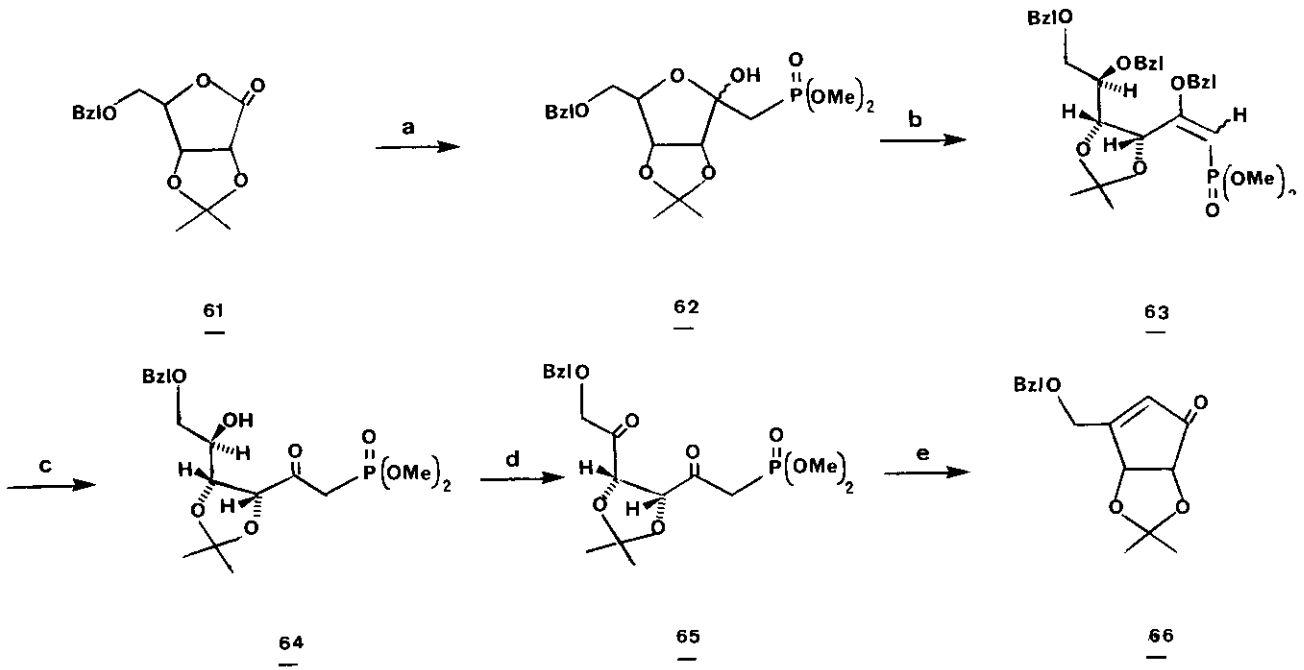
One of the most attractive uses of ribonolactone as a ready source of chirality is exemplified in the synthesis of antitumor antibiotic neplanocin A (74) by Lim and Marquez.[8] The synthesis begins with (-)5-O-benzyl-2,3,O-isopropylidene-D-ribonolactone (61)[52] (Scheme 7). Coupling of 61 with lithium dimethyl methyl phosphonate in THF afforded the hemiketal 62 in quantitative yield. Benzoylation gave the acyclic dibenzoate 63 as a mixture of geometrical isomers which, without purification, was debenzoylated to the β-ketophosphonate 64 in good yield. Oxidation of 64 with Collins reagent, followed by intramolecular cyclization under high dilution, gave the desired 2-cyclopentenone 66. A regio- and stereoselective reduction of the carbonyl group was achieved using sodium borohydride in a methanolic solution of 0.4 M $CeCl_3 \cdot 7H_2O$. Mesylation of 67 followed by nucleophilic displacement gave the azide 69 with inversion of configuration. Subsequent reduction of the azide 69 produced cyclopentenylamine 70, condensation of which with 5-amino-4,6-dichloropyridimine followed by ring closure and treatment with methanolic ammonia gave 73 in an overall yield of 58% for the three step sequence. Debenzylation with boron trichloride in dichloromethane was accompanied by removal of the isopropylidene group to afford neplanocin A, identical in all respects with the natural product.

2.5. Metal Carbene Mediated Methylenation of Aldonolactones

Recently titanium mediated methylenation of aldonolactones has been accomplished by Wilcox and co-workers[9] to prepare versatile intermediates for the synthesis of C-glycosides and oxygen heterocycles. Treatment of the protected D-ribonolactone 75 (Scheme 8) with the titanium carbene complex 76 in THF afforded the enol ether 77 in good yields. Conversion of the enol ether to acetate 78, followed by treatment with allyl trimethyl silane and zinc bromide, gave the allylic bis-alkylated C-glycoside 79 in high yields. The additional methyl group was found to improve the stereoselectivity of the reaction. This procedure provided an effective means of bis-alkylation at the anomeric carbon in carbohydrate rings. Moreover the intermediate enol ethers are expected to be versatile intermediates in the synthesis of several potential enzyme inhibitors.

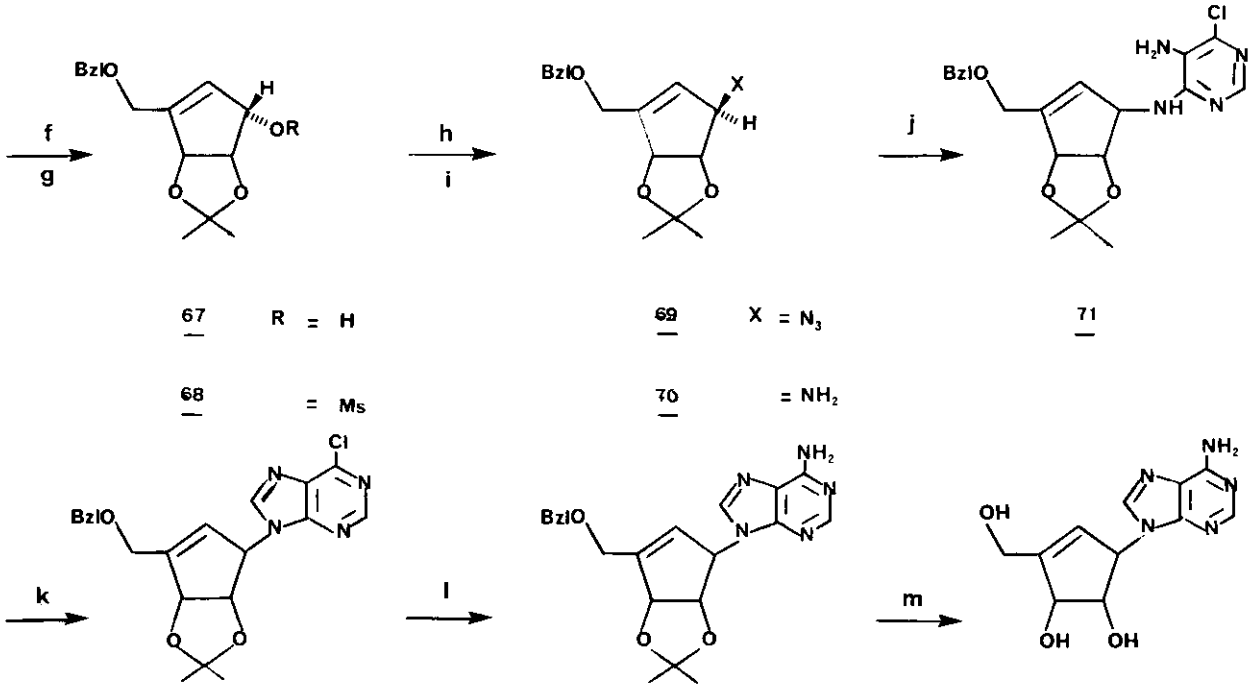
It is also pertinent to include the investigations of Ogura and co-workers[53,54] on the development of a one-step asymmetric synthesis of C-nucleoside analogs. The reaction of ethynyl

Scheme 7



[a] $LiCH_2\overset{O}{\overset{\|}{P}}(OMe)_2$, THF; [b] C_6H_5COCl, py; [c] NaOMe, MeOH; [d] CrO_3, py, CH_2Cl_2; [e] K_2CO_3, 18-crown-6, C_6H_6;

Scheme 7 (continued)



67 R = H

68 = Ms

69 X = N_3

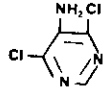
70 = NH_2

71

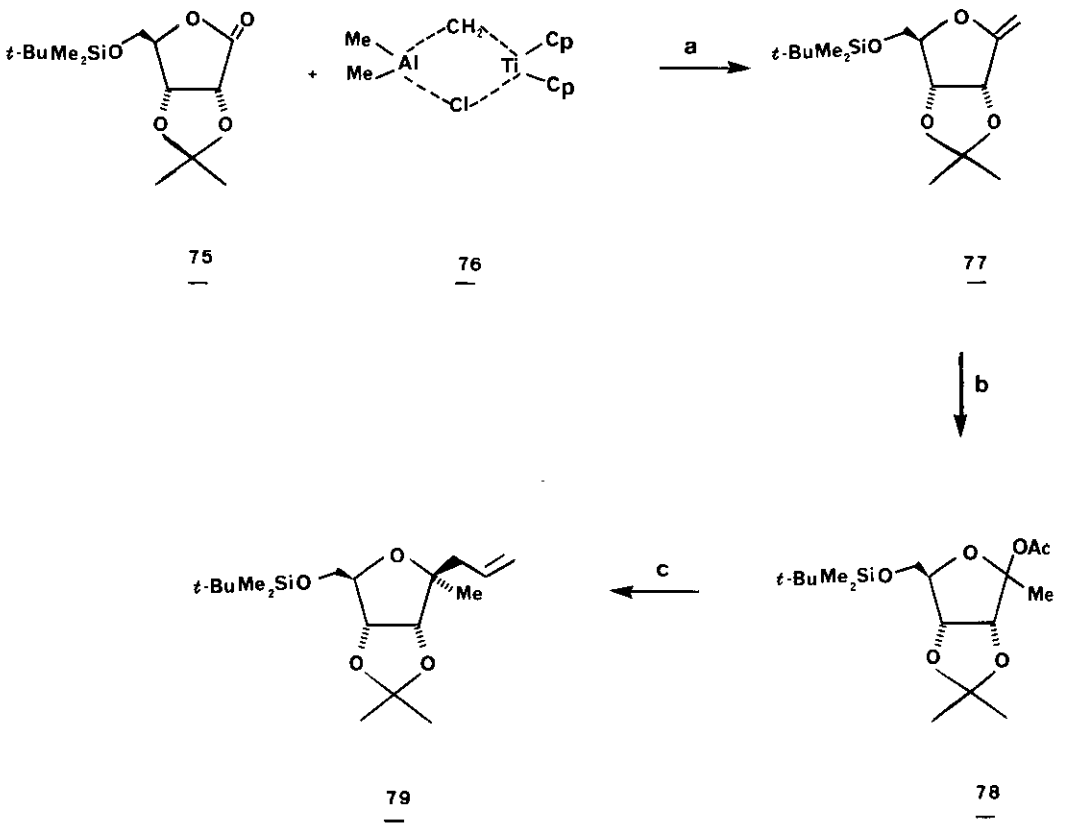
72

73

74

$^{f}NaBH_4$, $CeCl_3$, MeOH; $^{g}MsCl$, NEt_3, CH_2Cl_2; $^{h}LiN_3$, DMSO, HMPA; ^{i}  , NEt_3, MeOH; ^{j}  , n-BuOH; $^{k}CH(OEt)_3$, Ac_2O or HCl; $^{l}NH_3$, MeOH; $^{m}BCl_3$, CH_2Cl_2, MeOH.

Scheme 8



75 — 76 — 77 — 78 — 79

[a]THF, C_7H_8, -40°C; [b]HOAc, 25°, 1 hr; [c]  $SiMe_3$, $ZnBr_2$, CH_2Cl_2.

compounds and lithiated heterocycles with sugar lactones yielded a carbon linked nucleoside. Although treatment of 5-O-(tetrahydropyran-2-yl)-2,3-O-isopropylidene-D-ribonolactone (80) (Scheme 9) with n-butyllithium and phenyl acetylene in ether failed to afford the desired product, reaction of 2,3-O-isopropylidene-D-ribonolactone (25) with lithium acetylides gave 1-(2-substituted ethynyl)-2,3-O-isopropylidene-D-ribofuranose (81) in 30% yield. Under similar conditions, the C-nucleoside 82 was obtained in 23% yield.

2.6. Approaches to the Synthesis of Sugar Thiolactones

Dominguez and Owen[55] examined the possibility of using D-ribonolactone in the synthesis of sugar thiolactones. Thus, the reaction of 2,3-O-isopropylidene-5-O-tosyl-D-ribonolactone (83)[43] (Scheme 10) with potassium thioacetate in dimethyl formamide gave an excellent yield of 2,3-O-isopropylidene-5S-thioacetyl-D-ribonolactone (84), the displacement of the primary sulphonyloxy group taking precedence over attack on the lactone ring. Treatment of the product with dimethylamine in ether opened the lactone ring and also effected deacetylation to give amide 85. Subsequent desulphurization with Raney nickel followed by alkaline hydrolysis and lactonization afforded 5-deoxy-2,3-O-isopropylidene-D-ribonolactone (86).

2.7. A New Synthesis of L-Ribofuranose Derivatives

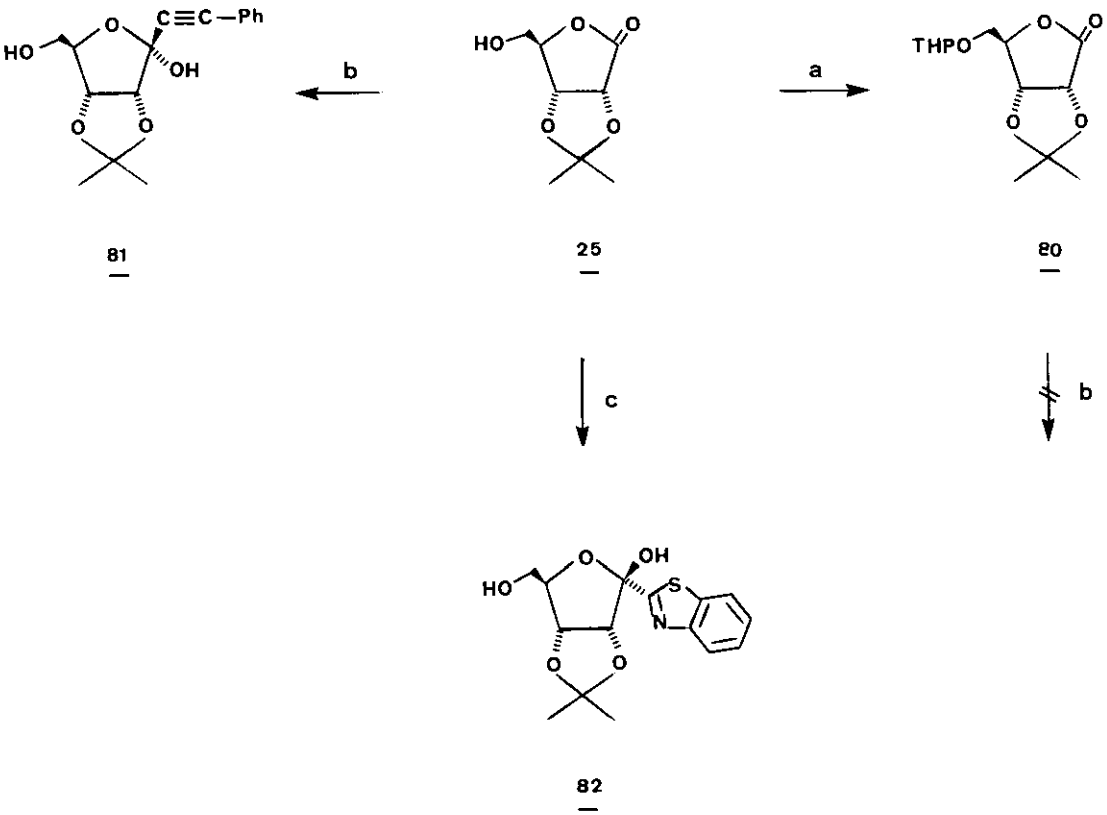
Using D-ribonolactone as starting material, a new and convenient synthesis of L-ribofuranose derivatives has been developed by Walker and Hogenkamp.[56] The two key reactions in this synthesis are: (a) oxidation of the hydroxymethyl group of 2,3-O-isopropylidene-D-ribonolactone (25) with dimethyl sulfoxide-N,N'-dicyclohexylcarbodiimide and (b) reduction of methyl (methyl α,β-L-ribofuranoside) uronate with sodium bis (2-methoxyethoxy)aluminum hydride.

Oxidation of 25 was attempted with several reagents, such as methyl sulfoxide-acetic anhydride, methyl sulfoxide-phosphorus pentoxide, chromium trioxide-dipyridine complex, etc. Only the dimethyl sulfoxide-dicyclohexylcarbodiimide reagent with pyridinium trifluoroacetate as catalyst was found to be a mild enough oxidant for the conversion of 25 to the aldehyde derivative of 2,3-O-isopropylidene-D-ribonolactone (87) (Scheme 11). Removal of the protecting group using 0.1 M hydrochloric acid in dioxane gave L-riburonic acid (88) in good yield. Treatment of 88 with methanolic hydrogen chloride gave a mixture of the two methyl (methyl α,β-L-ribofuranoside) uronates (89) in 98% yield. Reduction of 89 with sodium bis-(2-methoxyethoxy)aluminum hydride gave two chromatographically separable anomeric methyl-L-ribofuranosides (90 and 91).

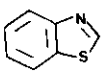
2.8. Synthesis of (±)-t-Butyl-8-O-t-butyldimethylsilylnonactate

Barrett and Sheth[6] have utilized a readily available derivative of D-ribonolactone in their seven step synthesis of the title compound, a monomeric species of the ionophore antibiotic nonactin produced by Streptomyces. 2,3,5-Tri-O-acetyl-D-ribonolactone (17) on reaction with

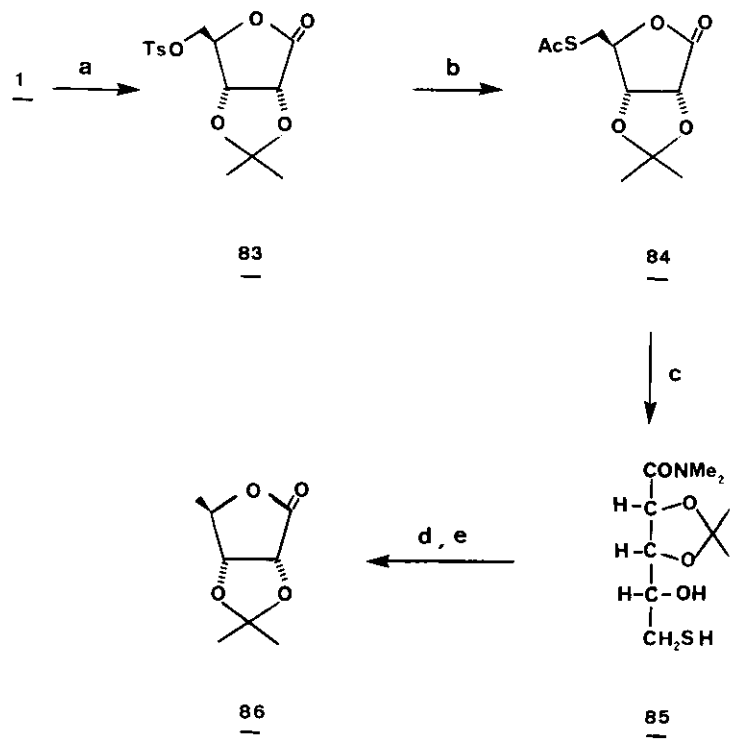
Scheme 9



81 25 80 82

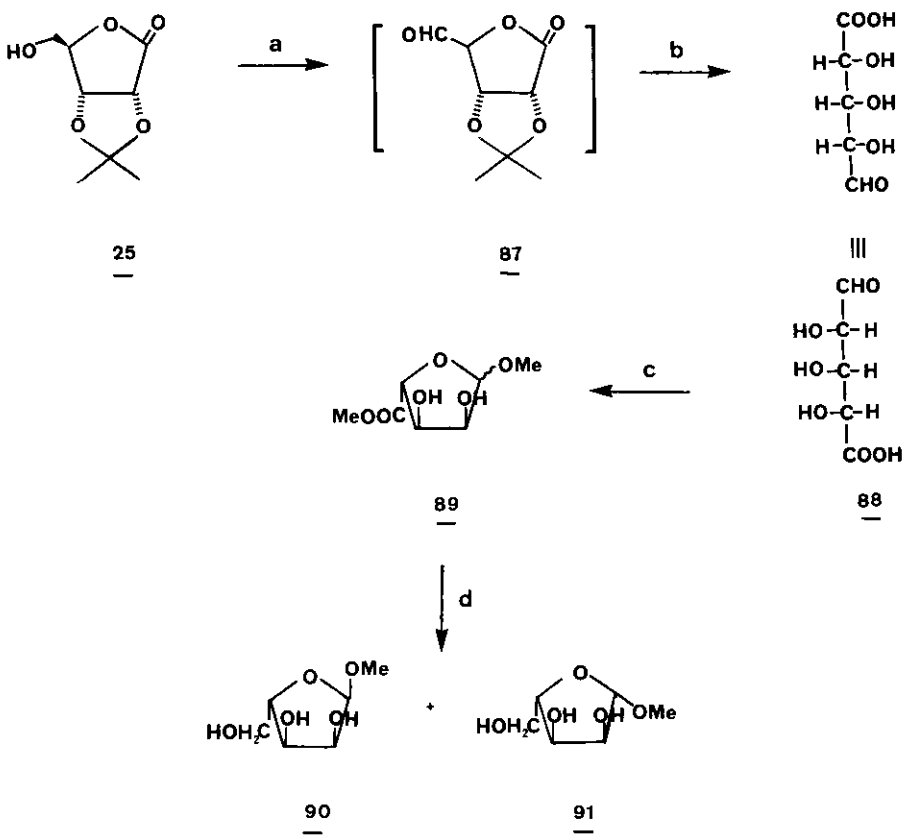
[a]DHP, TsOH, DMF; [b]Li-C≡C-C_6H_5; [c] 

Scheme 10



[a]Ref. 43; [b]KSAc, DMF; [c]$HNMe_2$, ether; [d]Raney Ni, EtOH; [e]NaOH, H^+.

Scheme 11



[a]DMSO, DCC, Py, TFA; [b]HCl, Dioxan; [c]MeOH, HCl; [d]Red-Al, THF.

DBU, underwent double elimination of acetic acid to afford the diene acetate 92 (Scheme 12). Stereocontrolled hydrogenation of compound 92 gave 93 in >97% yield in an isomerically pure form. DIBAL reduction of 93 gave lactol 94. Compound 94, on reaction with ethoxycarbonyl methylene triphenyl phosphorane, followed by in situ hydrogenation and acidification, produced the stereochemically pure lactone 96, presumably via the enoate 95. Silylation, followed by reaction of the lactone with t-butyl-2-lithiopropanoate, gave, after acidification, the enoate 98 with E-geometry. Hydrogenation of 98 afforded the title compound as a mixture of isomers in an 85:15 ratio in favor of the desired product. The overall yield for this sequence was >24%.

2.9. Studies Related to the Synthesis of Lasalocid A

Recently, Ireland and co-workers[57] have used D-ribonolactone in the synthesis of one of the intermediates, bromopentene 104, needed for the total synthesis of lasalocid A (X537A), an ionophore antibiotic. D-Ribonolactone (1) was first converted to its trityl ether in 84% yield by reaction with trityl chloride in pyridine. Treatment of the trityl ether with N,N'-thiocarbonyl-diimidazole (CDI) gave 101 (Scheme 13) in 79% yield. Raney nickel effected the conversion of 101 to the α,β-unsaturated ketone (8a) in 73% yield. A single isomer resulted from the 1,4-addition of lithium dimethyl cuprate to the unsaturated lactone. Catalytic detritylation of 102 was followed by conversion of the alcohol to the bromide via the mesylate. Reductive fragmentation of the bromide using lithium in liquid ammonia gave the methyl pentenoic acid (103). Subsequent reduction of the acid to the alcohol, followed by conversion to the bromide via the mesylate, completed the synthesis of the desired bromopentene in high enantiomeric purity.

2.10. Studies Related to the Synthesis of Methynolide

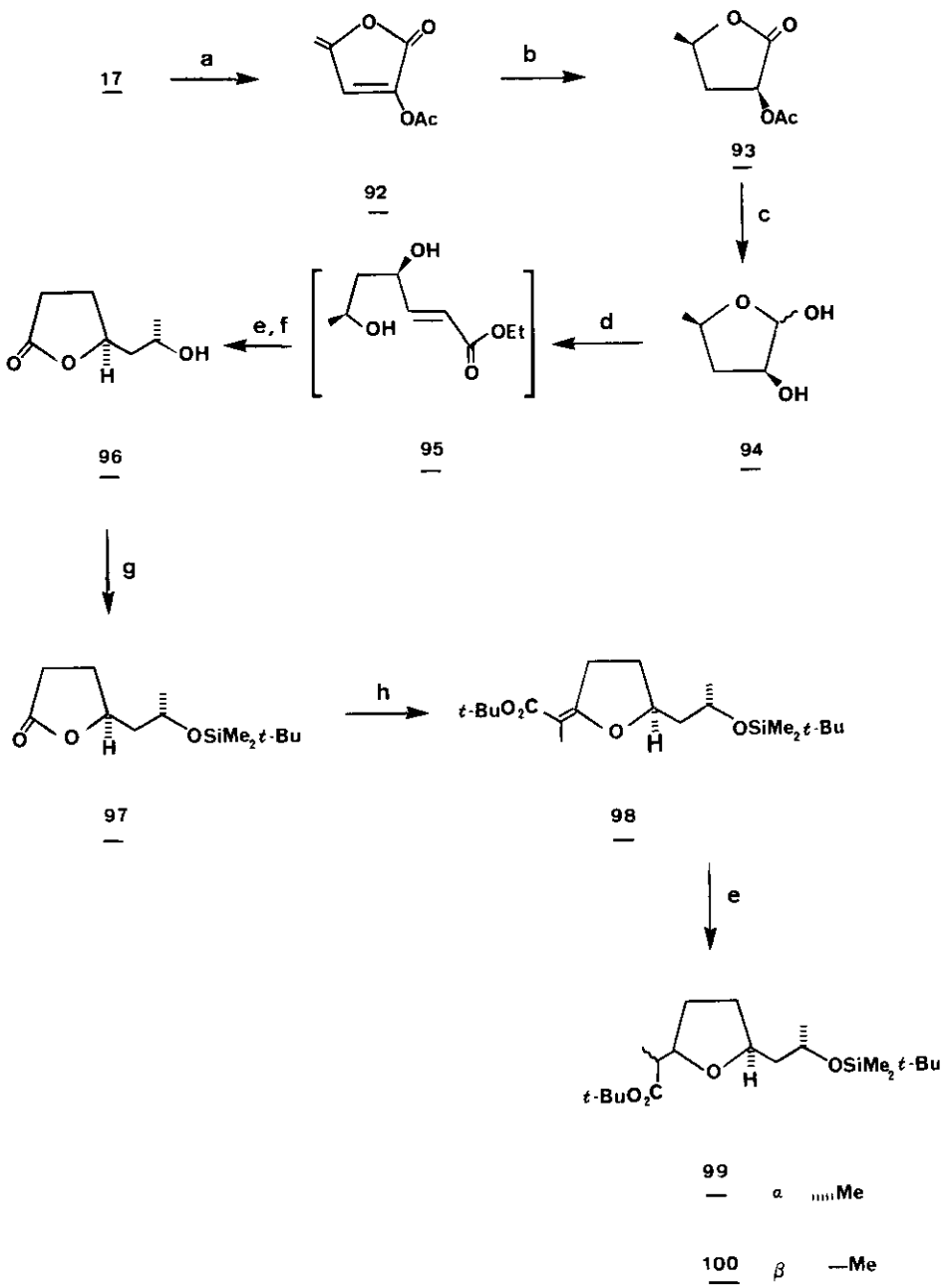
In connection with studies related to the partial synthesis of the aglycone methynolide, Hoffmann and Ladner[58] have used D-ribonolactone in the synthesis of one of the intermediates dioxolane carboxylic ester (107). The reaction of 2,3-O-isopropylidene-5-O-tosyl-D-ribonolactone (83)[43] with sodium methoxide (0.95 equiv.) in tetrahydrofuran gave the epoxy ester 105 (Scheme 14) in 89% yield. An excess of sodium methoxide caused partial epimerization at C-4. Deoxygenation of 105 using potassium selenocyanate yielded the olefin 106 in 59% yield which was hydrogenated to afford the desired dioxolane ester 107 in 88% yield.

Interestingly these investigators were unable to methylate the α-position of the lactone carbonyl in a suitably hydroxyl protected 2,3-O-isopropylidene-D-ribonolactone (8d, 108) although the formation of enolate was inferred[59] when lithium diisopropyl amide was used as the base.

2.11. Synthesis of Litsenolides

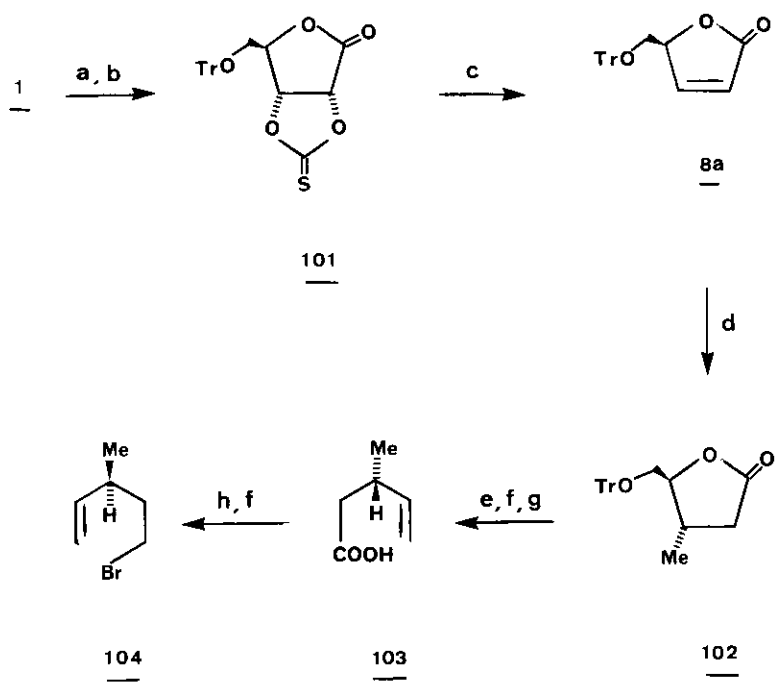
The scope and utility of D-ribonolactone in organic synthesis has been further demonstrated by Chen and Joullié,[4,5,34] in the synthesis of optically active γ-lactones. First, the regio- and stereoselective functionalization of 1 was examined. Selective bromination of the primary hydroxyl

Scheme 12



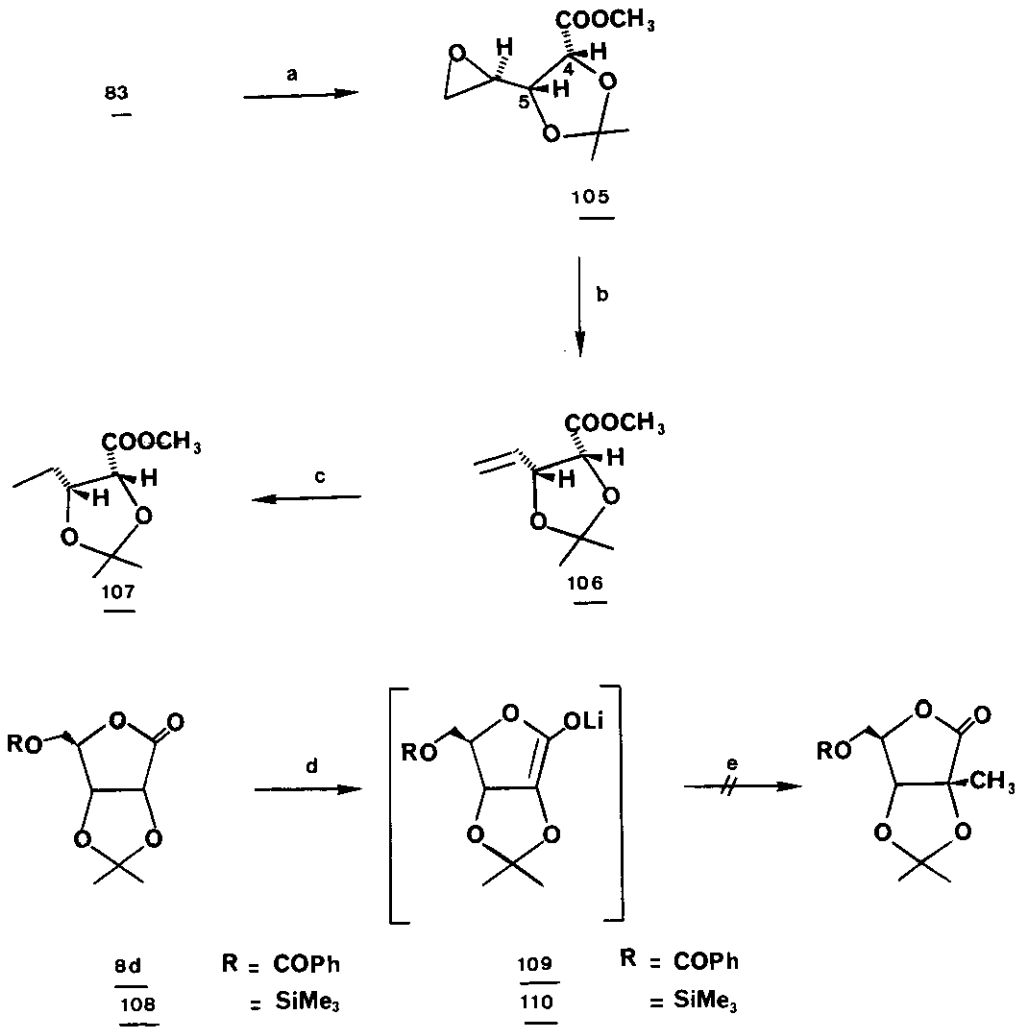
[a]DBU, THF, -20 to 0°; [b]H_2, Pd-$CaCO_3$, THF; [c]DIBAL, PhMe, -78°, HOAc; [d]Ph_3P=CH-COOEt, THF; [e]H_2, Rh-Al_2O_3, THF; [f]CF_3COOH; [g]t-$BuMe_2SiCl$, imidazole, DMF; [h]CH_3-CH=C(O-t-Bu)-OLi, THF, HOAc, Amberlite 120H.

Scheme 13



[a]Ph_3CCl, py; [b]CDI, acetone; [c]Ra-Ni, acetone; [d]$LiMe_2Cu$, ether; [e]5% Pd-C, EtOH, H_3O^+; [f]MsCl, NEt_3, CH_2Cl_2, LiBr, THF; [g]Li, $NH_3(l)$, THF; [h]$LiAlH_4$, Et_2O.

Scheme 14



8d R = COPh
108 = SiMe3

109 R = COPh
110 = SiMe3

[a]NaOMe, THF; [b]KSeCN; [c]H_2/Pt; [d]LDA; [e]CH_3I.

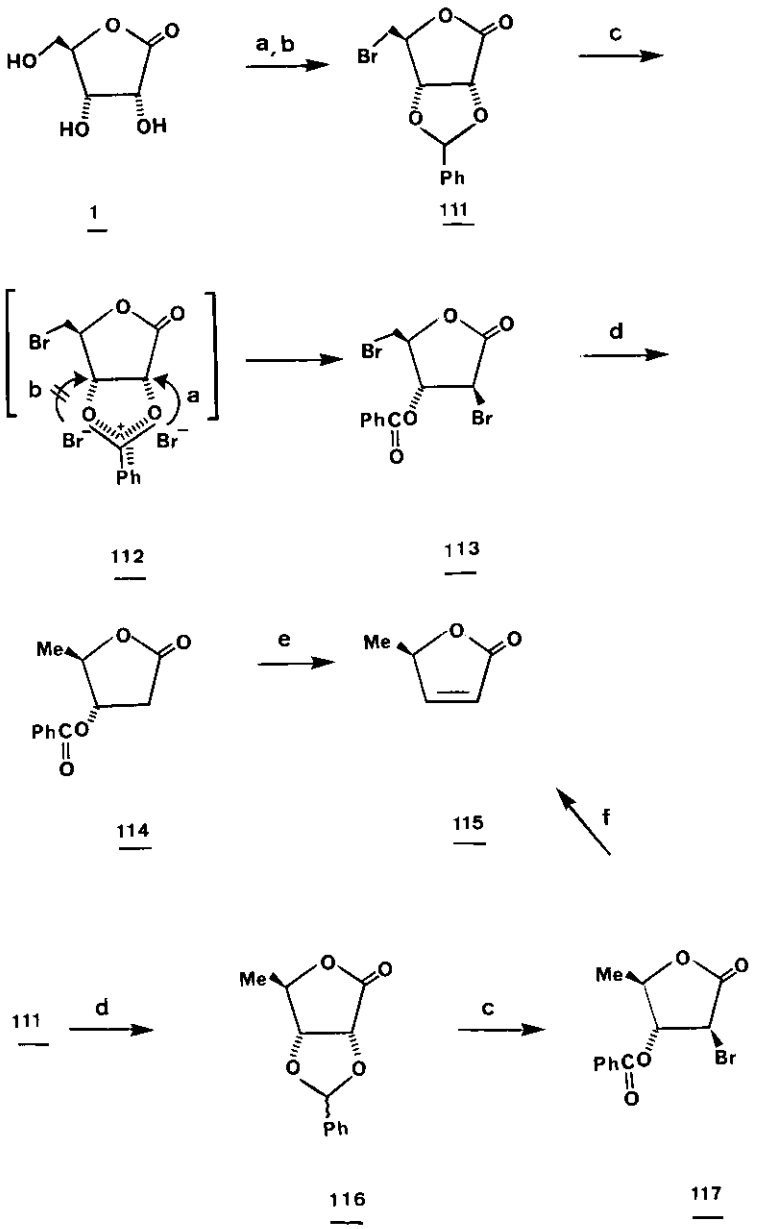
group of 1 with triphenylphosphine and carbon tetrachloride, followed by treatment with benzaldehyde and anhydrous zinc chloride afforded 2,3-O-benzylidene-5-bromo-5-deoxy-D-ribonolactone (111) (Scheme 15) in 58% yield as a 2:1 mixture of separable diastereomers. Using Hanessian's procedure,[60,61] the dibromobenzoate (113) was obtained in essentially quantitative yield. The exclusive formation of (113) was believed to proceed through ionic intermediate 112. SN_2 Attack of bromide ion from the more electrophilic and less sterically hindered position (path a) of the benzoxonium ion opened the ring in a regio- and stereoselective fashion. Tri-n-butyltin hydride reduction of 113 afforded benzoate 114 in 75% yield. Treatment of 114 with methanolic ammonia gave butenolide 115 in quantitative yield. Alternatively, reduction of 111 with tri-n-butyltin hydride afforded 116 in 78% yield. Stereoselective opening of the benzylidene ring in 116, using Hanessian's procedure,[60,61] gave bromobenzoate 117 in 88% yield. Treatment of compound 117 with zinc in refluxing ethanol afforded the previously prepared butenolide 115 in 93% yield.

With compounds 114 and 117 in hand, the possibility of functionalizing the α-position of these γ-lactones was next examined. All attempts to generate an enolate from 114 resulted in decomposition of the starting material; similarly treatment of 117 with triphenylphosphine or triethyl phosphite failed to yield the desired Wittig-type precursor. In both cases, these failures were due to the presence of the β-benzoxyl group and its facile elimination. Analogous results were obtained with other β-hydroxyl protecting groups such as t-butyldimethylsilyl ether and tetrahydropyran ether.

The next intermediate to be prepared was 2,5-dideoxy-D-erythro-pentono-γ-lactone (120) (Scheme 16). Benzylidene derivative 20 was prepared in 93% yield according to Zinner's procedure.[33] Reaction of 20 with carbon disulfide in the presence of sodium hydride in DMF was followed by methylation to give the corresponding xanthate, 118, in 76% yield. Reduction of 118 with tri-n-butyltin hydride afforded the 2-deoxy-γ-lactone (119) in 93% yield. Hydrolysis of 119 with 50% aqueous trifluoroacetic acid in chloroform was followed by selective bromination with triphenylphosphine and carbon tetrabromide to afford 53 in 30% yield. Debromination of 53 with tri-n-butyltin hydride gave 120 in 92% yield.

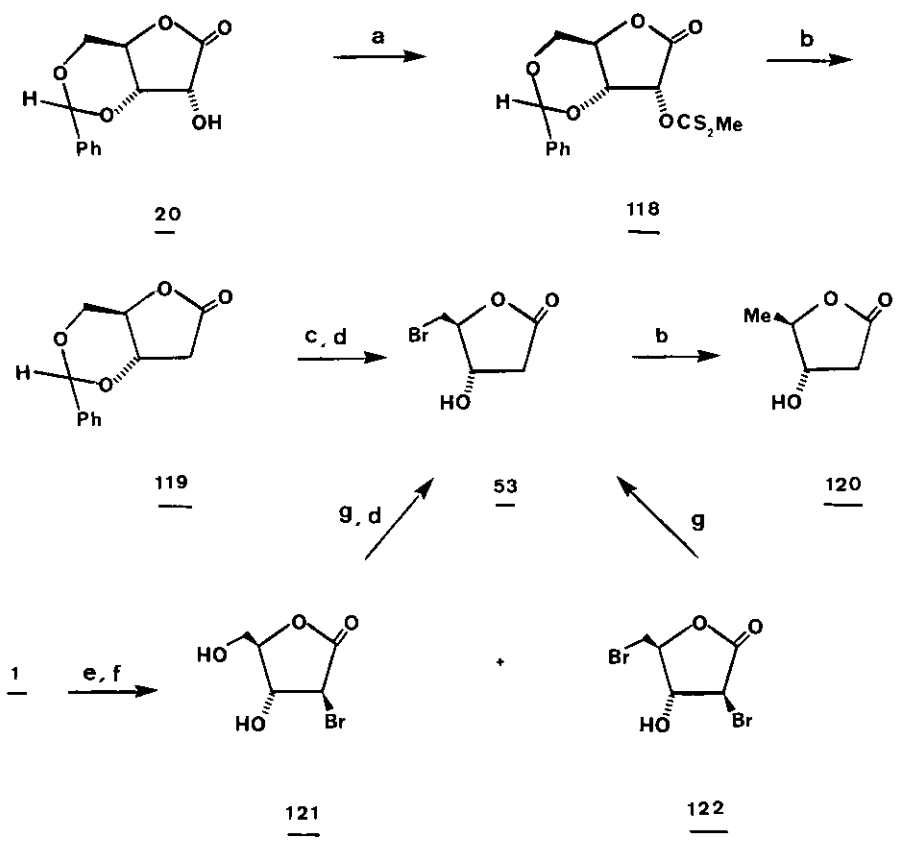
The low yield obtained for 120 created the need for an alternative approach to this intermediate. The conversion of 1 to 121 and 122 (65% and 44% yields, respectively) was accomplished by a procedure introduced by Golding[62] and Bock.[63] D-Ribonolactone was treated with a 35% solution of hydrogen bromide in acetic acid, followed by deacetylation with methanol. Catalytic hydrogenolysis of 121, followed by selective bromination afforded 53 in 72% yield. Selective catalytic hydrogenolysis of 122 also provided 53 in 85% yield. The overall yield for the preparation of 120 from 1 was 46%. The formation of 121 from 1 is believed to proceed through

Scheme 15



[a]PPh_3, CBr_4, MeCN; [b]PhCHO, $ZnCl_2$; [c]NBS, $BaCO_3$, CCl_4, Δ; [d]n-Bu_3SnH, AIBN, Tol, Δ; [e]NH_3, MeOH; [f]Zn, EtOH, Δ.

Scheme 16



[a]NaH, CS_2, MeI, DMF; [b] n-Bu_3SnH, AIBN, Tol, Δ; [c]CF_3CO_2H:H_2O:$CHCl_3$ = 1:1:4, Δ; [d]CBr_4, PPh_3, MeCN; [e]35% HBr, HOAc; [f]MeOH; [g]Pd/C, H_2, Et_3N, EtOAc.

the formation of 5-O-acetyl-D-ribonolactone which precipitates if 20% hydrogen bromide in acetic acid is used. When 35% hydrogen bromide in acetic acid is employed, the monoacetate does not precipitate and reacts further. The structure of 121 was unambiguously confirmed by X-ray crystal analysis.[34]

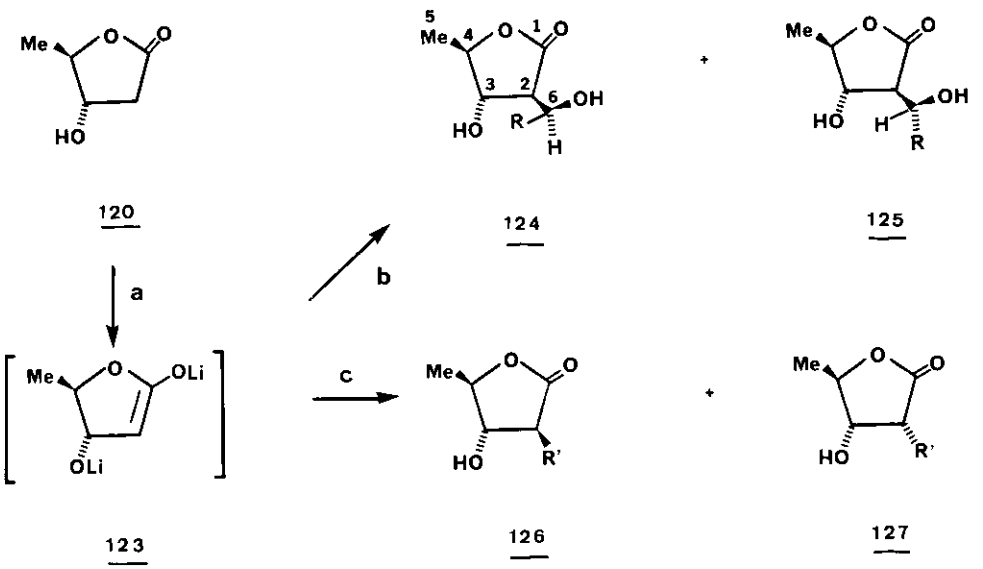
With key intermediate 120 in hand, the possibility of carrying out stereoselective aldol condensations and alkylations using the chiral hydroxyl group as a control element was then examined. Dianion 123 (Scheme 17) was prepared by the addition of 2.2 equiv of lithium diisopropylamide in THF at -78°C. Addition of aldehydes in the presence of 1 equiv of zinc chloride, raising the temperature to -50°C for 2 hr and quenching the reaction with 20% aqueous ammonium chloride at -50°C, afforded a mixture of diols (124 and 125) in good yield (Table 6). The structural assignments of these diols were based on the analysis of ^{1}H NMR spectra. Dianion 123 was also alkylated with methyl iodide, myristyl bromide and 1,10-dibromodecane using hexamethylphosphoramide (HMPA) as cosolvent. The results are shown in Table 7. While the methylation of the dianion at -50°C gave a 59% yield of both 126a and 127a in a 20:1 ratio, the alkylation of the dianion with myristyl bromide and 1,10-dibromodecane afforded low yields of a single product. In all cases, O-alkylation or dialkylation were not observed.

Having demonstrated the potential of D-ribonolactone as a precursor for the synthesis of optically active γ-lactones which, in turn, are important intermediates in the synthesis of many natural products the aldol condensation methodology was extended to the synthesis of the naturally occurring Lauraceae lactones, the litsenolides.

For the synthesis of (-) litsenolides C_1 and C_2, the intermediates 124c and 125c were obtained from the aldol condensation of dianion 123 with the commercially available myristyl aldehyde. For the synthesis of (-) litsenolides B_1 and B_2, the intermediates 124b and 125b were derived from the dianion 123 and 11-dodecynal. A three step synthesis of this aldehyde was developed during the course of these investigations.[64]

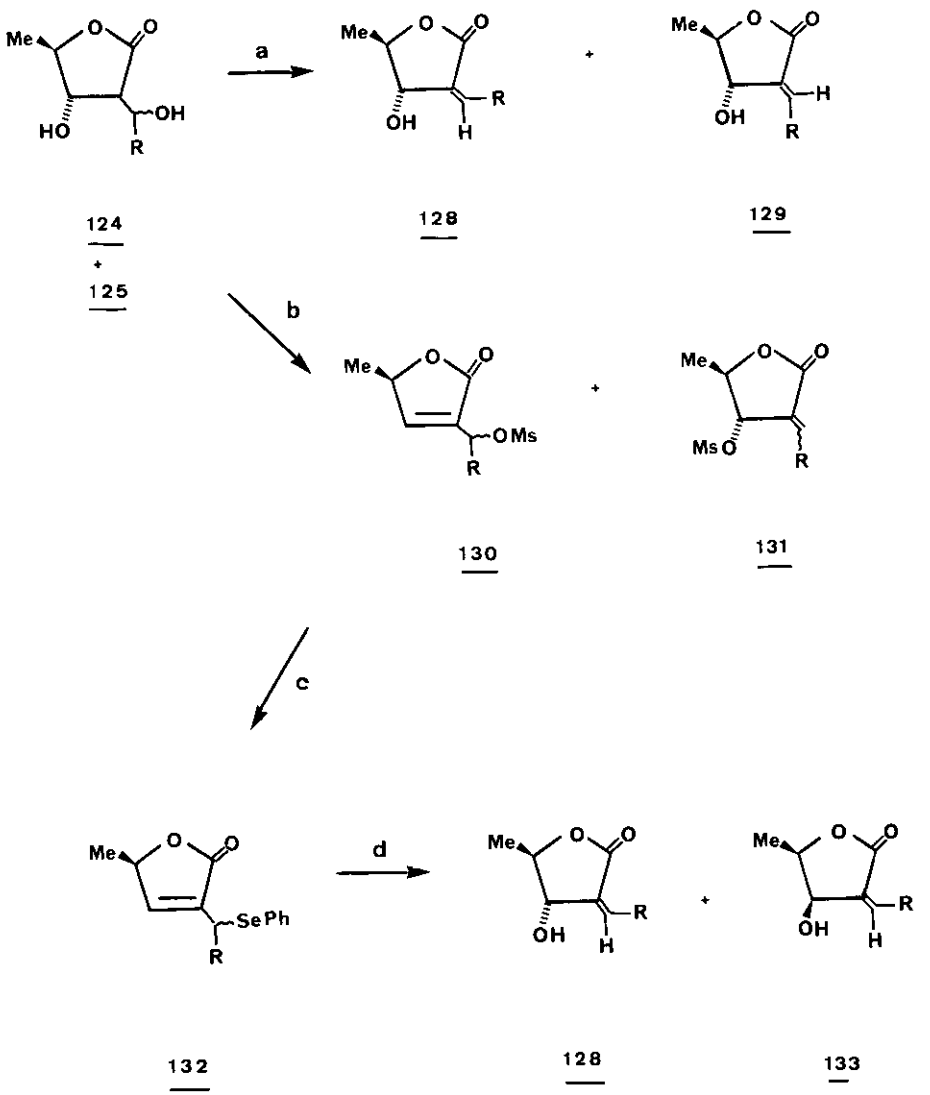
The conversion of intermediates 124c and 125c into (-) litsenolides C_1 and C_2 is outlined in Scheme 18 (R=n-$C_{13}H_{27}$). Pyrolysis of the mixture at 200°C afforded a 1:5 ratio of two products in 15% yield. The minor product was found to be identical to (-) litsenolide C_1 (128c) while the major product corresponded to (-) litsenolide C_2 (129c). Litsenolide C_1 was also prepared in better yield through a different sequence of reactions. The diastereomeric mixture of 124c and 125c, in methylene chloride, was treated with triethylamine and methanesulfonyl chloride (2 eq) to afford mesylates 130c and 131c in a 10:1 ratio (100% yield). This mixture of mesylates was converted to the corresponding allylic phenyl selenide (132c) in 78% yield with 1.5 equiv of sodium phenylselenide. Subsequent oxidation of 132c with 30% aqueous hydrogen peroxide in acetonitrile at -20°C gave litsenolide C_1 (128c) and epilitsenolide C_1 (133c) in a 7:1 ratio (85%

Scheme 17



[a]LDA (2 eq.), THF, -78°C; [b]$ZnCl_2$, RCHO, THF, -50°C; [c]R'X, HMPA, -50°C.

Scheme 18



124 + 125 → 128 + 129

124 + 125 → 130 + 131

132 → 128 + 133

R = n-$C_{13}H_{27}$ for litsenolide C series
R = $(CH_2)_9C{\equiv}CH$ for litsenolide B series

[a] Δ; [b] MsCl, NEt_3, CH_2Cl_2, 0°; [c] NaSePh, EtOH, -20°, 1 hr; [d] 30% H_2O_2, CH_3CN, -20°.

Table 6. Aldol Condensation of Dianion 123

Compd	R	% Yield	Ratio (124:125)	$^3J_{2,3}$, Hz		$^3J_{2,6}$, Hz	
				124	125	124	125
a	C_6H_5	75	3:1	7.5	8.9	3.8	8.7
b	$CH_3(CH_2)_{12}$	60	1:1.5	8.5	9.3	3.4	3.8
c	$HC{\equiv}C(CH_2)_8CH_2$	72	1:2	8.4	9.2	4.5	5.4

Table 7. Alkylation of Dianion 123

Compd	R'X	% Yield	$^3J_{2,3}$ (Hz)	
			126	127
a	CH_3-I	59	9.2	5.8
b	$CH_3(CH_2)_{12}CH_2$-Br	21	8.6	---
c	$BrCH_2(CH_2)_8CH_2$-Br	18	8.5	---

yield).

The conversion of intermediates 124b and 125b into (-) litsenolide B_1 and B_2 is also outlined in Scheme 18 ($R=(CH_2)_9C\equiv CH$). Pyrolysis of a mixture of 124b and 125b at 180°C afforded a 14% yield of two products in a 1:6 ratio which were identical to the naturally occurring (-) litsenolides B_1 (128b) and B_2 (129b). The diastereomeric mixture of 124b and 125b was similarly converted to mesylates 130b and 131b in a 8:1 ratio (93% yield). The mesylates were treated with sodium phenyl selenide (1.5 eq) to afford 132b in 82% yield. Further oxidation with 30% aqueous hydrogen peroxide in acetonitrile at -20°C also gave litsenolide B_1 (128b) and epilitsenolide B_1 (133b) in a 1:1 ratio (79% yield). Thus, the first synthesis of optically active litsenolides B and C has been accomplished from D-ribonolactone.

ACKNOWLEDGEMENT

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