Metathesis Route to Resin Glycosides: Formal Total Synthesis of Tricolorin A

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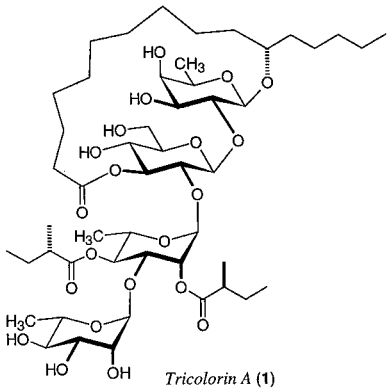
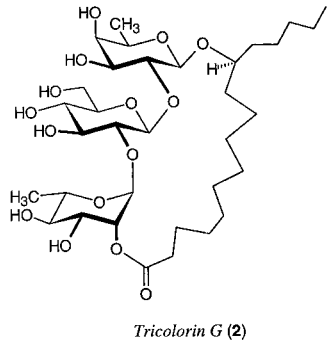
The tricolorin family of resin glycosides constitutes the allelochemical principle of *Ipomoea tricolor* Cav., a plant that is extensively used in traditional agriculture in Mexico as a cover crop for the protection of sugar cane.[1,2] Tricolorin A (**1**) was also found to exhibit significant cytotoxic properties against cultured P-388 and human breast cancer cell lines.[1] To probe this promising activity in more detail, a synthesis-driven mapping of its structure/activity profile is called for, which can only be achieved on the basis of a convergent approach to these complex oligosaccharide targets. The major challenge toward this end is posed by the macrolide entity formed by (11*S*)-hydroxyhexadecanoic acid spanning two (cf. **1**) or more (cf. **2**) units of their sugar backbones.



Tricolorin A (**1**)



Tricolorin G (**2**)

In recent studies directed toward the tricolorins, syntheses of the disaccharidic fragment **3** of tricolorin A via macrolactonization as the key step have been described.[3a,b] We now report an alternative approach to **3** employing ring closing metathesis (RCM) for the formation of the macrocycle. This strategy has the inherent advantage that systematic variations of the ring size and hence of the lipophilicity of the compound are easy to accomplish.

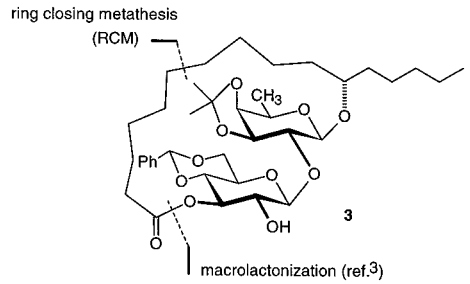


Figure 1.

Our previous investigations on RCM have uncovered the essential requirements for productive macrocyclizations and have revealed a truly remarkable scope of this method.[4−6] We found that neither the conformational predisposition of the substrates nor the ring size formed is of major concern, whereas the mere presence of a polar "relay" substituent, its proper distance to the alkene groups, and low steric hindrance close to the double bonds turned out to be the decisive parameters.[4] It should be possible to meet all of these criteria en route to **3**, provided that the large ring is closed at (or near) the site indicated in Figure 1.

The synthesis of the required fucose building block is shown in Scheme 1. Enantioselective addition of dipentylzinc to 5-hexenal (**4**) in the presence of Ti(O-*i*-Pr)$_4$ and catalytic amounts of bis-(*R*,*R*)-trifluoromethanesulfonamide **5** proceeded smoothly on a multigram scale, providing (*S*)-**6** in good yield and excellent enantiomeric purity (ee ≥ 99%).[7]

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(8) Prepared from D-fucose by acetylation (Ac_2O, DMAP, pyridine, 98%) and subsequent treatment with HBr (33% in HOAc) in Ac_2O/CH_2Cl_2 at 0 °C → rt.

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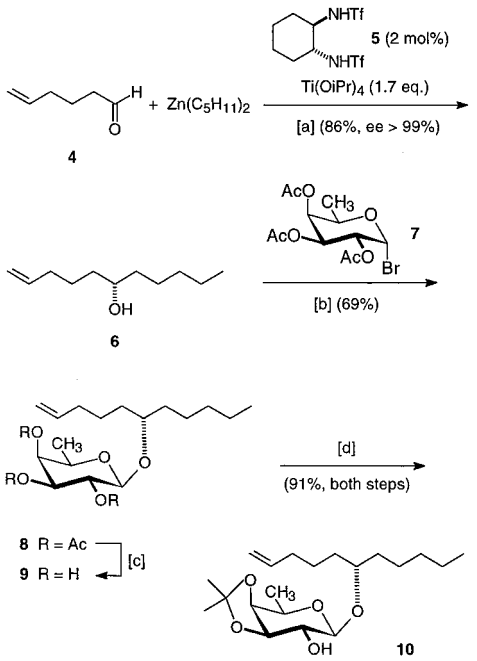
Scheme 1[a]

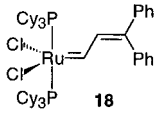


[a] Key: (a) reagents as indicated, toluene, rt; (b) $AgNO_3$ on silica/alumina,[9] MS 3 Å, CH_2Cl_2, −10 °C; (c) KOMe cat., MeOH, rt; (d) 2,2-dimethoxypropane, *p*-TsOH·H_2O cat., acetone, rt.

Its glycosylation with tri-*O*-acetyl-α-D-fucopyranosyl bromide (**7**)[8] in the presence of $AgNO_3$ on silica/alumina[9] gave compound **8** in 69% yield, which was deacetylated (**8** → **9**) and converted into acetal **10** under standard conditions.

The other monosaccharide unit was obtained from 4,6-*O*-benzylidene-D-glucopyranose (**11**)[10] as outlined in Scheme 2. Peracetylation of **11** followed by deprotection of the anomeric position gave compound **13**,[3a] which readily afforded trichloroacetimidate **14** on treatment with Cl_3CCN and Cs_2CO_3 in CH_2Cl_2. Reaction of this glycosyl donor (α:*β* ≈ 2:1) with the fucose derivative **10** in CH_2Cl_2/hexane at −20 °C in the presence of catalytic amounts of BF_3·Et_2O cleanly provided the desired *β*-configurated disaccharide **15** in 82% yield.[11] Deprotection followed by acylation of the resulting diol **16** with 6-heptenoic acid in the presence of DCC and DMAP proceeded selectively at the O-3 position, thus affording ester **17** as the only product in 71% yield. The site of acylation was unambiguously assigned by NMR and the reactivity pattern O-3 ≫ O-2 in diol **16** is in full accordance with Heathcock's observations in his macrolactonization approach toward compound **3**.[3a]

In line with our previous experiences,[4] diene **17** cleanly cyclized to the desired 19-membered ring **19** on reaction with the ruthenium carbene **18** (5 mol %)[12] in refluxing CH_2Cl_2.



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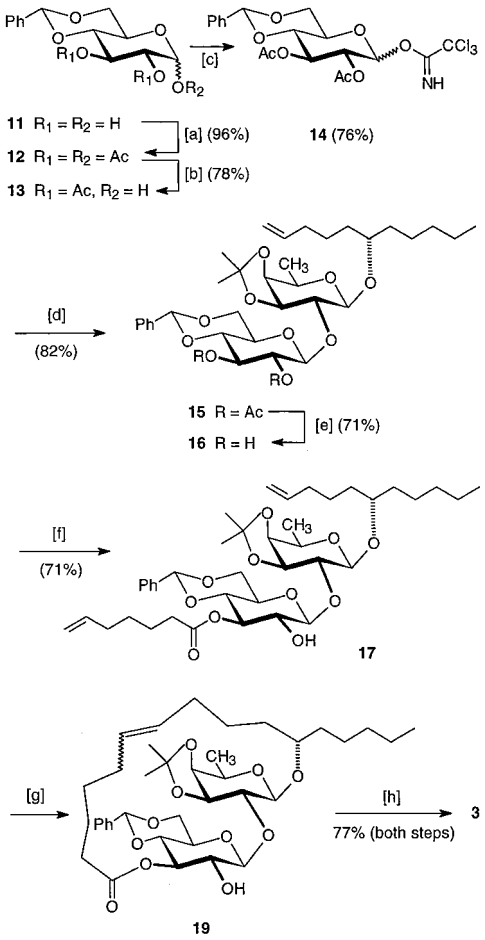
The fact that neither the free OH nor any other functional group in the substrate interfere with RCM illustrates again the excellent compatibility and selectivity of the Grubbs catalyst.[6] Hydrogenation of the crude cycloalkene **19** (*E*/*Z*-mixture) afforded the desired disaccharide **3** in 77% yield over both steps and completes a formal total synthesis of tricolorin A.[3b] Among the analytical and spectroscopic data of **3**, the strong solvent dependence of its ^1H NMR spectrum is most remarkable (cf. Supporting Information).

Scheme 2[a]



[a] Ket: (a) Ac_2O, DMAP cat., pyridine, 0 °C → rt; (b) (i) $BnNH_2$, THF, 0 °C → rt; (ii) 1 N HCl; (c) Cl_3CCN, Cs_2CO_3, CH_2Cl_2, rt; (d) **10**, BF_3·Et_2O cat., CH_2Cl_2/*n*-hexane (1/1), −20 °C; (e) KOMe cat., MeOH, rt; (f) 6-heptenoic Acid, DCC, DMAP, CH_2Cl_2, rt; (g) **18** (5 mol %), CH_2Cl_2, reflux, high dilution; (h) H_2 (1 atm), Pd/C (5 mol %), EtOH, rt.

The direct comparison of the metathesis route to **3** with the macrolactonization strategy previously reported confirms our earlier findings that RCM rivals all established methods for the synthesis of large rings, provided that the proper site of ring closure is chosen according to our previous rationale.[4] Moreover, it is obvious that esterification of diol **16** with acids other than 6-heptenoic acid or attachment of such an unsaturated appendage at other sites of the sugar backbone opens up a flexible entry into congeners and analogues of tricolorin A.

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Supporting Information Available: Procedures for all steps, details of ee determination, analytical data, and copies of the NMR spectra of all new products (34 pages).

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