Synthesis of the Macrolactone Disaccharide Subunit of Tricolorin A

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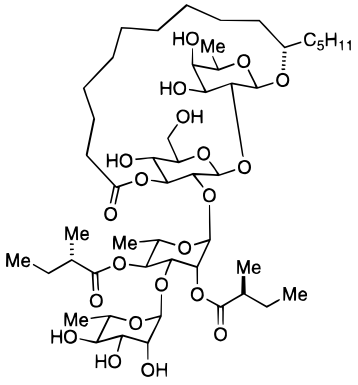
Farmers in the southeastern intertropical Mexican state of Morelos make extensive use of *Ipomoea tricolor* as a cover crop during the fallow period in sugar-cane fields. This tuberous plant has the useful property of suppressing the growth of other plants, including invasive weeds. In 1993, Pereda-Miranda and co-workers[1] reported the isolation of tricolorin A (**1**), the actual compound responsible for the biological activity of this plant. Compound **1** also demonstrated significant cytotoxicity against cultured P-388 and human breast cancer cells. We chose tricolorin A as a synthetic target because of the unique challenge in forming the macrolactone in this molecule. We now report the synthesis of a protected fucosyl β-D-glucoside that incorporates the 19-membered lactone characteristic of tricolorin A.



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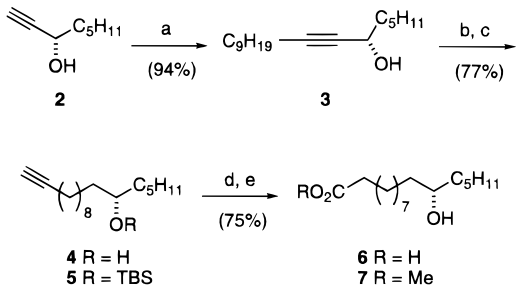
The synthesis of the hydroxy acid aglycone is summarized in Scheme 1. The (*S*)-propargylic alcohol **2**[2] was deprotonated with $LiNH_2$ and the resulting lithioalkyne treated with 1-iodononane to obtain **3** in 94% yield. Treatment of **3** with $KNH(CH_2)_3NH_2$ (KAPA)[3] provided terminal alkyne **4** in 79% yield. Protection of the alcohol with *tert*-butyldimethylsilyl chloride, followed by oxidative cleavage of the alkyne to the corresponding acid,[4] and subsequent Fisher esterification gave the methyl ester. Additionally, the acidic esterification reaction conditions conveniently cleaved the TBS ether to give the desired hydroxy ester **7** in good overall yield.

The fucose unit was prepared from the known benzyl α-D-fucopyranoside (Scheme 2).[5] Selective protection of the C-3 and C-4 hydroxyl groups as the acetonide followed by protection of the C-2 hydroxyl group as the pivaloyl ester gave the fully protected intermediate **10**. The anomeric position was then unmasked by catalytic hydrogenation of the benzyl ether. Activation of the fucose derivative for glycoside formation was achieved by treatment with Cl_3CCN and Cs_2CO_3[6] to furnish trichloroacetimidate **12**.

Coupling of hydroxy ester **7** and the crude trichloroacetimidate occurred smoothly in CH_2Cl_2 with catalytic TMSOTf[7] to give the desired β-glycosidic linkage in 79% yield. The C-2 hydroxyl group was exposed by cleavage of the pivaloyl ester with NaOMe in a MeOH/MeOAc cosolvent to give coupling partner **14**. A large excess of NaOMe was employed in this reaction to allow the reaction to proceed at a practical rate. We found that use of MeOAc in this step greatly minimized saponification of the methyl ester functionality in the molecule by a minor amount of hydroxide present in the NaOMe reaction solution.

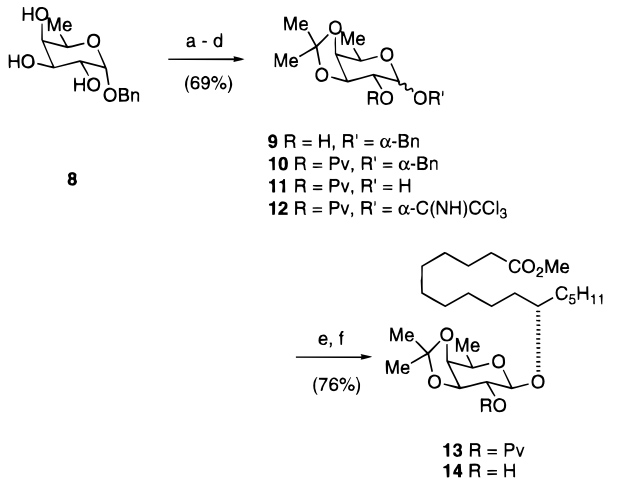
As shown in Scheme 3, the glucose unit preparation began by protection of the known glucopyranose **15**[8] to form the triacetyl compound **16**. Formation of the amino glycoside by treatment with $BnNH_2$ followed by selective hydrolysis with dilute aqueous acid[9] furnished pyranose

Scheme 1[a]



[a] Key: (a) (i) $LiNH_2$, NH_3, −33 °C; (ii) $C_9H_{19}I$, THF, −33 → 25 °C; (b) KAPA, THF; (c) TBSCl, imidazole, DMF; (d) $KMnO_4$, HOAc, H_2O, pentane; (e) H_2SO_4, MeOH.

Scheme 2[a]



[a] Key: (a) 2,2-dimethoxypropane, *p*-TsOH; (b) *t*-BuCOCl, pyridine, DMAP, 70 °C; (c) 50 psi H_2, $Pd(OH)_2$, EtOAc; (d) Cl_3CCN, Cs_2CO_3, CH_2Cl_2; (e) **7**, TMSOTf, CH_2Cl_2; (f) NaOMe, MeOH, MeOAc.

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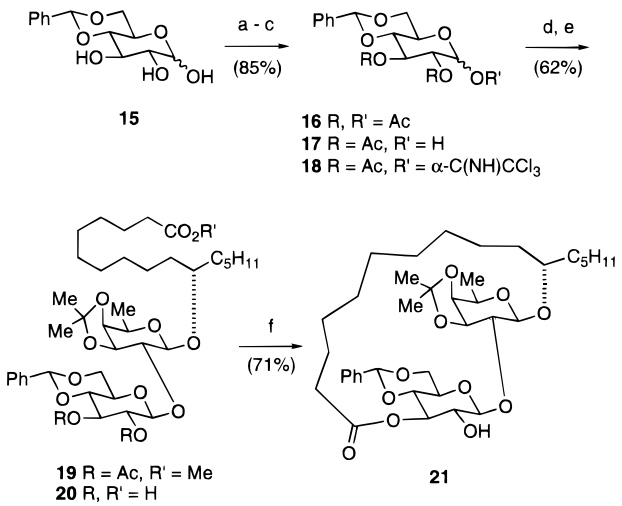
Scheme 3[a]



[a] Key: (a) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (b) (i) $BnNH_2$, THF, (ii) 1 N HCl; (c) Cl_3CCN, Cs_2CO_3, CH_2Cl_2; (d) **14**, AgOTf, CH_2Cl_2; (e) LiOH, THF, H_2O; (f) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, benzene.

17 in 87% yield.[10] Glycosyl donor **18** was obtained by treatment of **17** with Cl_3CCN and Cs_2CO_3.

Treatment of alcohol **14** with the crude trichloroacetimidate and anhydrous AgOTf[11] in CH_2Cl_2 gave an 84% yield of the β-disaccharide. Simultaneous saponification of the three ester groups in disaccharide **19** with LiOH gave the macrolactonization precursor **20** in good yield. Following the Yonemitsu protocol,[12] the acid diol lactonized at the C-3 hydroxyl position of the glucose ring with a high degree of selectivity over the C-2 position to give the target lactone **21** in 71% yield.

In summary, the target lactone disaccharide has been synthesized in a total of 17 steps, with a longest linear sequence of 10 steps and an overall yield of 18%. We are currently exploring the synthesis of a suitable rhamnosyl α-L-rhamnopyranoside to use as a glycosyl donor for converting **21** into tricolorin A.

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Supporting Information Available: Experimental procedures and spectral data for all compounds (9 pages).

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(10) Compounds **16** and **17** have been previously reported in the literature, but were prepared by different methods and no modern spectral data is available. For compound **16**, see: Zervas, L. *Chem. Ber.* **1931**, *64*, 2289. For compound **17**, see: Korytnyk, W.; Mills, J. A. *J. Chem. Soc.* **1959**, 636.

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