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Total Syntheses of Ipomoeassin B and E

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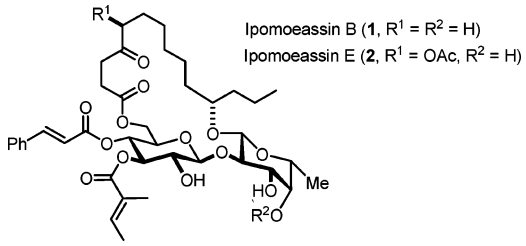
During an international biodiversity program aiming at the examination of the medicinal potential of various organisms from endangered habitats, it was found that the extracts of the morning glory *Ipomoea squamosa*, harvested in the Suriname rainforest, exhibit significant cytotoxicity.[1−3] Bioassay-guided fractionation of the crude material led to the discovery of five glycoresins named ipomoeassins A−E which inhibit the A2780 human ovarian cancer cell line with IC_{50} values as low as 35 nM.

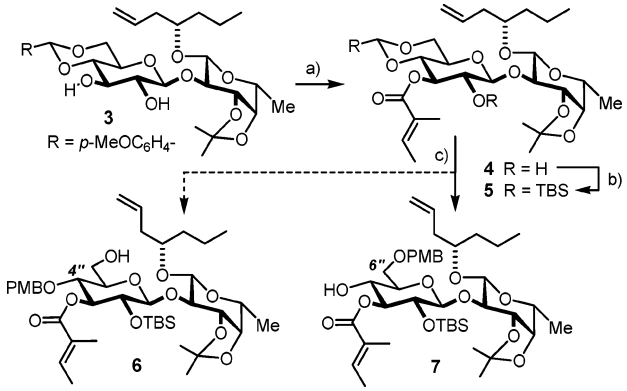


The available data suggest that seemingly minor variations in the peripheral oxygenation and acylation pattern modulate the cytotoxicity of the ipomoeassins to a significant extent, with the substituents R^1 and R^2 playing a particularly important role.[1] Intrigued by this ability to alter and, hence, hopefully optimize the biological profile of the ipomoeassins by structural editing of their molecular framework, we selected these compounds as candidates for a more detailed synthesis-driven evaluation.[4] As the initial foray, we now report the first total syntheses of ipomoeassin B (**1**) and ipomoeassin E (**2**) as two representative members of this family of bioactive glycoconjugates.

Previous investigations from this laboratory showed that ring closing olefin metathesis (RCM)[5] opens an inherently flexible and highly productive entry into structurally complex resin glycosides.[6] Although we had no doubt that RCM would allow us to forge the macrocyclic ring of the ipomoeassins too, the need to selectively reduce the resulting disubstituted double bond in the tether without affecting the unsaturated esters decorating the glucose moiety of **1** or **2** required careful planning. Since model studies suggested that the trisubstituted 2-methylbutenoate (tiglate) moiety at the 3′′-OH should pose no problems whereas the adjacent cinnamate is unlikely to survive,[7] it was planned to introduce the latter only after RCM and saturation of the resulting macrocycle. To this end, disaccharide **3** was assembled in high overall yield from three readily available building blocks.[7] In line with our expectations,[6a,e] a DCC-mediated acylation of **3** with tiglic acid occurred preferentially at the 3′′-OH site (Scheme 1). Reductive opening of the substituted benzylidene acetal in product **5** derived thereof to the corresponding 4′′-OPMB ether **6** was thought to remedy the selectivity issue during the envisaged hydrogenation because this particular protecting group is orthogonal to the remaining functionality and could therefore be replaced by the required cinnamate at a later stage.

Despite encouraging literature precedence and considerable experimentation,[7] however, this seemingly routine protecting group

Scheme 1[a]



[a] Conditions: (a) Tiglic acid, DCC, DMAP, CH_2Cl_2, 55%; (b) TBSCl, 2,6-lutidine, CH_2Cl_2, 96%; (c) $NaBH_3CN$, TMSCl, MS 4 Å, MeCN, 62%.

interconversion failed to afford the desired regioisomer **6**. While most of the established protocols turned out to be incompatible with the ester and/or the double bonds in **5**,[7] the use of $NaBH_3$-CN/TMSCl[8] furnished the 6′′-OPMB ether **7** rather than the expected isomer **6** as the major product (**7**:**6** ≥ 4:1, Scheme 1). *This regiochemical outcome is in striking contrast to the literature*;[8] comparison with the recorded cases suggests that steric hindrance is the cause for this unexpected result, as the bulky aglycone in **5** likely disfavors coordination of the Lewis acid to the 6′′-O-position of the benzylidene group. Anyway, the inability to form compound **6** in acceptable yield enforced a change in strategy with regard to the envisaged RCM/hydrogenation sequence.

A practical solution was found with the use of the C-silylated derivative **8** as cinnamic acid surrogate. Due to its trisubstituted double bond, this readily available compound[7] withstands hydrogenation in the presence of Wilkinson's catalyst, while its dimethylphenylsilyl group can be removed with ease, when appropriate. Specifically, attachment of **8** to the major isomer **7** followed by oxidative cleavage of the −OPMB ether and Yamaguchi esterification[9] of the released primary alcohol **10** with 4-oxo-8-nonenoic acid gave product **11** (Scheme 2). Exposure of this diene to catalytic amounts of the ruthenium carbene **12**[10] in refluxing CH_2Cl_2 afforded macrocycle **13** in excellent yield as a mixture of both geometrical isomers, which could be selectively hydrogenated with the aid of $RhCl(PPh_3)_3$ *without affecting the lateral unsaturated esters*. Pleasingly, the cleavage of the C-silyl group in **14** was achieved under notably mild conditions with TASF in MeCN; to the best of our knowledge, this is the first example of a protodesilylation of a $C(sp^2)$−Si bond with TASF.[11,12] Since the 2′′-OTBS ether was concomitantly removed, it sufficed to treat the resulting crude material with trifluoroacetic acid to deprotect the isopropylidene acetal and hence complete the first total synthesis of ipomoeassin B (**1**).

Extension of this concept to the preparation of ipomoeassin E (**2**), carrying an additional chiral center in the tether, was straight-

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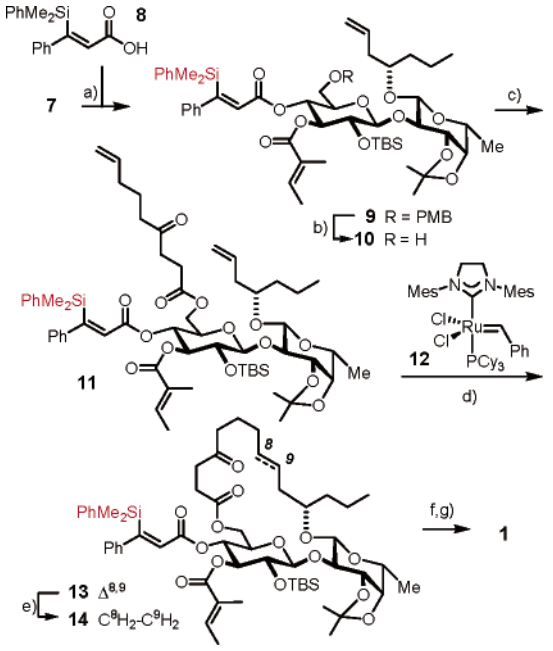
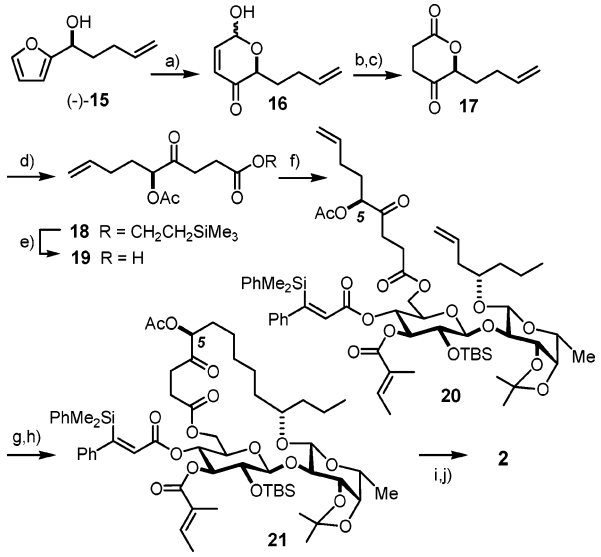
Scheme 2 [a]



[a] Conditions: (a) Acid **8**, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, 79% (over both steps from **5**); (b) DDQ, CH_2Cl_2/H_2O; (c) 4-oxo-8-nonenoic acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, 78% (over both steps); (d) complex **12** (10%), CH_2Cl_2, reflux, 71%; (e) H_2 (1 atm), $RhCl(PPh_3)_3$ (20%), EtOH, 81%; (f) TASF, MeCN; (g) trifluoroacetic acid (TFA), CH_2Cl_2, 45% (over both steps).

Scheme 3[a]



[a] Conditions: (a) *t*-BuOOH, $VO(acac)_2$ (2%), CH_2Cl_2, 71%; (b) CrO_3, H_2SO_4, acetone, 0 °C; (c) Zn, HOAc, CH_2Cl_2, 78% (over both steps); (d) (i) $HO(CH_2)_2SiMe_3$, *p*-TsOH cat., CH_2Cl_2; (ii) Ac_2O, DMAP cat., CH_2Cl_2, 93% (over both steps); (e) TASF, DMF, 68%; (f) compound **10**, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, 87%; (g) complex **12** (10%), CH_2Cl_2, reflux, 85%; (h) H_2 (1 atm), $RhCl(PPh_3)_3$ (20%), EtOH, 83%; (i) TASF, MeCN; (j) TFA, CH_2Cl_2, 63% (over both steps).

forward (Scheme 3). A scalable route to the required acid segment **19** was found by a Sharpless-type kinetic resolution of furyl alcohol (±)-**15**[7,13] followed by oxidative rearrangement of (−)-**15** (ee >99%) thus obtained with the aid of *t*-BuOOH and catalytic amounts of $VO(acac)_2$.[14] Subsequent oxidation of the hemiacetal in **16**, conjugate reduction of the resulting enone with Zn dust, opening of lactone **17** thus formed with trimethylsilylethanol, and fluoride-induced[11] cleavage of ester **18** gave acid **19** in good overall yield without racemization of the rather labile center at C-5. Esterification of **19** with disaccharide **10**, subsequent macrocyclization via RCM, and hydrogenation of the resulting *E/Z* mixture with the aid of Wilkinson's catalyst were all highly productive. Following the protocol outlined above, treatment of **21** thus obtained with TASF led to the simultaneous cleavage of the C-silyl and O-silyl groups;[12] final acid-catalyzed deprotection of the isopropylidene acetal afforded ipomoeassin E (**2**) in high overall yield. While the analytical and spectroscopic data of the synthetic material nicely matched those of the natural product,[1] we noticed a previously unrecognized dependence of its ^1H NMR spectrum in C_6D_6 from the chosen dilution; for details, consult the Supporting Information.

In summary, a concise and flexible entry into the family of the cytotoxic ipomoeassin resin glycosides has been developed. The successful route hinges upon the use of compound **8** as a new cinnamic acid surrogate which meets the requirement of being resistant to hydrogenation in the presence of homogeneous catalysts, yet is easy to deprotect without compromising its configurational integrity. An extension of our work to the other members of this family and a series of unnatural congeners, as well as a first round of biological evaluation, is ongoing and will be reported in due course.

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Supporting Information Available: Experimental section including the preparation of the building blocks and copies of the NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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