Bis-C-Glycosylation of Resorcinol Derivatives by an *O*→*C*-Glycoside Rearrangement

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Abstracts: An efficient method for bis-C-glycosylation of resorcinol derivatives was developed by utilizing the *O*→*C*-glycoside rearrangement, where each of the two phenols serves as the pivot for selective and high-yield installation of two same or different sugar moieties.

Key words: bis-*C*-glycoside, C-glycosylation, rearrangement, resorcinol, scandium(III) triflate, pluramycin

Aryl *C*-glycosides constitute a growing class of natural products, in which the sugar is directly connected to functionalized polyaromatic chromophore through a C–C bond (Figure 1).[1] Most of these compounds have one *C*-glycoside residue at the *ortho* position or at the *para* position of a phenolic hydroxyl group as in aquayamycin (**1**) and the gilvocarcins (**2**), while some of the 4*H*-anthra[1,2-*b*]pyran *C*-glycosides, e.g. pluramycin A (**3**) and kidamycin (**4**), have two *C*-glycoside residues.[2]

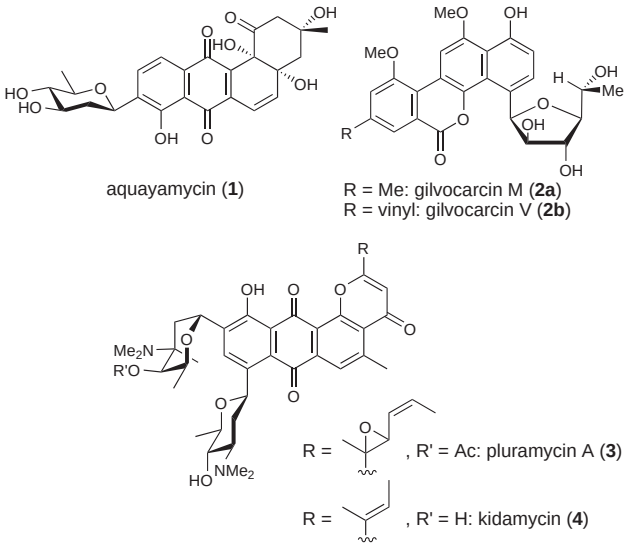
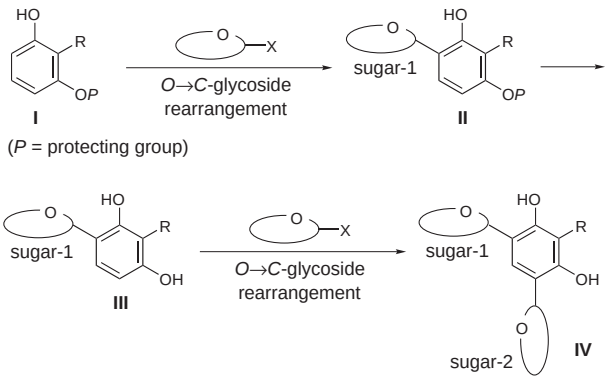


Figure 1 Natural aryl *C*-glycoside antibiotics

These bis-*C*-glycoside antibiotics are used as probe in biochemical research because of highly sequence-selective intercalation into DNA, resulting in specific alkylation.[3] Due to such biochemical significance as well as the unique structure, these compounds are attractive targets for total synthesis. To date, two elaborate approaches for constructing the key bis-*C*-glycosyl arene structure have appeared, i.e. the one based on the glycosyl anion chemistry by Parker[4a] and the other utilizing the Diels–Alder reaction of the C-glycosylated furan with a benzyne by Martin.[4b] However, there still exists a need to develop more efficient procedures towards the synthesis of these natural products and their analogues.

In our continuing study on the synthesis of aryl *C*-glycoside antibiotics, we previously reported a reliable method of aryl C-glycosidation, the *O*→*C*-glycoside rearrangement,[5,6a] which enables regioselective formation of the aryl *C*-glycoside linkage at the o*rtho* position of a phenol through the Lewis acid promoted one-pot reactions including the O-glycosylation of a phenol to form *O*-glycoside and the subsequent migration of the sugar moiety. Notably the reaction tolerates various functionalities on the phenol, enabling further manipulations of the aromatic nuclei. These features have been demonstrated in successful applications to the total synthesis of several natural aryl *C*-glycosides, including **1** and **2**.[5b,c]

In this communication, we wish to describe a new synthesis of aryl bis-*C*-glycosides by performing the *O*→*C*-glycoside rearrangement twice on a resorcinol derivative (Scheme 1). Use of two phenols as the pivots ensures regioselective and high yield *C*-glycoside formations, thereby enabling efficient access to various bis-*C*-glycosides possessing two same or different sugar moieties.



Scheme 1 Bis-C-glycosylation of resorcinol derivative by utilizing the *O*→*C*-glycoside rearrangement.

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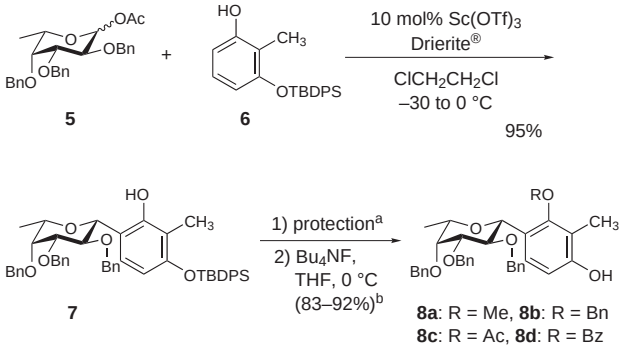
First, four model compounds **8a**–**d** were prepared for examining the introduction of the second *C*-glycoside residue, which possess a non-protected phenol at the *para* position of the sugar residue (Scheme 2).

According to the previously reported procedure,[6] fucosyl acetate **5** and mono-protected 2-methylresorcinol **6** were treated with 10 mol% of $Sc(OTf)_3$ in the presence of Drierite® in 1,2-dichloroethane at –30 °C, and the mixture was allowed to warm. The O-glycosidation and the subsequent migration of the sugar proceeded cleanly to give β-*C*-glycoside **7** in 95% yield, after quenching the reaction at 0 °C.[7] *C*-Glycoside **7** was converted to compounds **8a**–**d** by protecting the phenol with four different groups followed by desilylation.



Scheme 2 Synthesis of the model glycosyl acceptors possessing the *C*-glycoside residue. [a] *Reagents and conditions for the protections*: for **8a**: $(MeO)_2SO_2$, K_2CO_3, DMF, 40 °C (91%); for **8b**: BnBr, Et_4NHSO_4, CH_2Cl_2, 2 M NaOH aq (73%); for **8c**: Ac_2O, DMAP, pyridine (93%); for **8d**: PhCOCl, DMAP, pyridine (quant). [b] Yields for the desilylation.

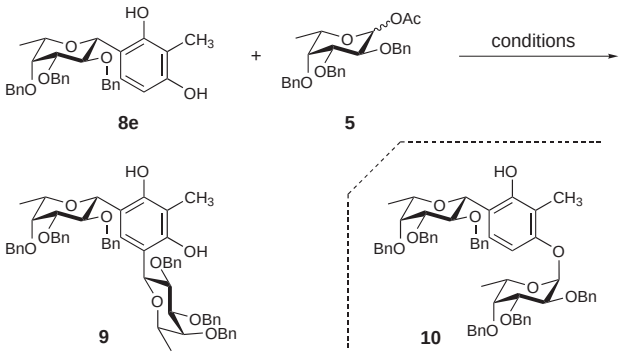
With mono-*C*-glycosides **8a**–**d** in hand, we examined the second C-glycosylation with the glycosyl donor **5**. Unfortunately, the reactions under various conditions were not productive, as the migration of the sugar proved to be very sluggish. Though we could obtain the desired bis-*C*-glycoside from **8a**, the yield was not satisfactory and many side products accompanied.[8] Compound **8b**–**d** failed to give the bis-*C*-glycoside.

However, we were pleased to find the reaction of the non-protected variant **8e**, prepared by desilylation of **7** [Bu_4NF, THF, 0 °C, 98%], nicely underwent the second C-glycosylation under catalysis of various Lewis acids to give stereoselectively bis-β-*C*-glycoside **9**.

Table 1 shows selected results of the reactions, where diol **8e** and 2 equivalents of **5** were treated with various Lewis acids in the presence of dehydrating agent (molecular sieves 3A, 4A, 5A, or Drierite®) in 1,2-dichloroethane at –30 °C and allowed to warm to the temperature designated by T (°C). The reaction with a combination of Cp_2HfCl_2 (1.2 equiv) and AgOTf (2.4 equiv)[5] in the presence of MS4A proceeded cleanly to give the desired bis-*C*-glycoside **9** in 86% yield by raising the temperature to 0 °C (run 1), while the reaction with a catalytic amount of the reagents was incomplete (run 2). However, it turned out that use of Drierite®, instead of MS4A, significantly facilitates the catalytic reaction to completion (run 3).[9] $Sc(OTf)_3$, $BF_3{\cdot}OEt_2$, Me_3SiOTf also catalyzed the reaction in combination with Drierite®. Among them, the $Sc(OTf)_3$–Drierite® combination was most effective, as the reaction was completed at 0 °C to give the bis-*C*-glycoside **9** in 98% yield (run 5).

Typical procedure for the synthesis of bis-*C*-glycoside **9** by the $Sc(OTf)_3$–Drierite® combination is as follows: to a stirred mixture of $Sc(OTf)_3$ (21.7 mg, 44 μmol), mono-*C*-glycoside **8e** (94.3 mg, 0.175 mmol), powdered Drierite® (0.55 g) in 1,2-dichloroethane (11 mL), was added acetate **5** (173 mg, 0.363 mmol) in 1,2-dichloroethane (4 mL) at –30 °C. After the temperature was gradually raised to 0 °C over 4 hours, the mixture was poured into saturated aqueous $NaHCO_3$ solution. After filtration through a Celite® pad, the products were extracted with EtOAc (3×), and the combined organic extracts were washed with brine, and dried over Na_2SO_4. Removal of the solvents in vacuo and purification on silica gel chromatography (hexane–acetone = 3:1) afforded bis-*C*-glycoside **9** as a foamy solid (163 mg, 98%), which was recrystallized from diethyl ether to give colorless prisms.[10]

Table 1 Reactions of Diol **8e** and Fucosyl Acetate **5** with Various Lewis Acids



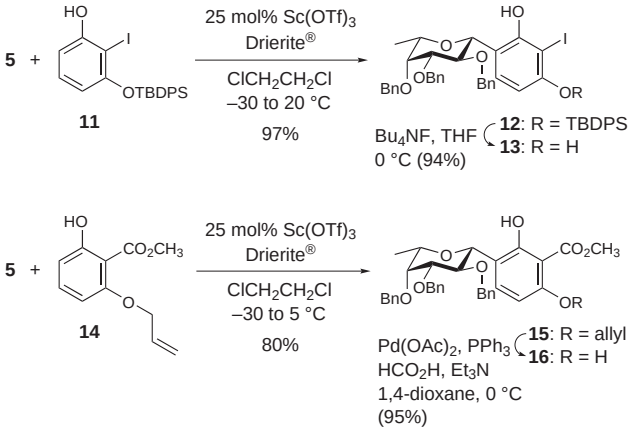
Run	Lewis acid (equiv)	Additive	Temp (°C)	Time (h)	Yield of **9** (%)[a]
1	Cp_2HfCl_2 (1.2), AgOTf (2.4)	MS4A	0	3	86
2	Cp_2HfCl_2 (0.25), AgOTf (0.5)	MS4A	20	5.5	36[b]
3	Cp_2HfCl_2 (0.25), AgOTf (0.5)	Drierite®	10	4	93
4	$Sc(OTf)_3$ (0.25)	MS4A	25	5.5	21[c]
5	$Sc(OTf)_3$ (0.25)	Drierite®	0	4	98
6	$BF_3{\cdot}OEt_2$ (0.25)	Drierite®	10	6	83
7	Me_3SiOTf (0.25)	Drierite®	25	4.5	93

[a] The stereoselectivity was β/α = >99/<1 in every run.
[b] Mono-*C*-mono-*O*-glycoside **10** was obtained in 44%, and 11% of the starting material **8e** was recovered.
[c] Compound **10** was obtained in 18%, and 37% of **8e** was recovered.

To examine applicability of this method, we prepared mono-*C*-glycosylated resorcinols **13** and **16**[11] as the glycosyl acceptors, which possess an iodine or an ester moiety, instead of the methyl in **8e**, at the position between the phenolic hydroxyl groups (Scheme 3). The reactions were examined for all possible combinations of the glycosyl acceptors **8e**, **13**, **16** and the glycosyl donors **5**, **17**, **18** (see Figure 2), according to the procedure described above. The results are summarized in Table 2.

Diol **8e** also reacted with rhamnosyl acetate **17** cleanly and stereoselectively (run 2). The configuration of the newly formed *C*-rhamnoside bond was exclusively β, and none of the β-*C*-fucosyl-α-*C*-rhamnosyl isomer or other stereoisomers was obtained.

Glycosyl acetate **18**, derived from 2-deoxy sugar (L-olivose), proved to be more reactive than **5** and **17** in both steps in the *O*→*C*-glycoside rearrangement, i.e. the O-glycosidation and the isomerization to the *C*-glycoside, so that the reaction with diol **8e** went to completion at lower temperature (run 3). Also in this case, the stereoselectivity was perfect to furnish the β-*C*-glycoside as a single isomer.



Scheme 3

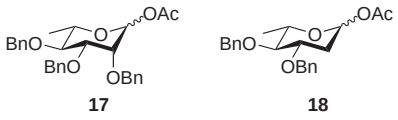
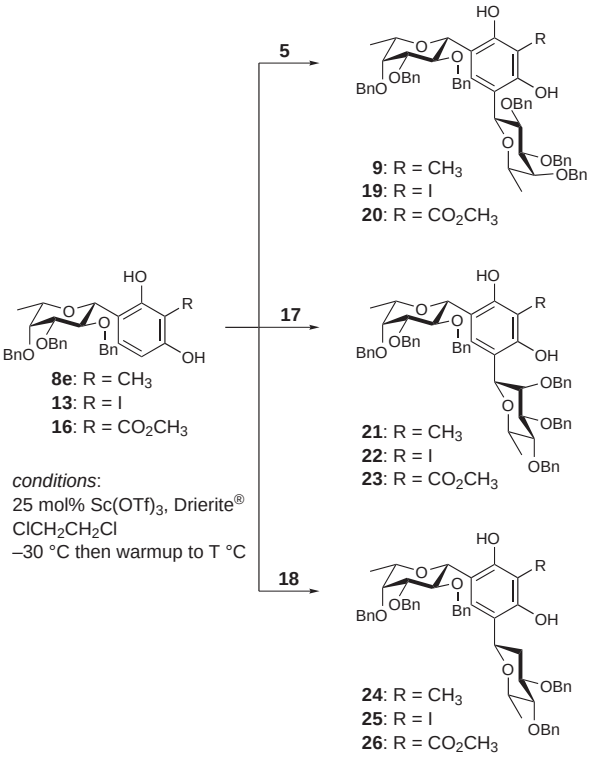


Figure 2

Diols **13** and **16** also worked nicely as glycosyl acceptors. The reactions with **5** (runs 4, 7) and **17** (runs 5, 8) afforded the corresponding bis-*C*-glycosides in high yields and stereoselectively. Unfortunately, the yields of the reactions with glycosyl donor **18** (runs 6, 9) were slightly lower. In these cases, decomposition of the highly reactive donor **18** took place before completion of the O-glycosylation.

In summary, we have described that two *C*-glycoside moieties can be efficiently installed stepwise in resorcinol derivatives by utilizing the two phenols as the pivots in the *O*→*C*-glycoside rearrangement. It was found that the second *C*-glycoside formation is remarkably facilitated by liberating both phenols in the mono-*C*-glycoside and that $Sc(OTf)_3$–Drierite® combination is most effective as the promoter. In light of the facile procedure as well as applicability to various sugars and 2-substituted resorcinol derivatives, the present method will find utility in the synthesis of bis-*C*-glycoside natural products and their analogues. Studies on the synthesis of the pluramycin-type antibiotics are currently under investigation.

Table 2 Reactions between Glycosyl Acceptors **8e**, **13**, **16** and the Glycosyl Donors **5**, **17**, **18**



Run	Glycosyl acceptor	Glycosyl donor	Temp (°C)	Product	Yield (%)[a]
1	**8e**	**5**	0	**9**	97
2		**17**	10	**21**	77
3		**18**	–10	**24**	85
4	**13**	**5**	5	**19**	91
5		**17**	5	**22**	70
6		**18**	–15	**25**	57
7	**16**	**5**	10	**20**	78
8		**17**	5	**23**	78
9		**18**	–10	**26**	53

[a] The stereoselectivity was β:α = >99:<1 in every run.

References and Notes

(1) (a) Hacksell, U.; Daves, G. D. Jr. *Prog. Med. Chem.* **1985**, *22*, 1. (b) Suzuki, K.; Matsumoto, T. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*, Vol. 2; Lukacs, G., Ed.; Springer: Berlin, **1993**, 353. (c) Postema, M. H. D. *C-Glycoside Synthesis*; CRC: Florida, **1995**.

(2) (a) Séquin, U. *Prog. Chem. Org. Nat. Prod.* **1986**, *50*, 58. (b) Pluramycin, A.; Kondo, S.; Miyamoto, M.; Naganawa, H.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1977**, *30*, 1143. (c) Séquin, U.; Ceroni, M. *Helv. Chim. Acta* **1978**, *61*, 2241. (d) Kidamycin: Furukawa, M.; Hayakawa, I.; Ohta, G.; Iitaka, Y. *Tetrahedron* **1975**, *31*, 2989.

(3) Hansen, M. R.; Hurley, L. H. *Acc. Chem. Res.* **1996**, *29*, 249.

(4) (a) Parker, K. A.; Koh, Y.-H. *J. Am. Chem. Soc.* **1994**, *116*, 11149. (b) Kaelin, D. E. Jr.; Lopez, O. D.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 6937. (c) Martin, S. F. *Pure Appl. Chem.* **2003**, *5*, 63.

(5) (a) Matsumoto, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1988**, *29*, 6935. (b) See also: Kometani, T.; Kondo, H.; Fujimori, Y. *Synthesis* **1988**, 1005. (c) Matsumoto, T.; Yamaguchi, H.; Tanabe, M.; Yasui, Y.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 8393. (d) Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, *116*, 1004.

(6) (a) Ben, A.; Yamauchi, T.; Matsumoto, T.; Suzuki, K. *Synlett* **2004**, 225. (b) For a review on the use of $Sc(OTf)_3$ in organic synthesis, see: Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15.

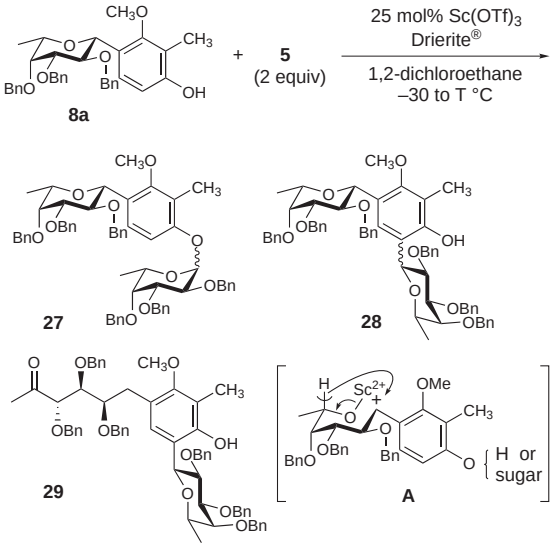
(7) **Procedure for the Preparation of Mono-*C*-Glycoside 7.** To a stirred mixture of $Sc(OTf)_3$ (67.0 mg, 0.136 mmol), mono-protected resorcinol derivative **6** (1.00 g, 2.76 mmol), powdered Drierite® (1.4 g) in 1,2-dichloroethane (27 mL), was added fucosyl acetate **5** (659 mg, 1.38 mmol) in 1,2-dichloroethane (8 mL) at –30 °C. After the temperature was gradually raised to 0 °C during 4.5 h, the mixture was poured into sat. aq $NaHCO_3$ solution. After filtration through a Celite® pad, the products were extracted with EtOAc (3×), and the combined organic extracts were washed with brine, and dried over Na_2SO_4. Removal of the solvents in vacuo and purification by silica gel chromatography (hexane–acetone–CH_2Cl_2 = 20:1:1) afforded *C*-glycoside **7** (1.02 g, 95%); mp 120–121 °C (hexane–EtOAc).

(8) The reaction of compound **8a** and fucosyl acetate **5** (2 equiv) under the $Sc(OTf)_3$-promoted conditions [25 mol% of $Sc(OTf)_3$, Drierite®, 1,2-dichloroethane, –30 °C to T °C] is shown below. The outcome was not satisfactory, but was better than those from other attempted conditions. When the reaction was stopped at 0 °C, the desired bis-*C*-glycoside **28** was obtained in 48% yield along with the *O*-glycoside **27** (29%). This shows that the protection of one of the phenolic hydroxyls remarkably retards both of the O-glycosylation and the migration of the sugar [note: the reaction of **8e** and **5** went to completion at 0 °C]. Further warming of the reaction accelerated the O-glycosidation and the migration of the sugar, but also caused undesired reactions to give many side products including **29** as the main constituent, which was most probably formed by the hydride shift from the C(5) of the sugar to the C(1) (see **A**). The yield of **28** did not exceed 68%. Prolongation of the reaction time around 0 °C did not give better result (Scheme 4).

(9) Molecular sieves (5A) are also usable but the reactions thereof required somewhat higher temperature and longer reaction period.

(10) Bis-*C*-glycoside **9**: mp 131–132 °C; $[\alpha]_D^{30}$ –18.0 (*c* 1.02, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (d, 6 H, *J* = 6.0 Hz, H-6), 2.17 (s, 3 H, ArCH_3), 3.60–3.61 (m, 4 H, H-2,5), 3.71 (d, 2 H, *J* = 1.6 Hz, H-4), 3.84 (d, 2 H, *J* = 10.2 Hz, benzylic), 4.14–4.15 (m, 4 H, H-1,3), 4.46 (d, 2 H, *J* = 10.2 Hz, benzylic), 4.76 (d, 2 H, *J* = 12.0 Hz, benzylic), 4.77 (d, 2 H, *J* = 12.2 Hz, benzylic), 4.82 (d, 2 H, *J* = 12.0 Hz, benzylic), 5.11 (d, 2 H, *J* = 12.2 Hz, benzylic), 6.71 (s, 1 H, Ar*H*), 7.04–7.41 (m, 30 H, *Ph*CH_2), 7.95 (s, 2 H, ArO*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.2, 17.5, 72.7, 74.4, 74.6, 75.3, 76.6, 78.5, 82.3, 83.9, 113.6, 114.3, 127.3, 127.4, 127.48, 127.53, 127.90, 127.95, 128.2, 128.4, 128.7, 137.9, 138.56, 138.64, 154.9. Anal. Calcd for $C_{61}H_{64}O_{10}$: C, 76.54; H, 6.74. Found: C, 76.24; H, 6.81. ORTEP drawing of **9** is shown below (Figure 3).

(11) TBDPS ether, when employed as the protecting group of a phenolic hydroxyl of methyl 2,6-dihydroxybenzoate, did not survive in the reaction. Thus, we opted for the allyl ether instead.



T (°C)	Yield (%)[a]			
	8a	**27**	**28**	**29**
–15	96	0	0	0
0	15	29	48[b]	0
25	0	0	68[c]	12
60	0	0	37	27

[a] Isolated yield of each product.
[b] α/β = 3.0/1.
[c] α/β = 1/2.4.

Scheme 4

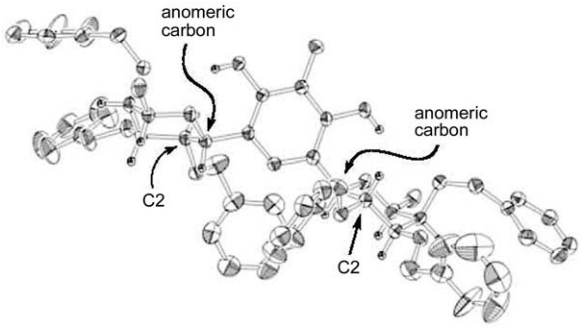


Figure 3