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SmI_2 cleavage of chromomycin A_3 sugars

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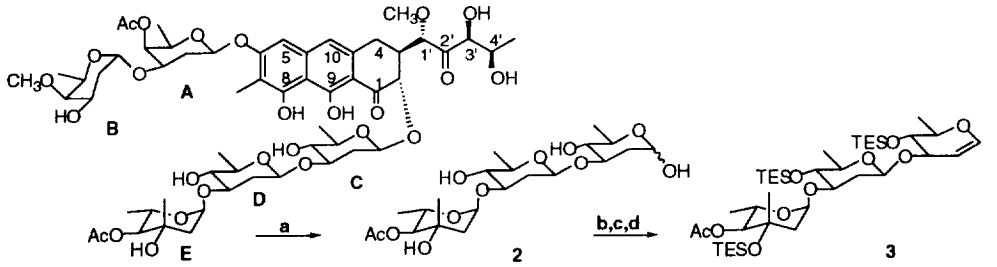
Abstract: The CDE-trisaccharide of chromomycin A_3 was cleaved with samarium diiodide and converted to a protected glycal for coupling to an aglycone.

Chromomycin A_3 (CRA_3), **1**, is an antitumor antibiotic that binds to DNA[1, 2]. The sugar components have been shown to be critical for DNA binding[3-5]. To study the roles of the CRA_3 sugars in greater detail[6, 7], we wanted the CDE-trisaccharide in a form suitable for attachment to various synthetic aglycons. Although aureolic acid derived trisaccharides have been chemically synthesized[8-10], the syntheses are lengthy because the monomers are not readily available. Therefore, we opted to cleave the trisaccharide from the natural product and convert it to an intermediate useful for glycosylation. Because CRA_3 is difficult to obtain in large amounts[11], it was important that the yields for all transformations be very good in order for the degradation-reattachment strategy to succeed. Attachment of the trisaccharide to a synthetic aglycon requires construction of a 2-deoxy β-glycosidic linkage alpha to a ketone. Both Roush[12] and Franck[13] have previously developed good methods to form 2-deoxy β-glycosidic linkages in CRA_3 or related systems [6, 7] by going through a glycal intermediate. Hence, our goal was to obtain a suitably protected CDE trisaccharide glycal.

The glycosidic linkage from the trisaccharide to the aglycon is adjacent to a ketone. Cleavage of α-oxygenated ketones has been accomplished in many systems using a variety of different reducing conditions[14], the classical method being Zn/AcOH. For sensitive systems, however, samarium diiodide cleavage is the best option[14] because the conditions are very mild. Initial investigations into the SmI_2 cleavage of CRA_3 produced yields of CDE-trisaccharide that varied from 25% to 65%[15]. Because a large excess of SmI_2 is needed to effect cleavage, large quantities of samarium (III) salts are produced upon workup. When the reaction is quenched with saturated sodium bicarbonate, the product lactol adheres strongly to



1 Chromomycin A_3

a) SmI_2, THF, -78° to -0°C (85%); b) Ac_2O (1eq), py(10eq), cat. DMAP, CH_2Cl_2, -78°C (90%); c)TESOTf (6eq), Et_3N(10eq), CH_2Cl_2, -78°C (69%); d)SiO_2, 10:1 toluene:propylene oxide, mol sieves, reflux (72%)

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these insoluble salts and cannot be reliably washed off. Little *et al.* have reported a basic workup procedure for the SmI_2 reaction using potassium sodium tartrate (Rochelle's Salt), which chelates the salts so that they are soluble in aqueous solution[16]. Using a modification of Little's conditions in which the reaction was quenched with a saturated solution of Rochelle's salt in the absence of additional base, we were able to obtain the product lactol in 85% yield[17]. No byproduct from reduction of the aldehyde on the C-ring was observed[18].

The CDE-lactol was converted to the glycal as shown in Figure 1 [19]. The overall yield for this four step sequence from degradation to glycal formation is 38%. The degradation route described is an efficient way of obtaining useful quantities of the CDE-trisaccharide glycal for attachment to a variety of aglycons. This chemistry should make it possible to investigate some of the structural requirements for DNA binding and activity in CRA_3.

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References and Notes

[1] Skarbek, J.D.; Speedie, M.K. "Antitumor Antibiotics of the Aureolic Acid Group: Chromomycin A_3, Mithramycin A, and Olivomycin A", In: *Antitumor Compounds of Natural Origin: Chemistry and Biochemistry* , Florida: CRC Press, 1981, Vol. 1: 191-235.
[2] Pullman, B.; Jortner, J. Eds. *Molecular Basis of Specificity in Nucleic Acid-Drug Interactions*; Klurver Academic Publishers: Dordrecht, The Netherlands, 1990, Vol. X 414-422.
[3] Hayasaka, T.; Inoue, Y. *Biochemistry* **1969**, *8*, 2342-2347.
[4] Silva, D.J.; Goodnow, R.; Kahne, D. *Biochemistry* **1993**, *32*, 463-471.
[5] Silva, D.J.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 7962-7970.
[6] Silva, D.J.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 2641-2642.
[7] Silva, D.J.; Kraml, C.M.; Kahne, D. *Biorg., & Med.Chem.* **1994**, *2*, 1251-1259.
[8] Thiem, J.; Schöttmer, B. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 555-557.
[9] Sebesta, D.P.; Roush, W.R. *J. Org. Chem.* **1992**, *57*, 4799-4802.
[10] Toshima, K.; Noazki, Y.; Mukaiyama, S.; Tamai, T.; Nakata, M.; Tatsuta, K.; Kinoshita, M. *J. Am. Chem. Soc.* **1995**, *117*, 3717-3727.
[11] CRA_3 costs $361.75/50 mg from Sigma. We received a gift of 25 g from K. Nakanishi.
[12] Roush, W.R.; Briner, K.; Kesler, B.S.; Murphy, M.; Gustin, D.J. *J. Org. Chem.* **1996**, *61*, 6098-6099.
[13] Franck, R.W.; Marzabadi, C.H. *J. Org. Chem.* **1998**, *63*, 2197-2208.
[14] Molander, G.A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135-1138. and refs. therein.
[15] In 1988, S. Ramesh and R.W. Franck examined the SmI_2 cleavage of olivomycin A and chromomycin A_3, with the side chain ketones blocked as semicarbazones, and obtained the trisaccharides in approximately 40% yield - personal communication from R. Franck, Hunter College / CUNY.
[16] Schwaebe, M.K.; Little, R.D. *Synth. Commun.* **1997**, *27*, 837-840.
[17] SmI_2: 25mL dry, degassed THF (distilled from potassium benzophenone) was added by canula to 480mg (3.2mmol) Sm (Aldrich) in a flame dried flask wrapped in foil. While stirring vigorously, distilled CH_2I_2 (200µL, 2.5mmol) was added and stirring continued at ambient temperature for two hours. Cleavage: The SmI_2 solution (25mL, 0.1M) was cooled to -78°C, and transferred by canula to a flask containing a solution of dry CRA_3 (39mg, 0.03mmol) in 5mL degassed THF also at -78°C and wrapped in foil. The reaction was stirred for 1 hour at -78°C and then placed in a 0°C bath and stirred for 1/2 hour. The reaction was quenched with a saturated Rochelle's salt solution and extracted 8 times with EtOAc, washed with brine, and dried over $MgSO_4$. Product is purified by column chromatography 95:5 EtOAc:Hex, and then 95:5 $CHCl_3$:MeOH to give 13mg of **2**(85%).
[18] For a review of SmI_2 chemistry see: Molander, G.A. *Org. React.* **1994**, *46*, 211-367.
[19] (**3**) ^{1}H NMR ($CDCl_3$) δ 6.35 (d, *J* = 6.7 Hz, 1 H, C-1), 5.04 (t, *J* = 4.3 Hz, 1 H, E-1), 4.78 (dd, *J* = 6.1 Hz, 3.0 Hz, 1 H, C-2), 4.63 (d, *J* = 6.7 Hz, 1 H, E-4), 4.59 (dd, *J* = 9.4 Hz, 1.5 Hz, 1 H, D-1), 4.24 (dd, *J* = 5.5 Hz, 2.4 Hz, 1 H, C-3), 3.91 (m, 2 H, E-5, C-5), 3.68 (m, 2 H, D-3, C-4), 3.22 (m, 2 H, D-5, D-4), 2.23 (m, 1 H, D-2), 2.07 (s, 3 H, OAc), 1.89 (dd, *J* = 13.4 Hz, 3.7 Hz, 1 H, E-2), 1.84 (dd, *J* = 13.4 Hz, 4.3 Hz, 1 H, E-2'), 1.42 (m, 1 H, D-2'), 1.37 (s, 3 H, E-3 Me), 1.32 (d, *J* = 6.7 Hz, 3 H, C-6), 1.25 (m, 6 H, D-6, E-6), 0.95 (m, 27 H), 0.73-0.55 (m, 18 H).