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# C-Glycosyl Nucleosides. V. A Novel One-Step Asymmetric Synthesis of C-Nucleoside Analogs[1]

Haruo Ogura* and Hiroshi Takahashi

*School of Pharmaceutical Sciences, Kitasato University, Shirokane, Minato-ku, Tokyo 108, Japan*

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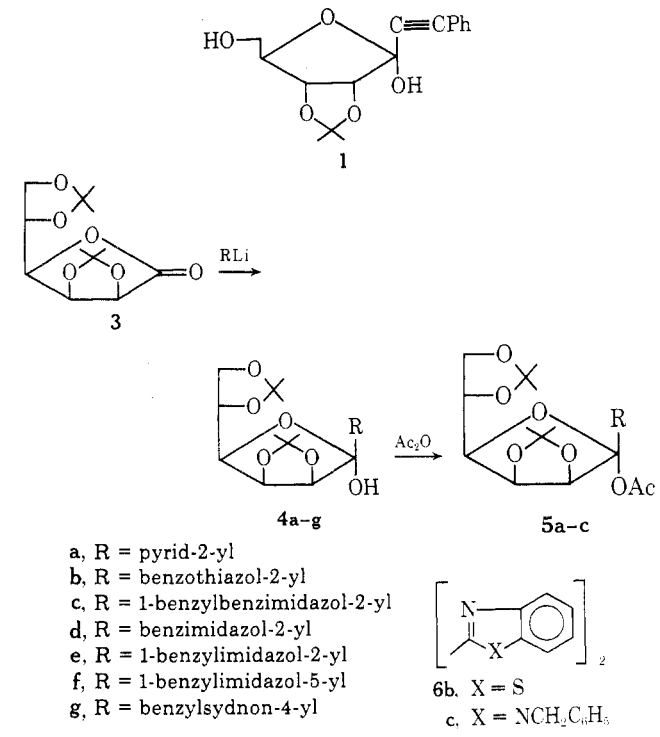
Reaction of lithiated heterocycles such as pyridine, benzothiazole, imidazole, benzimidazole, and sydnone with sugar lactones, 2,3:5,6-di-*O*-isopropylidene-L-gulono-1,4-lactone (3) or 2,3-*O*-isopropylidene-D-ribono-1,4-lactone (7), afforded a variety of 1-(2-substituted heterocyclic)-2,3:5,6-di-*O*-isopropylidene-β-L-gulofuranose (4) or 1-(2-substituted heterocyclic)-2,3-*O*-isopropylidene-β-D-ribofuranose (8). Attempted dehydroxygenation of the anomeric hydroxyl group failed. These C-nucleoside analogs were reduced with sodium borohydride to gulitols and ribitols. The configuration of gulitols, which had a π-electron ring system, was determined with CD and ORD spectra to confirm their absolute configuration. It was concluded that a similar Cotton effect is observed in furanose-type and gulitol-type nucleosides.

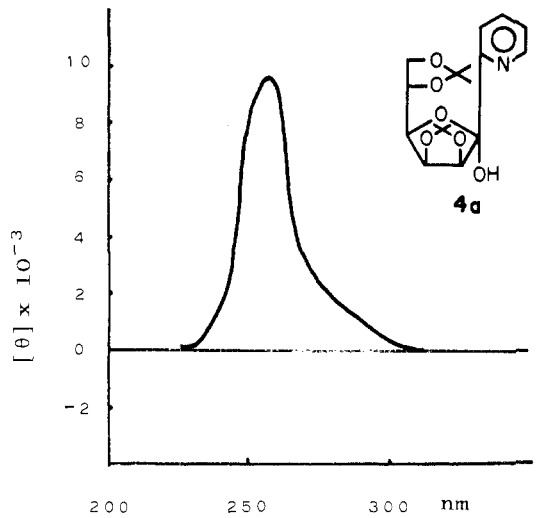
Synthetic studies on the nucleoside antibiotic, pyrazomycin, have been reported by Tronchet and Perret.[2] On the other hand, Townsend and his collaborators synthesized its analogous N-nucleoside[3] and pyrazolopyrimidine nucleosides.[4] Several synthetic routes directed to C-nucleosides have also been reported by Fox and Ohrui.[5] In the previous paper,[6] we reported the reaction of ethynyl compounds with lactones, and the resulting compound had been expected as an intermediate for the preparation of the carbon-linked nucleoside. In another paper,[7] we reported the ethynylation of glucosyl bromide with ethynylmagnesium bromide, although we could not obtain the desired carbon-linked nucleoside. The attempted 1,3-dipolar cycloaddition reaction of 1-ethynylphenyl-2,3-*O*-isopropylidene-α-D-ribofuranose (1) and *N*-benzylsydnone failed.

The present paper concerns itself with a direct reaction of some lithiated heterocycles with sugar lactones to yield a carbon-linked nucleoside. The reaction of 2,3:5,6-di-*O*-isopropylidene-L-gulono-1,4-lactone (3) or 2,3-*O*-isopropylidene-D-ribono-1,4-lactone (7) with various lithiated heterocycles gave gulofuranosyl derivatives (**4a–g**) or ribofuranosyl derivatives (**8b,c**).

By application of the reported method[6] of ethynylation with lactones to the reaction of heterocycles with sugar lactones, it has been possible to obtain heterocyclic sugar lactols. Treatment of 3 with *n*-butyllithium and α-bromopyridine, benzothiazole, or 1-benzylbenzimidazole gave 1-substituted 2,3:5,6-di-*O*-isopropylidenegulonolactols (**4a–c**) in a good yield (74, 56, and 40%, respectively, Chart I). The ir spectra of these compounds showed hydroxyl bands in the 3200–3380-$cm^{-1}$ region, and no lactonic band at around 1780 $cm^{-1}$. Gulonolactols (**4a–c**) were acetylated with acetic anhydride in pyridine to yield their acetyl derivatives (**5a–c**). This result was similar to those of ethynyl derivatives.[6] In the case of 1-benzylbenzimidazole, the lithiation does occur at the 2 position similar to that of benzothiazole,[8] and this fact was confirmed from the nmr spectra of **4b**. Micetich[9] reported that lith-

**Chart I**





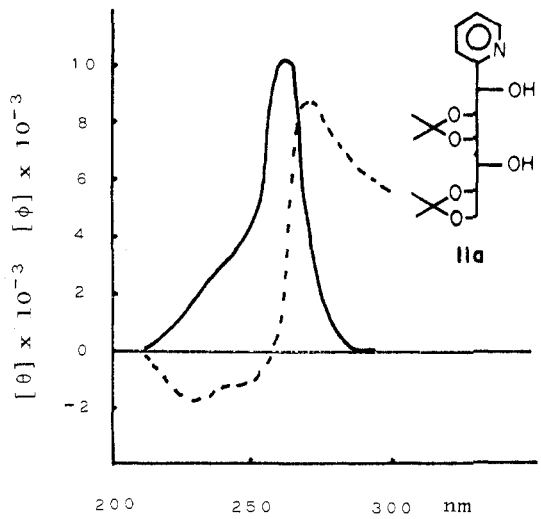
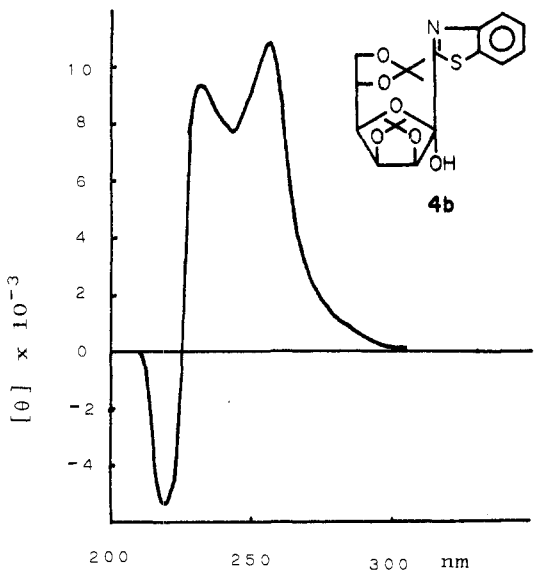




Figure 1. CD (——) and ORD (- - - - -) curves in methanol at 28°.



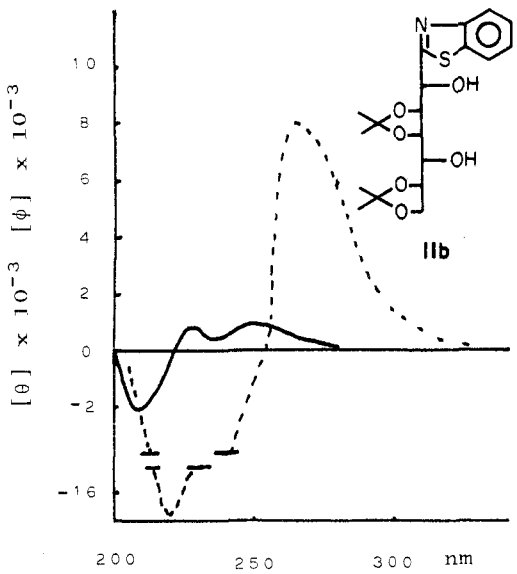
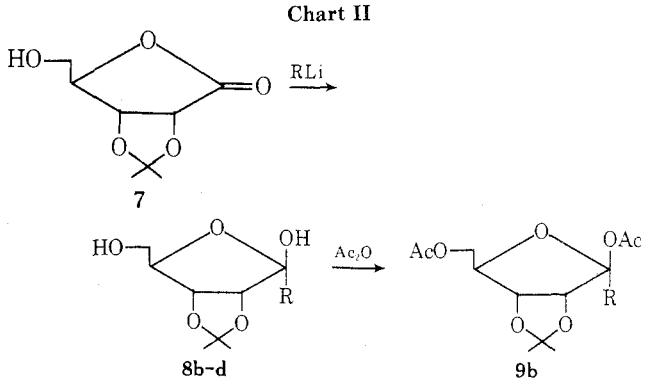




Figure 2. CD (——) and ORD (- - - - -) curves in methanol at 28°.

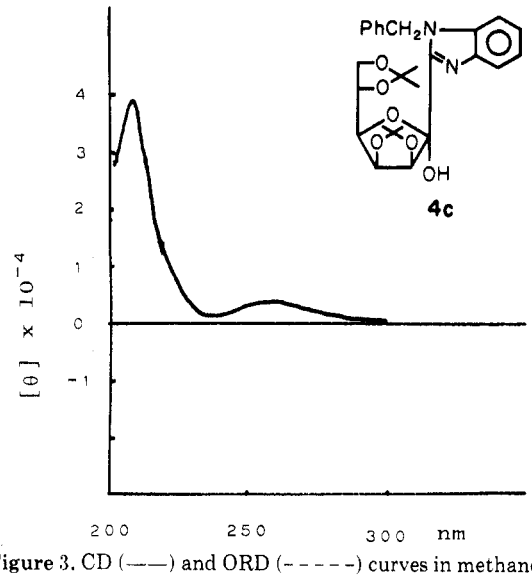
iation of isothiazoles and thiadiazoles gave the 5-lithio compounds. The lithiation of 1-benzylbenzimidazole by *n*-butyllithium at the 2 position is supported by the formation of 1,1′-dimethyl-2,2′-bibenzimidazole from the lithiation of 1-methylbenzimidazole.[10] On the other hand, treatment of 1-benzylimidazole under the same condition as above afforded 30% of 2-substituted compound **4e** and 12% of 5-substituted compound **4f**. The nmr spectrum of 2-substituted benzylimidazole (**4e**) showed a pair of doublets at $\delta$ 6.77 and 6.98 ppm ($J$ = 5 Hz) corresponding to H-4 and H-5, respectively, in the imidazole ring. On the other hand, 5-substituted compound **4f** showed a pair of singlets at $\delta$ 7.10 and 7.92 ppm, corresponding to H-4 and H-2, respectively. Shirley and Alley[11] reported that lithiation of 1-substituted imidazole with *n*-butyllithium resulted in lithiation at the 2 position, and did not give a 5-substituted compound. The direct lithiation[12] of benzothiazole or 1-benzylbenzimidazole gave only the bis compounds **6b** and **6c**, respectively.

A similar reaction of 2,3-*O*-isopropylidene-D-ribono-1,4-lactone (7) (Chart II) with benzothiazole of 1-benzylbenzimidazole gave 1-(benzothiazol-2-yl)-2,3-*O*-isopropylidene-$\beta$-D-ribofuranose (**8b**) and 1-(1-benzylbenzimidazol-2-yl)-2,3-*O*-isopropylidene-$\beta$-D-ribofuranose (**8c**), and **8b** was acetylated to the 1,5-di-*O*-acetyl derivative (**9b**) in a usual manner. The reaction of sugar lactones with lithiated heterocycles progressed stereospecifically and isomeric lactols were not detected by thin layer and gas chromatography. Reductive elimination of 1-benzylbenzimidazol-2-yl derivatives (**4c**, **8c**) over palladium on charcoal in a hydrogen atmosphere afforded the corresponding benzimidazolyl derivatives (**4d**, **8d**) in a good yield (70 and 65%, respectively).

Chart II




**b**, R = benzothiazol-2-yl
**c**, R = 1-benzylbenzimidazol-2-yl
**d**, R = benzimidazol-2-yl



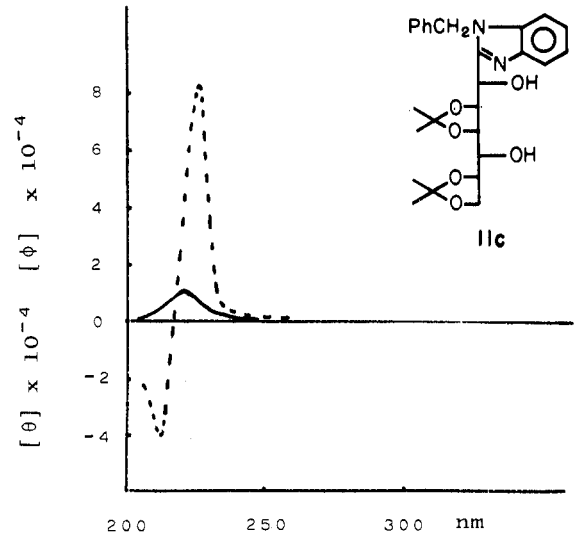
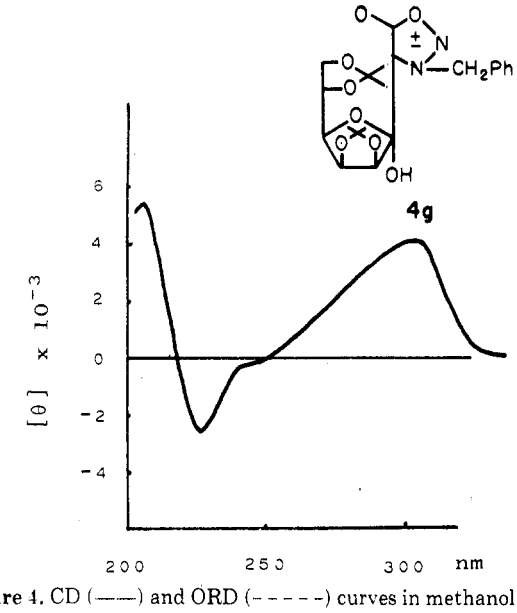




Figure 3. CD (——) and ORD (- - - - -) curves in methanol at 28°.



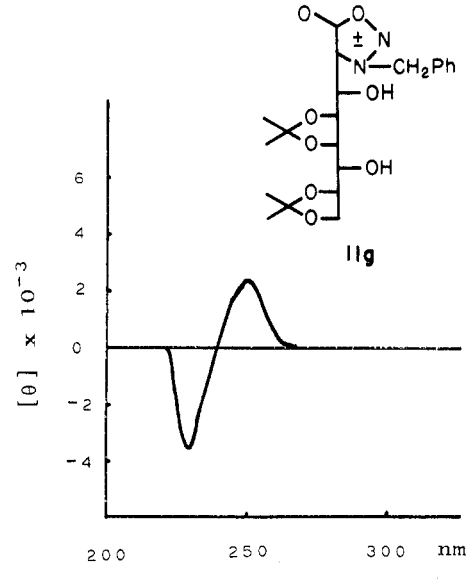



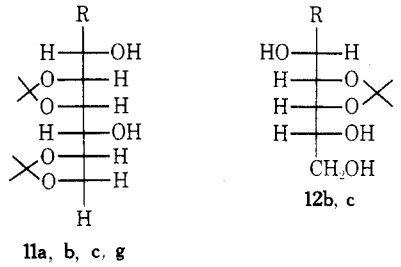

Figure 4. CD (——) and ORD (- - - - -) curves in methanol at 28°.

Chilton and Krahn,[13] and Moffatt, *et al.*,[14] already reported the relationship between the absolute configuration at the C-1 position of sugar heterocycles, such as benzimidazole, quinoxaline, flavazole, and anhydroosazone derivatives, and the Cotton effect of the ORD. Satoh, *et al.*,[15] also reported that the absolute configuration of 1-nitroheptitols was determined by ORD and CD. Snatzke and his coworkers[16] had reported the CD spectra of benzothiazole and benzothiazoline derivatives on aldoses and its acetates. Previously, we also reported[12] the Cotton effect and the structural relation of 1,2-dideoxy-4,5:7,8-di-*O*-isopropylidene-1-phenyl-L-glycero-D-galacto-oct-1-ynitol and 1,2-dideoxy-4,5-*O*-isopropylidene-1-phenyl-D-allohept-1-ynitol. Moreover, the ethynylation reaction of sugar lactones **3** and **7** with lithiated ethynyl compounds using *n*-butyllithium or by the direct lithiation resulted in the attack of the reagent from the less hindered face to form the β-C-nucleoside.[6,12]

The stereochemistry of the gulofuranosyl derivatives **4a–g** and ribofuranosyl derivatives **8b–d** was confirmed by the Cotton effect of CD curves of ring-opened alcohols, which were formed by sodium borohydride reduction.

As shown in Figures 1–3, the positive Cotton effect was observed from CD and ORD curves of gulofuranosyl compounds (**4a–c**) and 2,3:5,6-di-*O*-isopropylidene-1-(2-substituted)hexane-L-glycero-D-galacto-1,2,3,4,5,6-hexol (**11a,b,c,g**) (Chart III). From this result, gulofuranosyl

**Chart III**




compounds and L-glycerohexol compounds should have the β configuration at the 1 position; therefore compounds **4a,c,g** and **11a,c,g** should have *S* chirality at the 1 position and *R* chirality for **4b** and **11b**.

On the other hand, the negative Cotton effect was observed in the ribonosyl compounds **8b,c** and 2,3-*O*-isopropylidene-1-(2-substituted)pentane-D-altro-1,2,3,4,5-pentol (**12b,c**) (Figures 4–6). From these results, ribonosyl compounds and D-altropentol should have the β configuration

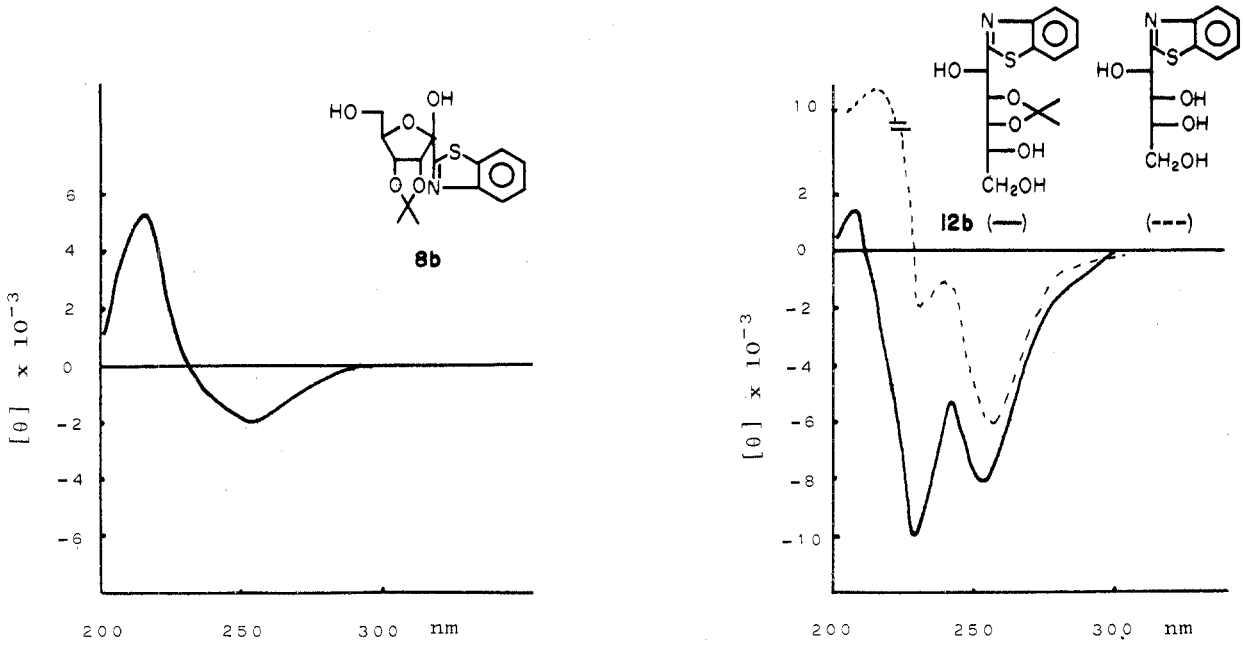



Figure 5. CD curves in methanol at 30°.

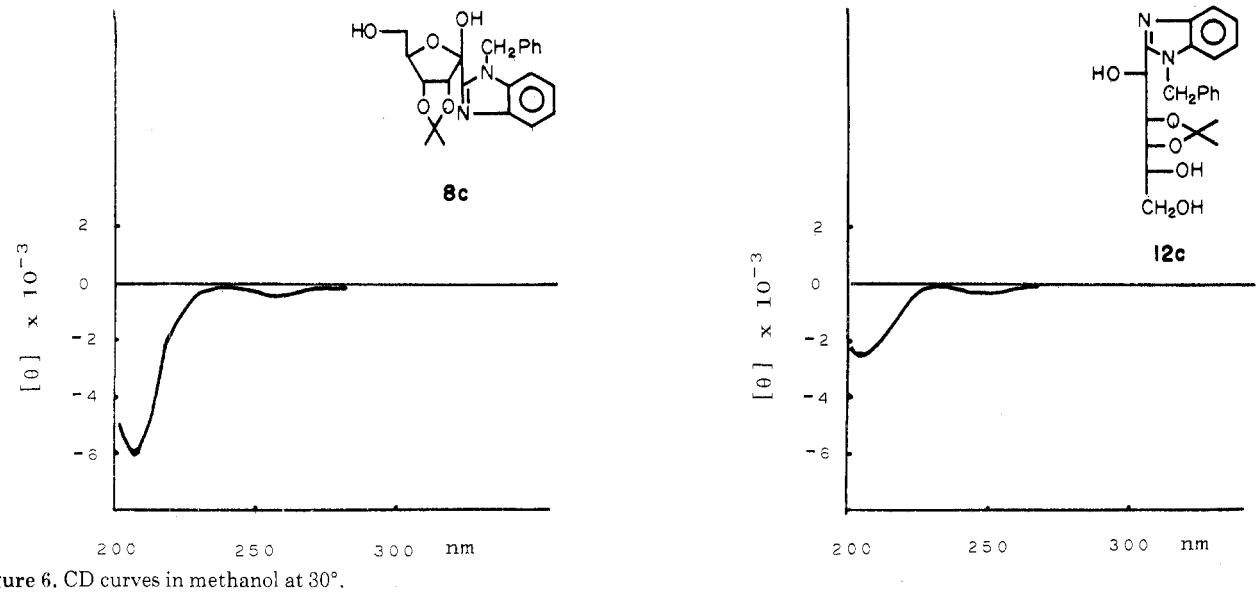



Figure 6. CD curves in methanol at 30°.

at the 1 position; therefore compounds **8c** and **12c** should have the *R* chirality at the 1 position and *S* chirality for compounds **8b** and **12b**.

In conclusion, asymmetric synthesis of C-nucleoside analogs was effected *via* lithiated heterocycles by a one-step synthesis. The absolute configuration of the products was confirmed from the Cotton effect. Ethynylation of isopropylidenegulonolactone (**3**) or -ribonolactone (**7**) afforded lactols which have the same chirality at the anomeric position.[6,12] This conclusion differs from the results of C-nucleoside analogs, in which gulofuranosyl derivatives (**4**) obtained had the same stereochemistry with ethynyl derivatives: *S* chirality (**4a,c,g**) and *R* chirality (**4b**) at the anomeric position. However, ribofuranosyl derivatives (**8**) have *R* chirality (**8c,d**) and *S* chirality (**8b**) at the anomeric position.

Attempted elimination of the anomeric hydroxyl group failed. When 1-benzylbenzimidazolylgulonolactol (**4c**) was treated with formic acid in trimethylamine or sodium carbonate in formic acid, only 1-benzylbenzimidazole was obtained. Treatment of **4c** with thionyl chloride–pyridine or phosphoryl chloride–pyridine also resulted in cleavage of the carbon–carbon bond to form 1-benzylbenzimidazole and sugar lactone (**3**). Hydrogenolysis of **4c** with lithium aluminum hydride–aluminum chloride at room temperature gave many products on tlc, and the desired product was not obtained.

## Experimental Section[17]

**Reaction of 1-Phenylethynyl-2,3-*O*-isopropylidene-α-D-ribofuranose (1) with Benzylsydnone.** A solution of **1** (160 mg, 0.55 mmol) and benzylsydnone or *N*-nitrosobenzylglycine (106 mg, 0.55 mmol) in acetic anhydride (10 ml) was heated under reflux for 8 hr. When cooled, the reaction mixture was poured into ice-water and extracted with chloroform. Evaporation of dried chloroform solution left a brown syrup, which was chromatographed over silica gel and eluted with hexane–benzene. There was obtained 70 mg (26%) of an unidentified compound (**2**) as colorless needles: mp 125–127°; ir (KBr) 2180 (C≡C), 1380, 1370 ($CH_3$), 1590, 765 $cm^{-1}$ (phenyl); nmr ($CDCl_3$) δ 4.47 (2 H, dd, $=CH_2$), 4.78 (1 H, d, H-1), 1.38, 1.58 ppm (6 H, s, isopropylidene).

*Anal.* Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29; *m/e* 256.110. Found: C, 74.95; H, 6.30; *m/e* 256.108 ($M^+$).

**General Procedure for Preparation of 2,3:5,6-Di-*O*-isopropylidene-β-L-gulofuranosyl Derivatives (4a-c, e-g) (Table I) and 2,3-*O*-Isopropylidene-β-D-ribofuranosyl Derivatives (8b,c)**

**Table I**
**2,3 : 5,6-Di-*O*-isopropylidene-β-L-gulofuranosyl Derivatives (4a–g)**

| Compd | R | Yield, % | Mp, °C | Formula | Calcd, % C | Calcd, % H | Calcd, % N | Found, % C | Found, % H | Found, % N | Mass, *m/e* (M⁺) Calcd | Mass, *m/e* (M⁺) Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **4a** | Pyrid-2-yl | 74[a] | 86–87 | $C_{17}H_{23}NO_6$ | 60.52 | 6.87 | 4.15 | 60.69 | 6.48 | 3.89 | 322.129 | 322.129[c] |
| **4b** | Benzothiazol-2-yl | 56 | 170–171 | $C_{19}H_{23}NO_6S$ | 58.01 | 5.89 | 3.56 | 58.10 | 5.96 | 3.47 | 393.123 | 393.125 |
| **4c** | 1-Benzylbenzimidazol-2-yl | 40 | 155–156 | $C_{26}H_{30}N_2O_6$ | 66.93 | 6.48 | 6.01 | 66.68 | 6.68 | 6.10 | 466.210 | 466.210 |
| **4d** | Benzimidazol-2-yl | 70 | 175–176 | $C_{19}H_{24}N_2O_6$ | 60.63 | 6.43 | 7.44 | 60.94 | 6.50 | 7.47 | 376.163 | 376.163 |
| **4e** | 1-Benzylimidazol-2-yl | 30 | 87–88 | $C_{22}H_{28}N_2O_6$ | | | | | | | 416.195 | 416.193 |
| **4f** | 1-Benzylimidazol-5-yl | 12 | 199 dec | $C_{22}H_{28}N_2O_6$ | 63.44 | 6.78 | 6.73 | 63.15 | 6.95 | 6.69 | 416.195 | 416.196 |
| **4g** | Benzylsydnon-4-yl | 29<br>32[b] | 157–158 | $C_{21}H_{26}N_2O_8$ | 58.06 | 6.03 | 6.45 | 57.71 | 6.06 | 6.23 | 434.169 | 434.165 |

[a] From α-bromopyridine. [b] From 3-benzyl-4-bromosyndnone. [c] $(M - CH_3)^+$.

**Table II**
**2,3-*O*-Isopropylidene-β-D-ribofuranosyl Derivatives (8b–d and 9b)**

| Compd | R | Yield, % | Mp, °C | Formula | Mass, *m/e* (M⁺) Calcd | Mass, *m/e* (M⁺) Found |
|---|---|---|---|---|---|---|
| **8b** | Benzothiazol-2-yl | 23 | 110–111 | $C_{15}H_{17}NO_5S$ | 323.083 | 323.083 |
| **8c** | 1-Benzylbenzimidazol-2-yl | 25 | 175–176 | $C_{22}H_{25}N_2O_5$ | 396.169 | 396.169 |
| **8d** | Benzimidazol-2-yl | 65 | 173–174 | $C_{15}H_{18}N_2O_5$ | 306.122 | 306.123 |
| **9b** | 1,5-Di-*O*-acetyl **8a** | 32 | 166–167 | $C_{19}H_{21}NO_7S$ | 407.104 | 407.104 |

**Table III**
**1-*O*-Acetyl-2,3 : 5,6-Di-*O*-isopropylidene-β-L-gulofuranosyl Derivatives (5a–c)**

| Compd | R | Yield, % | Mp, °C | Formula | Mass, *m/e* (M⁺) Calcd | Mass, *m/e* (M⁺) Found |
|---|---|---|---|---|---|---|
| **5a** | Pyrid-2-yl | 24 | 147–148 dec | $C_{19}H_{25}NO_7$ | 379.163 | 379.165 |
| **5b** | Benzothiazol-2-yl | 36 | 163–164 | $C_{21}H_{25}NO_7S$ | 435.135 | 435.129 |
| **5c** | 1-Benzylbenzimidazol-2-yl | 24 | 176–177 | $C_{28}H_{32}N_2O_7$ | 493.197 | 493.198[a] |

[a] $(M - CH_3)^+$.

**Table IV**
**β-L-Gulitols (11a–c, g) and β-D-Ribitols (12b,c)**

| Compd | R | Yield, % | Mp, °C | Formula | Calcd, % C | Calcd, % H | Calcd, % N | Found, % C | Found, % H | Found, % N | Mass, *m/e* (M⁺) Calcd | Mass, *m/e* (M⁺) Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **11a** | Pyrid-2-yl | 54 | 84–85 | $C_{17}H_{25}NO_6$ | 60.16 | 4.13 | 7.43 | 59.82 | 3.94 | 7.59 | 339.168 | 339.168 |
| **11b** | Benzothiazol-2-yl | 57 | 97–98 | $C_{19}H_{25}NO_6S$ | 57.71 | 6.37 | 3.54 | 57.65 | 6.65 | 3.25 | 395.140 | 395.140 |
| **11c** | 1-Benzylbenzimidazol-2-yl | 40 | 178–179 | $C_{23}H_{32}N_2O_6$ | 66.65 | 6.88 | 5.98 | 66.43 | 7.09 | 5.72 | 468.222 | 468.225 |
| **11g** | Benzylsydnon-4-yl | 42 | 148–149 | $C_{21}H_{28}N_2O_8$ | 57.79 | 6.47 | 6.42 | 57.81 | 6.62 | 6.38 | 421.161 | 421.158 |
| **12b** | Benzothiazol-2-yl | 70 | 64–65 | $C_{15}H_{19}NO_5S$ | 55.37 | 5.89 | 4.30 | 55.35 | 5.87 | 4.32 | 325.098 | 325.098 |
| **12c** | 1-Benzylbenzimidazol-2-yl | 54 | 76–78 | $C_{22}H_{26}N_2O_5$ | 66.32 | 6.58 | 7.03 | 66.33 | 6.59 | 7.01 | 398.183 | 398.184 |

**Table V**
**Acetates of 11b and 12b**

| Compd | Yield, % | Mp, °C | Formula | Calcd, % C | Calcd, % H | Calcd, % N | Found, % C | Found, % H | Found, % N | Mass, *m/e* Calcd | Mass, *m/e* Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Acetyl β-L-gulitol | 15 | 95–96 | $C_{23}H_{29}NO_8S$ | 57.61 | 6.10 | 2.92 | 57.72 | 6.33 | 2.66 | 479.161 | 479.161 $(M^+)$ |
| Acetyl β-D-ribitol | 30 | 129–130 | $C_{21}H_{25}NO_8S$ | 55.87 | 5.58 | 3.10 | 55.90 | 5.70 | 3.16 | 436.107 | 436.106 $(M - CH_3)^+$ |

**(Table II).** To an ether solution of *n*-butyllithium prepared from lithium (0.2 g, 0.03 mol) and *n*-butyl bromide (2.5 g, 0.02 mol), the heterocyclic compound (0.01 mol) in ether (5–10 ml) was added slowly during 20–30 min at below −70°. After the reaction solution was stirred for 2 hr at room temperature, 2,3:5,6-di-*O*-isopropylidene-γ-L-gulonolactone (**3**, 2.5 g, 0.01 mol) in freshly distilled tetrahydrofuran (10–20 ml) was added dropwise into the cooled reaction solution, and the stirring was continued for 2–3 hr. The reaction mixture was then allowed to stand overnight at room temperature. The reaction mixture was treated with saturated ammonium chloride solution and extracted with ether (150 ml). The organic layer was washed with water and dried over magnesium sulfate. The extracts were concentrated under reduced pressure to give **4a–c,e–g.**

**Acetylation of 4a–c (Table III).** The compounds **4a–c** were acetylated with acetic anhydride (4 ml) and pyridine (5 ml). The reaction solution was stirred for 20–30 hr at room temperature and poured into ice-water. The solution was extracted with chloroform and the organic layer was washed with saturated sodium bicarbonate solution and water. The extract was dried and concentrated under reduced pressure.

**Reductive Elimination of Benzyl Group from 4c and 8c (Tables I and II).** A methanol (60 ml) solution of **4c** or **8c** (0.01 mol) was hydrogenated over 5% palladium on charcoal. After the reaction; the filtered solution was concentrated under reduced pressure to give 1-(2-benzimidazolyl)-2,3:5,6-di-*O*-isopropylidene-β-L-gulofuranose (**4d**) or 1-(2-benzimidazolyl)-2,3-*O*-isopropylidene-β-D-ribofuranose (**8d**).

**Reduction of 4a–c,g with Sodium Borohydride (Table IV).** The compound (**4a–c,g**, 0.01 mol) was dissolved in methanol (10 ml), and sodium borohydride (0.15 g) was added. After the reaction solution was stirred for 2–24 hr at room temperature, excess reagent was decomposed with ethyl acetate and water, and the organic layer was washed with 0.1 *N* hydrochloric acid and water, dried, and evaporated to give **11a–c,g.**

**Reduction of 8b,c with Sodium Borohydride (Table IV).** After a similar procedure as above, the obtained syrup was chromatographed over silica gel with hexane–chloroform (85:15) and the desired product was isolated as an oily product.

**Acetylation of 11b and 12b (Table V).** The compound (**11b, 12b**) was acetylated with acetic anhydride in pyridine, and the acetate was obtained after chromatography and recrystallization from chloroform–ether.

**Attempted Elimination of Tertiary Hydroxyl Group. A. With**

**Formic Acid.** A solution of **4c** (50 mg) in 5 ml of trimethylammonium formate [bp 92° (18 mm)] was stirred for 2 hr at room temperature and left overnight. This solution was gently refluxed in an oil bath for 3 hr until the reaction mixture was colored dark brown. When cooled, the separated crystals were collected and recrystallized from hexane–chloroform to colorless needles, mp 195–196°. This was treated with 1 *N* sodium hydroxide form 1-benzylbenzimidazole, mp and mmp with authentic sample 115°.

**B. With Phosphoryl Chloride or Thionyl Chloride in Pyridine.** To a solution of **4c** (400 mg) in pyridine or pyridine–chloroform, phosphoryl chloride (5 ml) or thionyl chloride (4 ml) was added at 0–5°. After the reaction mixture was stirred for 1 hr at room temperature, it was poured into ice–water. Extraction of the reaction mixture with benzene afforded 1-benzylbenzimidazole.

**C. With Lithium Aluminum Hydride–Aluminum Chloride.** To an ether solution of **4c** (450 mg), lithium aluminum hydride (50 mg) and aluminum chloride (25 mg) were added under stirring at 0–5°. After stirring overnight at room temperature, the reaction mixture was treated with ethyl acetate and then with 0.1 *N* hydrochloric acid. Evaporation of the dried ether solution left a brownish syrup, which showed four spots on tlc ($R_f$ 0.79, 0.45, 0.30, and 0.14), and the main spot ($R_f$ 0.45) was found to be 1-benzylbenzimidazole.

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**Registry No.**—**1**, 32257-18-4; **3**, 7306-64-1; **4a**, 51057-41-1; **4b**, 51057-42-2; **4c**, 51057-43-3; **4d**, 51057-44-4; **4e**, 51057-45-5; **4f**, 51057-46-6; **4g**, 51108-10-2; **5a**, 51057-47-7; **5b**, 51057-48-8; **5c**, 51057-49-9; **8b**, 51057-50-2; **8c**, 51057-51-3; **8d**, 51057-52-4; **9b**, 51057-53-5; **11a**, 51057-54-6; **11b**, 51057-55-7; **11b** acetate, 51057-56-8; **11c**, 51057-57-9; **11g**, 51057-58-0; **12b**, 51057-59-1; **12b** acetate, 51057-60-4; **12c**, 51057-61-5; benzylsydnone, 16844-42-1; α-bromopyridine, 109-04-6; 3-benzyl-4-bromosydnone, 4918-27-8.

## References and Notes

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# Synthesis of Macrolide Antibiotics. I.[1] Stereospecific Addition of Methyllithium and Methylmagnesium Iodide to Methyl α-D-*xylo*-Hexopyranosid-4-ulose Derivatives. Determination of the Configuration at the Branching Carbon Atom by Carbon-13 Nuclear Magnetic Resonance Spectroscopy

Momčilo Miljković,* Miodrag Gligorijević, Toshio Satoh, and Dušan Miljković

*Department of Biological Chemistry, The Milton S. Hershey Medical Center, The Pennsylvania State University, Hershey, Pennsylvania 17033*

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Methyllithium (LiBr-free) adds stereospecifically to methyl 2,3-di-*O*-methyl-6-*O*-triphenylmethyl-α-D-*xylo*-hexopyranosid-4-ulose (**1**) and methyl 3-*O*-methyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-α-D-*xylo*-hexopyranosid-4-ulose (**2**) in an ethereal solution at −80° to give methyl 2,3-di-*O*-methyl-4-*C*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (**9**) and methyl 3-*O*-methyl-4-*C*-methyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (**11**), respectively. Methylmagnesium iodide adds to the oxo sugars **1** and **2** in an ethereal solution at −80° again stereospecifically, giving methyl 2,3-di-*O*-methyl-4-*C*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (**8**) and methyl 3-*O*-methyl-4-*C*-methyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (**10**), which are, however, the C-4 epimers of the branched-chain sugars **9** and **11**. The stereochemistry of the addition of Grignard reagent to the oxo sugars **1** and **2** depended upon the reaction temperature, the solvent, and the nature of the halogen atom. Carbon-13 nmr spectroscopy was used for unequivocal configurational assignments at the branching-carbon atom in branched-chain sugars **8**–**11**. A rationalization of the observed stereospecificity was proposed.

In the course of our studies directed toward the stereoselective synthesis of the 14-membered lactone ring of erythromycins A and B from appropriate sugar derivatives, it was necessary to introduce an axial methyl group at the C-4 carbon atom of a methyl D-*xylo*-hexopyranosid-4-ulose derivative and to develop a simple but reliable method for configurational assignment of the thus obtained branching carbon atom.[2]

It is well known that the addition of Grignard reagents and organolithium compounds to carbonyl groups in carbohydrates is highly stereoselective[4] yielding in certain cases products epimeric at the quaternary carbon atom,[5,6] whereas in other instances branched-chain sugars with the same configuration at the branching carbon atom[7] are obtained. Since a clear rationalization of these findings[8] does not exist, many stereochemical "anomalies"[4] re-