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Synthesis of a Novel Polyhydroxylated Salicylic Acid Lactone Framework

J. S. Shane Rountree[†] and Paul V. Murphy[*,†,‡]

UCD School of Chemistry and Chemical Biology and Centre for Synthesis and Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland, and School of Chemistry, National University of Ireland, Galway, University Road, Galway, Ireland

paul.v.murphy@nuigalway.ie

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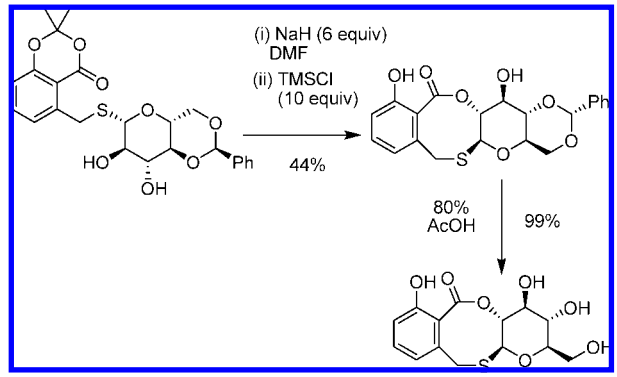
ABSTRACT



The facile preparation of a novel 8-membered polyhydroxylated salicylic acid lactone from 2,6-dihydroxybenzoic acid and sodium thio-D-glucose is described. The key step involved a sodium hydride promoted intramolecular lactonization in the presence of excess TMSCl, which led to isolation of the "natural product like" lactone.

As part of our wider research into the preparation of macrolide structures with desirable biological activities for use as biochemical probes or potential medicinal agents,[1] we were interested in the preparation of novel salicylate-based lactones. Some naturally occurring compounds of this type, such as apicularen A **1** (from a variety of strains of myxobacterial *Chondromyces*),[2] salicylhalamide A **2** (from marine sponge *Haliclona* sp.),[3] and lobatamide C **3** (from marine tunicate *Aplidium lobatum*),[4] exhibit antitumor activities. In particular, apicularen A **1** exhibits extremely potent cytostatic activity against a variety of human cancer cell lines and is also an inhibitor of angiogenesis.[5] Structurally, the compound is interesting as it contains an embedded pyran ring, an inner 10-membered lactone ring, and an outer 12-membered lactone ring. Resorcylic acid lactones, which are closely related to salicylic acid lactones, have 14-membered lactone rings and also have interesting biological activities.[6] The diverse biological effects displayed by these agents suggest that the inherent benzolactone motif is a privileged[7] or evolutionarily selected scaffold[8] that encodes properties

[†] University College Dublin.
[‡] National University of Ireland, Galway.

(1) (a) Matos, M.-C.; Murphy, P. V. *J. Org. Chem.* **2007**, *72*, 1803–1806. (b) Anquetin, G.; Rawe, S. L.; McMahon, K.; Murphy, E. P.; Murphy, P. V. *Chem.—Eur. J.* **2008**, *14*, 1592–1600. (c) Anquetin, G.; Horgan, G.; Rawe, S.; Murray, D.; Madden, A.; MacMathuna, P.; Doran, P.; Murphy, P. V. *Eur. J. Org. Chem.* **2008**, *195*, 3–1958.

(2) (a) Kunze, B.; Jansen, R.; Sasse, F.; Hofle, G.; Reichenbach, H. *J. Antibiot.* **1998**, *51*, 1075–1080. (b) Jansen, R.; Kunze, B.; Reichenbach, H.; Hofle, G. *Eur. J. Org. Chem.* **2000**, *91*, 3–919.

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(4) Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 7889–7901.

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for binding to proteins. Carbohydrates are also privileged structures,[9] having been applied widely as scaffolds for the development of bioactive compounds.[10] This approach has been in part successful because the carbohydrate framework contains hydroxyl groups that provide sites for attachment of pharmacophoric groups. A recent analysis of scaffolds investigated in organic chemistry showed that a small number of frameworks are found in a large number of all known compounds, indicating that there is considerable scope for the generation of new frameworks that will provide a basis for future drug discovery.[11] If these scaffolds are "natural product like" they may be more biologically relevant.[12]

Hence, we describe a concise synthesis of a novel polyhydroxylated salicylic acid lactone framework **4** containing an inner 8- and an outer 12-membered ring that resembles the natural salicylic acid lactones (Figure 1). The retrosynthetic analysis of **4** is outlined in Scheme 1.

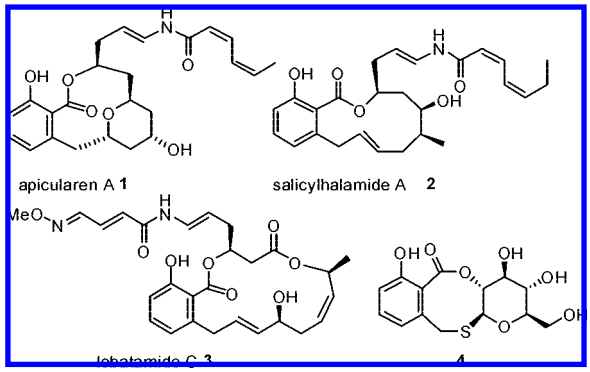
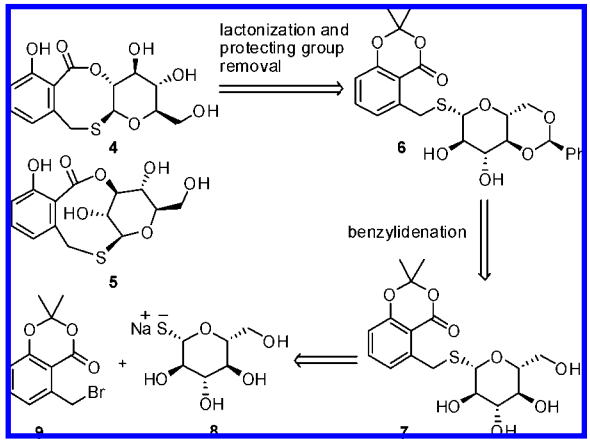


Figure 1. Structures **1**−**4**.

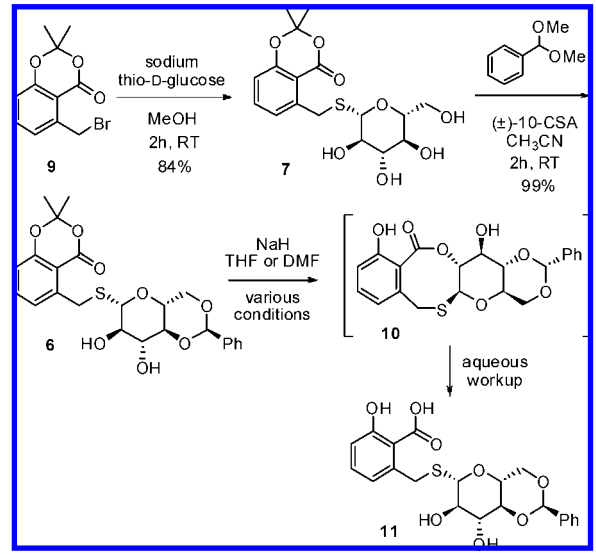
Scheme 1. Retrosynthetic Analysis



It was envisaged that reaction of sodium thio-D-glucose **8** and known salicylic acid derivative **9**[13] would give **7**. After benzylidene acetal protection of the sugar moiety to give **6**, we envisaged that a study of the regioselectivity of the intramolecular lactonization reactions of **6** would be interesting. The alkoxide generated by reaction of **6** with sodium hydride would act as a nucleophile at the salicylate ester and could give **4** or **5** after deprotection, generating two novel natural product inspired frameworks. Intramolecular lactonization reactions of this type have previously been utilized by others in order to prepare various lactones with yields varying from 33 to 77%.[4,14]

The benzylic bromide **9** was first prepared as described previously.[13] Reaction of this bromide with sodium thio-D-glucose in methanol proceeded smoothly and gave the thioglycoside **7** in good yield (84%, Scheme 2). The 4- and

Scheme 2. Preparation of **6** and Initial Lactonization Attempts



6-OH groups of the tetrol **7** were protected as the benzylidene acetal by reaction with benzaldehyde dimethyl acetal and catalytic (±)-10-camphorsulfonic acid (1 mol %) in freshly distilled acetonitrile to give **6** (99%). The formation of an 8- or 9-membered ring lactone was next investigated. When diol **6** was treated with excess sodium hydride in DMF or THF and water was added (to react with excess hydride during workup), acid **11** was the only product isolated. During the course of the reactions, the reaction mixture was analyzed by ESI-MS, which suggested that a lactone, presumably **10** based on observations described below, was

(7) Structural analogues based on the same scaffold which bind to more than one type of receptor are known as privileged structures. See: Hirschmann, R. *Angew. Chem., Int. Ed.* **1991**, *30*, 1278–1301.

(8) Koch, M. A.; Waldmann, H. *Drug Discovery Today* **2005**, *10*, 471–483.

(9) Hirschmann, R.; Cichy-Knight, M. A.; van Rijn, R. D.; Sprengler, P. A.; Spoors, P. G.; Shakespere, W. C.; Pietranico-Cole, S.; Barbosa, J.; Liu, J.; Yao, W.; Roher, S.; Smith, A. B., III. *J. Med. Chem.* **1998**, *41*, 1382–1391.

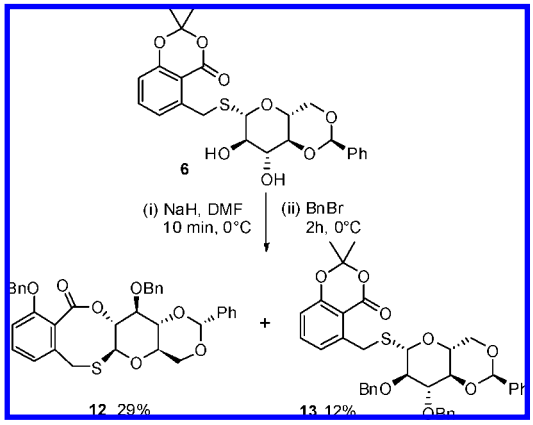
(10) For recent reviews on carbohydrates as scaffolds, see: (a) Dunne, J. L.; Murphy, P. V. *Curr. Org. Synth.* **2006**, *3*, 403–437. (b) Velter, I.; La Ferla, B.; Nicotra, F. *J. Carbohydr. Chem.* **2006**, *25*, 97–138. (c) Becker, B.; Condie, G. C.; Le, G. T.; Meutermans, W. *Mini-Rev. Med. Chem.* **2006**, *6*, 1299–1309. (d) Meutermans, W.; Le, G. T.; Becker, B. *ChemMedChem* **2006**, *1*, 1164–1194.

(11) Lipkus, A. H.; Yuan, Q.; Lucas, K. A.; Funk, S. A.; Bartelt, W. F., III.; Schenck, R. J.; Trippe, A. J. *J. Org. Chem.* **2008**, *73*, 4443–4451.

formed initially and that it was subsequently hydrolyzed after water had been added to the reaction mixture.

The lactonization reaction was next carried out in the presence of benzyl bromide with a view to trapping the lactone **12**. It was believed that the incorporation of the relatively apolar groups onto the free hydroxyl groups in the presence of the lactone would protect the lactone from basic hydrolysis by increasing steric hindrance and by decreasing solubility of the lactone in water. Thus, when diol **6** was treated with sodium hydride in DMF for 5 min, with subsequent addition of benzyl bromide, the 8-membered ring lactone **12** (29%) was isolated as the major product along with the di-*O*-benzylated derivative **13** (12%) (Scheme 3). The 500 MHz

Scheme 3. Lactonization in the Presence of Benzyl Bromide



^{1}H and COSY NMR data in $CDCl_3$ for lactone **12** clearly showed that the chemical shift of the signal for H-2 on the sugar ring shifted by ~1 ppm downfield when compared with the signal for the H-2 of both **6** and **13**, supporting the assignment of the 8-membered ring structure to **12**. It is generally accepted that medium size rings including 8-membered ring lactones are difficult to prepare.[15] However, there is literature precedent for the formation of an 8-membered ring salicylic acid lactone by intramolecular reaction with alkoxide generated by sodium hydride.[16]

As the use of benzyl bromide in the lactonization had some success it was decided to investigate the use of TMSCl to likewise trap the intermediates of the reaction and facilitate isolation of the lactone. The reactions of **6** with 6 equiv of sodium hydride in DMF, followed by the addition of 4 equiv of TMSCl after 15 min, resulted in the isolation of silylated compounds **14** and **15** (Figure 2). The presence of a signal

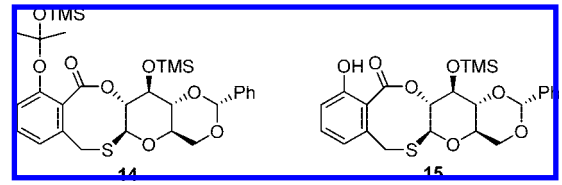
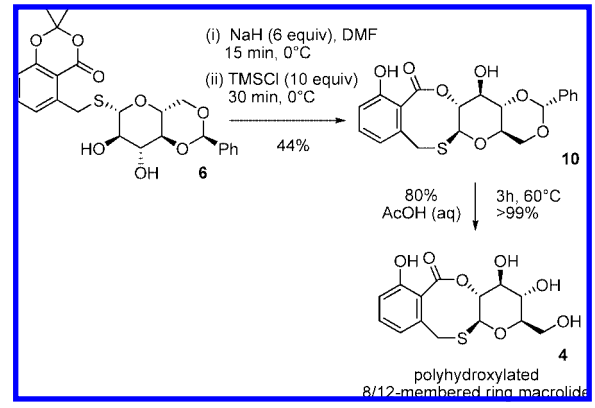


Figure 2. Silylated lactones **14** and **15**.

for a phenolic proton in the ^{1}H NMR spectrum (500 MHz) of **15** in $CDCl_3$ at δ 9.11 ppm confirmed that the TMS group was located on the thioglucose residue.

When the amount of TMSCl in these reactions was increased to 10 equiv, the 8-membered lactone **10** (44%) was the major product (Scheme 4). The isolation of **10**

Scheme 4. Preparation of Lactone **10** and Deprotection to **4**



required careful workup involving the addition of saturated aqueous sodium bicarbonate solution 30 min after the addition of TMSCl, followed by dilution with water after a further 20 min and extraction into diethyl ether, before drying the organic phase (magnesium sulfate) and subjecting it to flash chromatography. Under these conditions, the reaction was replicated successfully several times.

It is interesting to note that after using these favorable workup conditions, almost none of the starting material was

(12) For selected publications on "natural product like" compounds, see: (a) Smith, A. B., III.; Kim, W.-S.; Wuest, W. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7082–7086. (b) Milroy, L.-G.; Zinzalla Giovanna, Pr.; Giuseppe Michel, P.; Ley, S. V.; Gunaratnam, M.; Beltran, M.; Neidle, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 2493–2496. (c) Ganesan, A. Combinatorial Synthetic Design: The Balance of Novelty and Familiarity. In *Exploiting Chemical Diversity for Drug Discovery*; Bartlett, P. A., Entzeroth, M., Eds.; RSC Biomolecular Sciences, Royal Society of Chemistry : Cambridge, UK, 2006; pp 91−111. (d) Boldi, A. M. *Curr. Opin. Chem. Biol.* **2004**, *8*, 281–286.

(13) From 2,6-dihydroxybenzoic acid, acetonidation: (a) Hadfield, A.; Schweitzer, H.; Trova, M. P.; Green, K. *Synth. Commun.* **1994**, *24*, 1025–1028. Triflation: (b) Uchiyama, M.; Ozawa, H.; Takuma, K.; Matsumoto, Y.; Yonehara, M.; Hiroya, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5517–5520. For methylation and benzylic bromination, see ref 4.

(14) (a) Bhattacharjee, A.; De Brabander, J. K. *Tetrahedron Lett.* **2000**, *41*, 8069–8073. (b) Holloway, G. A.; Hugel, H. M.; Rizzacasa, M. A. *J. Org. Chem.* **2003**, *68*, 2200–2204. (c) Nicolaou, K. C.; Kim, D. W.; Baati, R.; O'Brate, A.; Giannakakou, P. *Chem.—Eur. J.* **2003**, *9*, 6177–6191. (d) Hilli, F.; White, J. M.; Rizzacasa, M. A. *Org. Lett.* **2004**, *6*, 1289–1292.

(15) (a) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777–2849. (b) Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911–939. (c) Shiina, I. *Chem. Rev.* **2007**, *107*, 239–273.

(16) Under similar reaction conditions, Shen et al. reported the formation of an undesired 8-membered ring lactone in preference to a desired 15-membered ring lactone. See ref 4.

observed by TLC analysis. However, **6** was generated after employing other workup conditions. In these cases, the starting material was isolated with high recovery (30−50%), suggesting that the lactone intermediate of the reaction can be hydrolyzed back to give **6** (Figure 3). The reversible

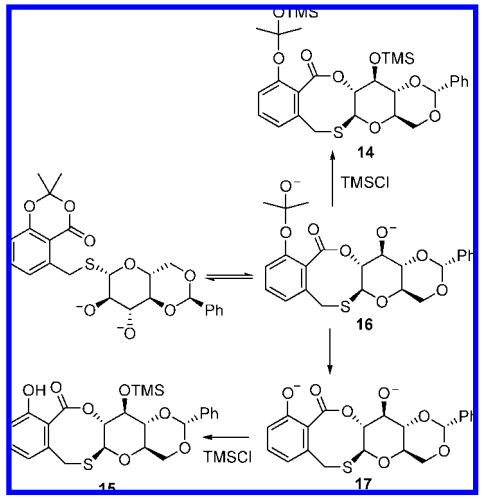


Figure 3. Formation of **14** and **15**.

formation of intermediate **16** or a protonated variant thus seems plausible, since its silylated variant **14** was observed and **6** can be recovered after certain workup conditions.

The reason for the removal of TMS under the conditions that led to **10** is not understood and would need to be investigated more thoroughly. One possibility is that when TMSCl (10 equiv) is in excess compared to sodium hydride (6 equiv) HCl is generated due to the presence of residual water in the solvent. If enough water is present, acid-catalyzed hydrolysis of the hemiacetal of **16** may result and lead to removal of any acid-sensitive TMS groups from intermediates such as **14** or **15** to yield **10**. It is not inconceivable that the addition of bicarbonate during workup contributes to this scenario.

The benzylidene acetal was successfully removed from **10** using 80% acetic acid to give the polyhydroxylated derivative **4** in quantitative yield (Scheme 4). The NMR data for **4** was carefully analyzed to confirm that transesterification (i.e., ester migration from 2-OH to either the 3-, 4-, or 6-OH) had not occurred under the acidic conditions. The preparation of **4** from 2,6-dihydroxybenzoic acid was achieved in 10% overall yield for the eight steps (37% in four steps from sodium thio-D-glucose).

In summary, we have described the concise synthesis of a novel hybrid of a saccharide and salicylic acid lactone that contains an 8-membered ring. Naturally occurring medium-sized lactones are considered to be rare in organic chemistry, possibly due to the difficulty of their biosynthesis.[15a,c] Those that occur do exhibit interesting biological properties. Lactone **4** exhibits some structural similarity with (−)-ovatolide **18**, which is a naturally occurring indole alkaloid found in the leaves of *Bridelia ovata*, which are used in traditional Thai medicine as a laxative, febrifuge, and astringent (Figure 4).[17]

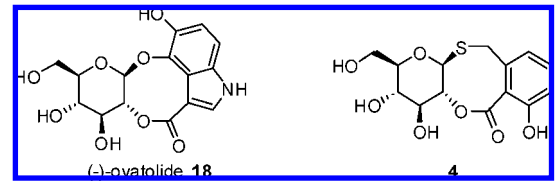


Figure 4. Structures of (−)-ovatolide **18** and **4**.

The approach described herein may be helpful in the synthesis of other natural product-like medium size lactones that are fused to organic structures, expanding further the number of frameworks available for investigations into bioactive compound discovery. Lactone **4** did not show ability to inhibit the proliferation of tumor cells in preliminary biological studies. However, more diverse and detailed biological studies of **4** and derivatives may be interesting.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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