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Total Synthesis and Biological Evaluation of the Cytotoxic Resin Glycosides Ipomoeassin A–F and Analogues

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Abstract: A multitasking *C*-silylation strategy using the readily available compound **26** as a surrogate for cinnamic acid represents the key design element of a total synthesis of all known members of the ipomoeassin family of resin glyosides. This protecting group maneuver allows the unsaturated acids decorating the glucose subunit of the targets to be attached at an early phase of the synthesis, prevents their participation in the ruthenium-catalyzed ring-closing metathesis (RCM) used to form the macrocyclic ring, and protects them against reduction during the hydrogenation of the resulting cycloalkene over Wilkinson's catalyst. As the *C*-silyl group can be concomitantly removed with the *O*-TBS substituent using tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) in acetonitrile, no separate protecting group manipulations were necessary in the final stages, thus contributing to a favorable overall "economy of steps". In addition to the naturally occurring ipomoeassins, a small set of synthetic analogues has also been prepared by "diverted total synthesis". The cytotoxicity of these compounds was assayed with two different cancer cell lines. The recorded data confirm previous findings that the acylation- and oxygenation pattern of these amphiphilic glycoconjugates is highly correlated with their biological activity profile. Ipomoeassin F turned out to be the most promising member of the series, showing IC_{50} values in the low nanomolar range.

Keywords: cytotoxicity · glycolipids · macrocycles · metathesis · protecting groups

Introduction

Plants of the morning glory family (*Convolvulaceae*) are known as rich sources of alkaloids and resin glycosides and have been extensively used in traditional medicine as herbal remedies for various diseases.[1] Although chemical investigations into their sugar components had already been undertaken in the 19th century, it was not until the advent of the powerful modern spectroscopic techniques that the intriguing structures of these glycoconjugates could be elucidated. They consist of differently acylated oligosaccharides glycosylated with hydroxylated fatty acid derivatives which are usually tied back to form macrolactone rings of various sizes.[1–4] The resulting amphiphilic architectures caught the imagination of preparative chemists, with the conquest of the tricolorin family[5–7] and the total synthesis of woodrosin being representative.[8–10]

Resin glycosides exhibit a broad spectrum of biological activities, ranging from laxative, purgative, haemolytic, antibacterial, antifungal or plant growth inhibitory properties to significant cytotoxicity.[1–4] However, the understanding for their mode of action is largely missing,[11] as are systematic studies into structure–activity relationships. The available information, however, suggests that these compounds offer ample opportunity for optimization of their bioactivity profiles. An instructive case is the ipomoeassin family, which was recently isolated from the morning glory *Ipomoea squamosa* collected in the Suriname rainforest during a biodiversity program (Figure 1).[12,13] The recorded data for the six naturally occurring members indicate that variations in the peripheral oxygenation and acylation pattern alter the cytotoxicity against the human A2780 OVCAR cell line to a

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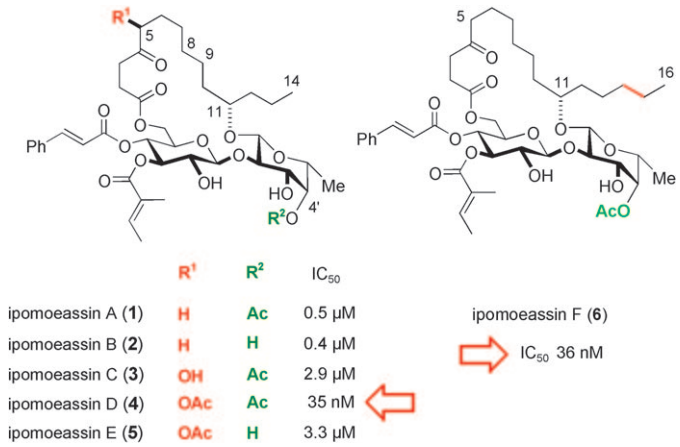


Figure 1. The family of ipomoeassin resin glycosides and survey of their surprisingly different cytotoxicity data (IC_{50}) against the human ovarian cancer cell line A2780 published in the literature.[12,13,15]

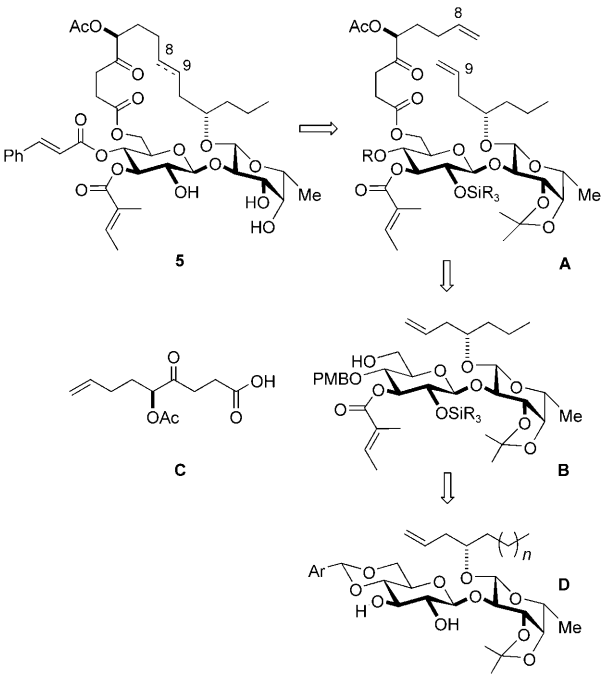
significant extent.[12] "Hot spots" on the pharmacophoric landscape seem to be the 4′-O site of the D-fucose moiety as well as C-5 within the fatty acid tether, as evident from the fact that ipomoeassin D (**4**) and F (**6**) are up to two orders of magnitude more potent than their congeners. However, peracetylation of **4** drastically reduces the activity.[12] Overall, the available information suggests that ipomoeassin F (**6**)[13] incorporating a fatty acid that is two methylene units longer than that of its sister compounds,[14] is the most promising member, which seems to indicate that the lipophilicity of the backbone exerts an additional subtle influence on the bioactivity of such amphiphilic glycoconjugates. The IC_{50} values of **6** against various human cancer cell lines lie in the single-digit nanomolar range.[13,15] Moreover, the discoverers of the ipomoeassins claimed that the cytotoxicity profile of these compounds has no significant COMPARE correlation with that of the recorded anticancer agents in the National Cancer Institute (NCI) database, thus raising questions as to their possible mode of action.[16]

As part of our investigations into the chemistry and biology of complex glycolipids,[3,7–9,17–21] our group has reported in 2007 the first total synthesis of two members of the ipomoeassin family based on a ring-closing olefin metathesis (RCM) reaction for the formation of the macrocycle at the C8–C9 bond.[22] The exact same strategy was later used by a team from the Eisai Research Institute, which disclosed a synthesis of ipomoeassin F earlier this year.[23] Outlined below is a full account of our work in this area, which provided access to all naturally occurring ipomoeassins as well as to a few selected analogues. Additional data on the bioactivity of these compounds are also presented.

Results and Discussion

Strategic considerations: Ring-closing olefin metathesis (RCM) has emerged over the last years as a powerful method for the formation of macrocyclic rings.[24] Based on our previous excellent experiences,[25,26] it seemed likely that RCM would allow us to forge the backbone of the ipomoeassins. Yet, the need to reduce the resulting disubstituted C8=C9 double bond in the tether during the further elaboration of the targets either mandates that the unsaturated acids decorating the D-glucose ring are introduced at a late stage, or requires a chemo- and regioselective hydrogenation of the cycloalkene without affecting this unsaturated periphery. In an attempt to minimize the necessary protecting group manipulations, we opted for the second strategy, in particular since we had noticed in the past that a macrocyclic backbone may impose serious constraints onto an oligosaccharide that render even seemingly trivial manipulations of the sugar periphery highly capricious.[8,9,27]

The plan to selectively hydrogenate the macrocycle in the presence of lateral unsaturation, however, is not without risk either. Model studies had shown that a disubstituted (cyclo)alkene can be reduced over Wilkinson's catalyst without difficulty in the presence of a 2-methyl-2-butenoic acid ester (tiglic acid ester), but that a cinnamate is hydrogenated with similar rates.[22] A metal-free reduction using diimine led to an even less favorable outcome. Therefore it was planned to have the tiglate in place, whereas the cinnamate would be installed only after RCM and saturation of the macrocycle. The resulting synthesis blueprint, as spelled out for ipomoeassin E in Scheme 1, might be reduced to practice

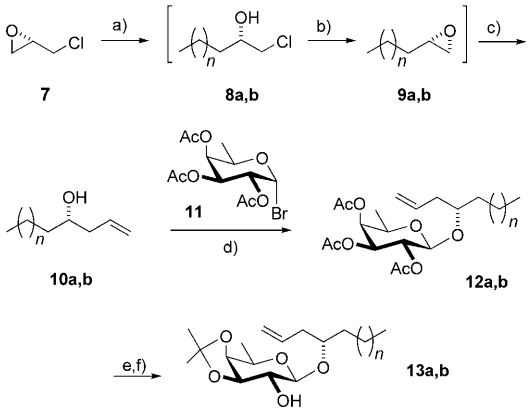


Scheme 1. Original retrosynthetic analysis exemplified for ipomoeassin E.

using compound **B** as a key intermediate, in which the secondary alcohols of the glucose are already adequately differentiated. **B**, in turn, can be accessed by reductive opening of the corresponding 4,6-*O*-benzylidene acetal derivative **D**

($n=1$). Whereas ipomoeassin A–D should be available from the very same building block, preparation of ipomoeassin F would require the homologous compound **D′** ($n=3$) featuring the appropriately elongated appendix.

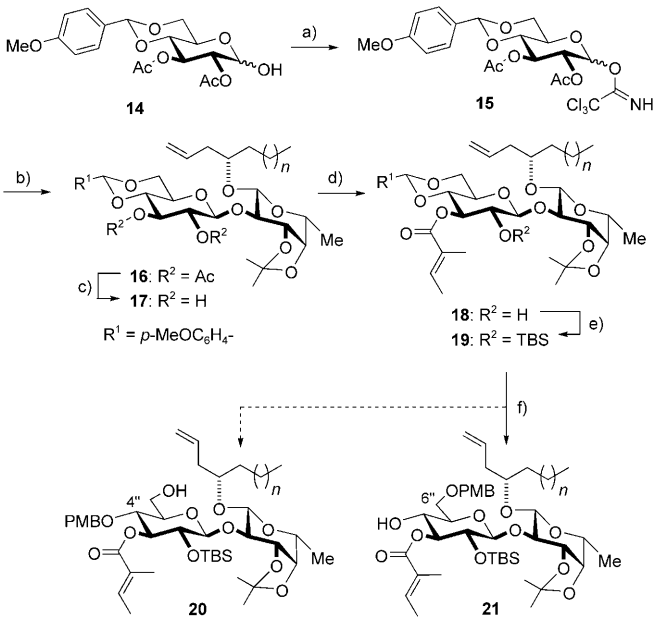
Assembly of the disaccharide building block: The optically pure (99% *ee*) heptenol **10a** was conveniently prepared on treatment of commercial (*S*)-epichlorohydrine **7** with EtMgBr in the presence of CuCN (10 mol%), treatment of the resulting adduct **8a** with powdered NaOH or KOH in Et_2O, and opening of the resulting epoxide **9a** with vinylmagnesium bromide, which was again catalyzed by CuCN (Scheme 2).[28] Subsequent silver-mediated[29] glycosylation



Scheme 2. a) $CH_3(CH_2)_nMgCl$, CuCN (10 mol%), THF, −78 → −20°C; b) NaOH, Et_2O; c) CH_2=CHMgBr, CuCN (10 mol%), THF, −78 → 0°C, **10a** ($n=1$, 69–77% overall, 99% *ee*); **10b** ($n=3$, 74–80% overall, 99% *ee*); d) AgOTf, 2,6-di-*tert*-butylpyridine, MS 4 Å, CH_2Cl_2, 0°C → RT, **12a** ($n=1$, 84%); **12b** ($n=3$, 67%); e) KOMe cat., MeOH; f) 2,2-dimethoxypropane, *p*TsOH·H_2O cat., acetone, **13a** ($n=1$, 95–98% over both steps); **13b** ($n=3$, 79–83% over both steps).

with fucosyl bromide **11** afforded compound **12a** in good yield, which was transformed into product **13a** by saponification of the acetates followed by selective ketalization of the released triol. The homologous building block **13b** required for the synthesis of ipomoeassin F was prepared analogously.

The necessary glucosyl donor **15** was obtained from the hemiketal **14**, which is accessible in multigram quantities by following the literature route (Scheme 3).[18] A BF_3·Et_2O-mediated reaction with alcohol **13a** furnished disaccharide **16a** in excellent yield,[30] which was deacetylated in preparation for the esterification with tiglic acid. As expected, this reaction occurred regioselectively at the more nucleophilic O-3″ site of the β-glucoside.[7] The remaining -OH group in **18a** was then



Scheme 3. a) Cl_3CCN, Cs_2CO_3 cat., CH_2Cl_2, 86–89%; b) compound **13a**, BF_3·Et_2O cat., CH_2Cl_2/pentane 1:1, −20°C, **16a** ($n=1$, 75–77%); *or*: compound **13b**, TMSOTf (1.05 equiv), CH_2Cl_2, −30°C, **16b** ($n=3$, 82–95%); c) KOMe cat., MeOH, **17a** ($n=1$, 82–84%); **17b** ($n=3$, 73–77%); d) tiglic acid, DCC, DMAP, CH_2Cl_2, **18a** ($n=1$, 55–78%); **18b** ($n=3$, 66–73%); e) TBSOTf, 2,6-lutidine, CH_2Cl_2, **19a** ($n=1$, 93–96%); **19b** ($n=3$, 91–97%); f) $NaBH_3CN$, TMSCl, MS 4 Å, MeCN, see Table 1.

TBS-protected to give compound **19a** ready for reductive opening of the substituted benzylidene acetal.

Despite a host of literature precedence and extensive experimentation, this seemingly routine step turned out to be problematic and ultimately enforced a change in strategy. Although many reagent combinations are known to convert sugar 4,6-*O*-benzylidene acetals into the corresponding 4-*O*-benzyl ether derivatives,[31] most of them simply decomposed substrate **19a**. These failures are ascribed to the incompatibility of the reducing agents with the ester group and/or double bonds of this substrate. Only the use of $NaBH_3CN$ in combination with TMSCl[38] furnished a mixture of the corresponding PMB-ether derivatives in up to 84% combined yield with a 4:1 isomeric ratio (Table 1). In contrast to the literature,[32,38] however, the 6″-*O*-PMB ether **21** rather than

Table 1. Reductive opening of the benzylidene acetal in **19**.

Entry	Reducing agent	Conditions	*n*	**21**/**20**	Isolated yield [%] (**21**)	Ref.
1	BH_3·THF	$Cu(OTf)_2$ (15 mol%), THF, RT, 1 h	1		decomposition	[33]
2	BH_3·THF	Bu_2BOTf (1 equiv), CH_2Cl_2, RT, 4 h	1		decomposition	[34]
3	Dibal-H	CH_2Cl_2, 0°C, 5 min	1		reduction of ester	[35]
4	PMHS	$AlCl_3$, CH_2Cl_2/Et_2O, RT, 15 h	1		decomposition	[36]
5	Et_3SiH	$PhBCl_2$, MS 4 Å, CH_2Cl_2, −78°C, 1 h	1		decomposition	[37]
6	$NaBH_3CN$[a]	TMSCl, 0°C	1	2.0:1	48	[38]
7	$NaBH_3CN$[a]	TMSCl, 0°C → RT (1 h)	1	3.5:1	61–65	
8	$NaBH_3CN$[a]	TMSCl, 0°C/RT[b]	1	4.0:1	81–84	
9	$NaBH_3CN$[a]	TMSCl, 0°C/RT[b]	3	4.0:1	51	

[a] $NaBH_3CN$ (10 equiv), TMSCl (10 equiv) in the presence of MS 4 Å in MeCN; [b] The temperature was quickly raised to room temperature immediately after the addition of TMSCl.

the 4″-*O*-PMB derivative **20** was formed as the major product. Steric hindrance is the most likely reason for this unexpected regiochemical outcome, as the bulky aglycone in **19** might disfavor ligation of the Lewis acid with the 6″-O position of the benzylidene group relative to coordination to the 4″-*O*-site. Even though the conformation of **19** in solution is unknown, the structure of the precursor compound **17a** in the solid state (Figure 2) seems to corroborate this interpretation.

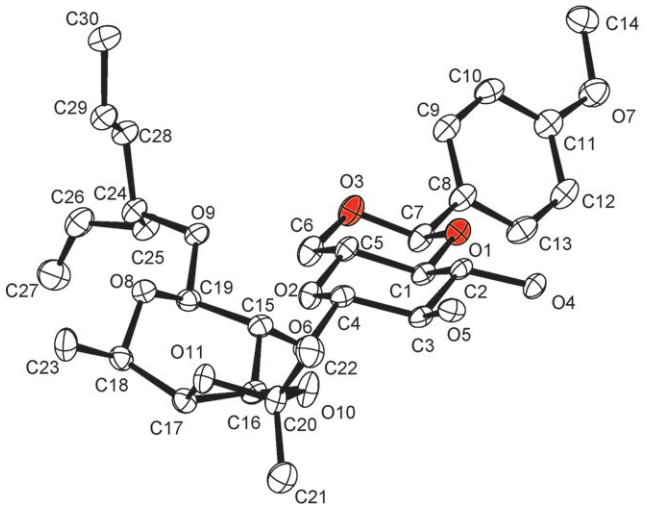
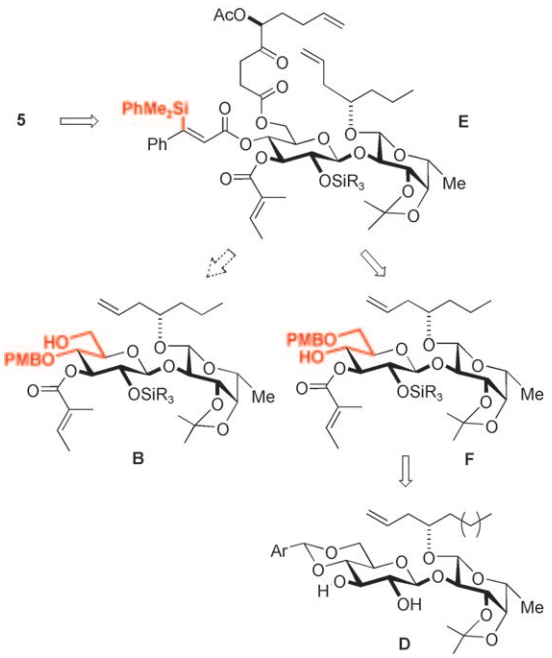


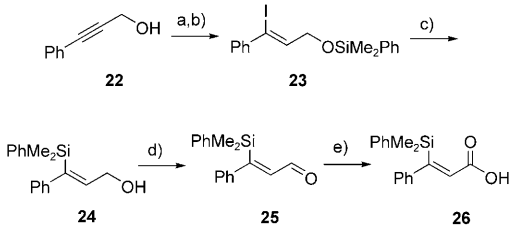
Figure 2. Structure of compound **17a** in the solid state. Anisotropic displacement parameters are drawn at the 50% probability level. The oxygen atoms of the 4,6-*O*-benzylidene acetal are shown in red; they correspond to the oxygen atoms in the derived compound **19** which compete for coordination to the Lewis acid during the reductive ring opening reaction.

Revised strategy and completion of the total synthesis of ipomoeassin A and B: The inability to procure larger amounts of the envisaged key intermediate **20** by reductive opening of the benzylidene precursor **19** enforced a change in strategy with regard to the planned RCM/hydrogenation sequence. Rather than opting for further orthogonal manipulation of the hydroxy groups, it was envisaged to protect the cinnamate moiety of the targeted ipomoeassin by a *C*-silyl substituent (Scheme 4). As a trisubstituted alkene, such a cinnamic acid surrogate should neither interfere with the metathetic ring closure nor should it be touched during the hydrogenation of the alkene in the macrocyclic tether. Moreover, it is expected that a *C*-silyl group can be concomitantly removed with the 2″-*O*-TBS ether under mild conditions, thus avoiding any extra manipulations during the end game of the synthesis.[39]

The required acid **26** was conveniently obtained as shown in Scheme 5. Hydroalumination of **22** followed by addition of iodine[40] and subsequent *O*-silylation under standard conditions furnished product **23**. Lithium for halogen exchange triggered a retro-Brook rearrangement that installed the *C*-silyl substituent and released the primary alcohol in **24**,[41] which was then oxidized to the corresponding acid **26** in excellent overall yield.

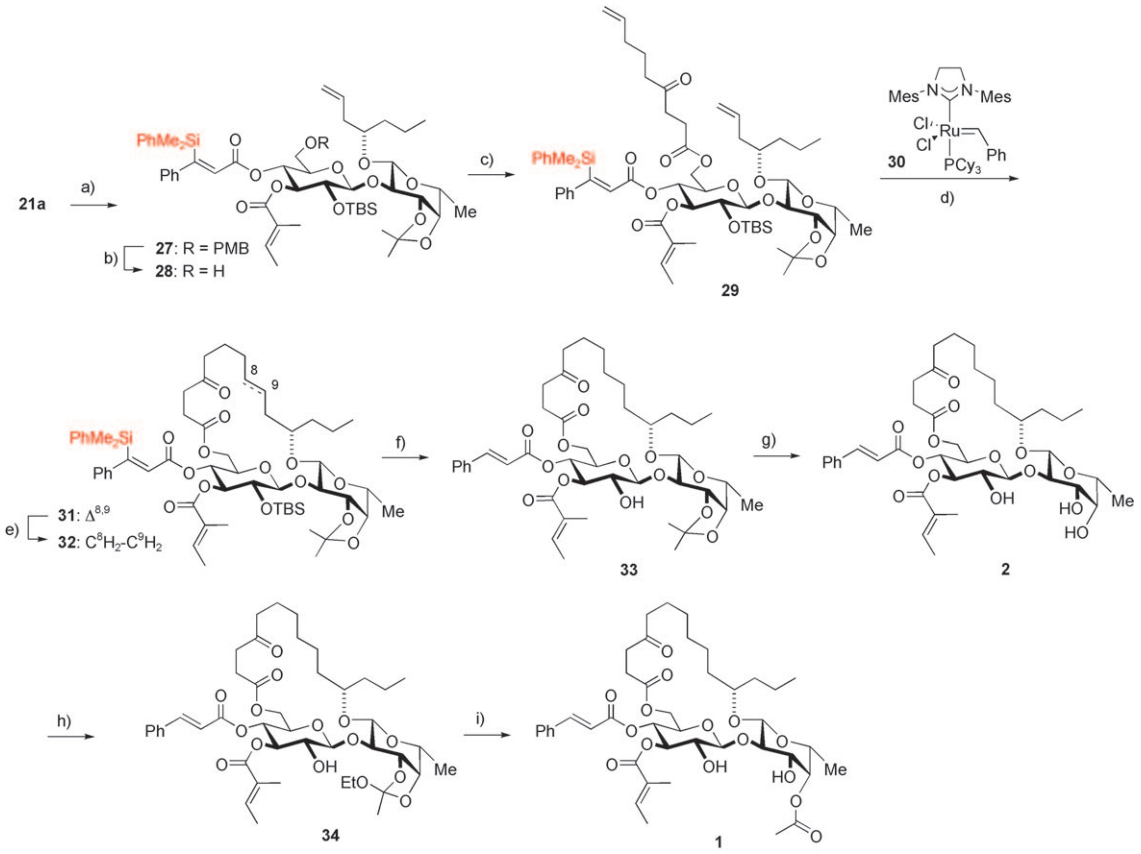


Scheme 4. Revised retrosynthetic plan exemplified for ipomoeassin E based on a multitasking *C*-silylation strategy.



Scheme 5. a) $NaAlH_2(OCH_2CH_2OMe)_2$, Et_2O, then I_2, 86–88%; b) $PhMe_2SiCl$, Et_3N, DMAP cat, CH_2Cl_2, 95–97%; c) *t*BuLi, THF, −78°C → RT, 50–57%; d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C; e) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*BuOH/H_2O, 88–93% (over both steps).

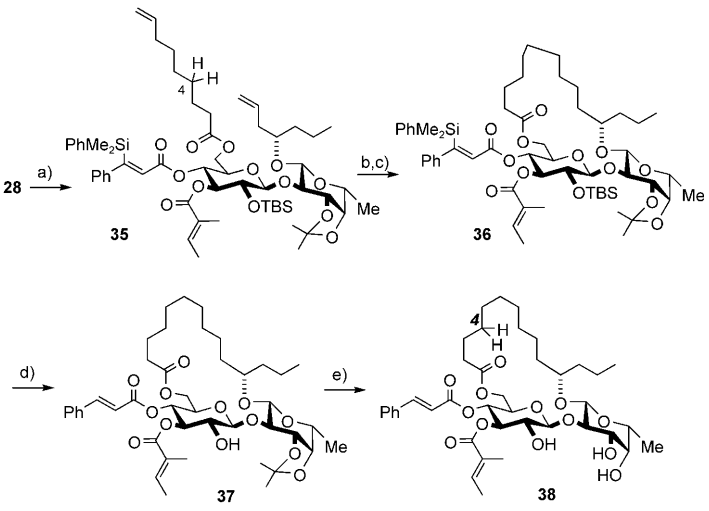
With this *C*-silylated cinnamic acid in hand, it was the major isomer derived from the benzylidene cleavage that could be used en route to the target. Specifically, alcohol **21a**[42] was esterified with **26** under Yamaguchi conditions[43] to give product **27**, which was then subjected to oxidative PMB cleavage[44] followed by attachment of the 4-oxo-8-nonenoic acid ester segment (Scheme 6).[45] In line with our expectations, treatment of the resulting diene **29** with catalytic amounts of the commercial "second-generation" ruthenium alkylidene complex **30**[46,47] in refluxing CH_2Cl_2 afforded macrocycle **31** as an *E*/*Z* mixture in high yield, which was hydrogenated with the aid of $[RhCl(PPh_3)_3]$ without affecting the lateral sites of unsaturation.[48] The *C*-silyl group and the *O*-TBS ether in **32** were then concurrently removed with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) in MeCN[49–51] before the remaining isopropylidene acetal in **33** was cleaved off with dilute trifluoroacetic acid.



Scheme 6. Total synthesis of ipomoeassin A and B: a) **26**, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, 79–83% (over both steps from **19a**);[42] 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 **30** (10%), CH_2Cl_2, reflux, 71%; e) H_2 (1 atm), $[RhCl(PPh_3)_3]$ (20%), EtOH, 81%; f) TASF, MeCN; g) trifluoroacetic acid, CH_2Cl_2, 45% (over both steps); h) $MeC(OEt)_3$, camphersulfonic acid cat; i) aq. HOAc, 95%.

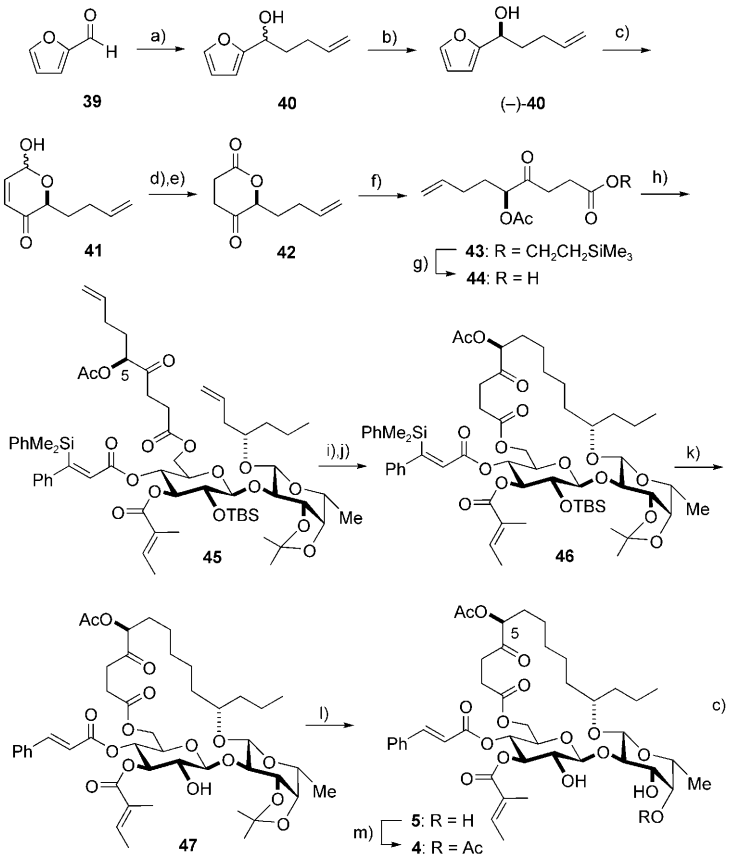
Hence, the novel multitasking *C*-silylation strategy has fully met our expectations. The analytical and spectral properties of synthetic ipomoeassin B (**2**) thus obtained were in excellent agreement with those reported in the literature.[12] Moreover, **2** could be further elaborated into ipomoeassin A (**1**) by treatment with $MeC(OEt)_3$ in the presence of camphersulfonic acid, followed by an HOAc-induced rearrangement of the resulting orthoester **34** to the conspicuous axial acetate group present in this particular target.[52] The data of the synthetic samples of **1** were again in full accord with those of the natural product.[12]

As an initial foray into the preparation of synthetic analogues by "diverted total synthesis",[53–55] product **38** was targeted in which the ketone residing in the lipophilic tether was formally edited out (Scheme 7). This incremental but deep seated structural change was easily secured by esterification of **21a** with commercial 8-nonenoic acid followed by ring-closing metathesis of the resulting diene **35** and elaboration of the isomeric cycloalkenes by the selective hydrogenation/deprotection sequence outlined above. Although these steps were not fully optimized, a good overall yield of 4-deoxy-ipomoeassin B (**38**) was obtained, thus illustrating the robustness of the chosen route.



Scheme 7. Preparation of 4-deoxy-ipomoeassin B. a) 8-nonenoic acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, 72%; b) complex **30** (10%), CH_2Cl_2, reflux, 93%; c) H_2 (1 atm), $[RhCl(PPh_3)_3]$ (20%), EtOH, 80%; d) TASF, MeCN; e) trifluoroacetic acid, CH_2Cl_2, 56% (over both steps).

Total synthesis of ipomoeassin D and E: The success of the *C*-silylation strategy in combination with the flexibility inherent to RCM brings all other members of the ipomoeassin series into reach. The necessary acid fragment **44** required for the synthesis of ipomoeassin D (**4**) and E (**5**) was best prepared by oxidative rearrangement of furyl alcohol **40**,[56] which was obtained in optically pure form (>99% *ee*) by the Sharpless-type kinetic resolution shown in Scheme 8.[57,58] Treatment of (−)-**40** with catalytic amounts



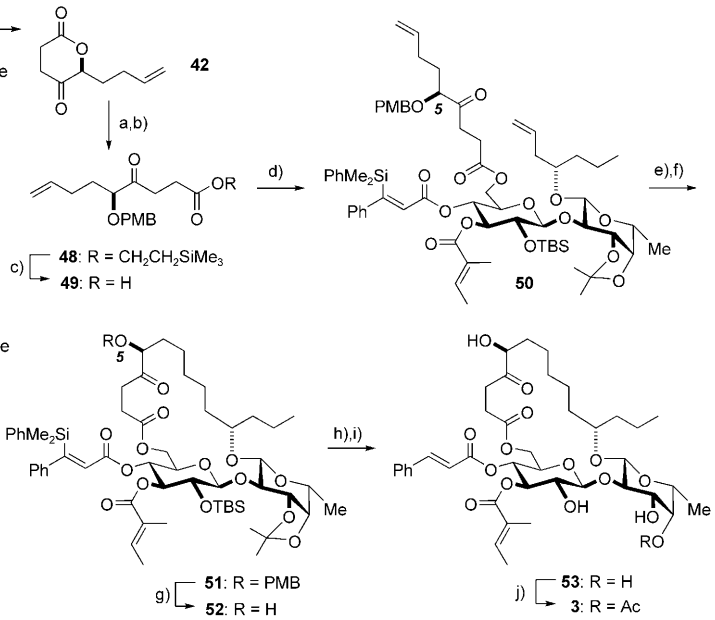
Scheme 8. Total syntheses of ipomoeassin D and E. a) 1-bromo-3-pentene, Mg, THF, 82–89%; b) Ti(O*i*Pr)$_4$, D-(−)-diisopropyltartrate (DIPT), *t*BuOOH, CH_2Cl_2, −20°C, 47% (=94% theoretical yield), >99 *ee*; c) *t*BuOOH, VO(acac)$_2$ (2 mol%), CH_2Cl_2, 71–73%; d) CrO_3, H_2SO_4, acetone, 0°C; e) Zn, HOAc, $CHCl_3$, 75–78% (over both steps); f) (i) HO-$(CH_2)_2SiMe_3$, *p*TsOH·H_2O cat., CH_2Cl_2; ii) Ac_2O, DMAP cat., CH_2Cl_2, 86–93%, 97% *ee* (over both steps); g) TASF, DMF, 68%; h) **28**, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, 87%; i) complex **30** (10–15 mol%), CH_2Cl_2, reflux, 85–96%; j) H_2 (1 atm), [RhCl(PPh$_3$)$_3$] (20 mol%), EtOH, 83%; k) TASF, MeCN; l) TFA, CH_2Cl_2, 63% (over both steps); m) i) $MeC(OEt)_3$, camphersulfonic acid cat; ii) aq. HOAc, 90%.

of VO(acac)$_2$ and *t*BuOOH as the stoichiometric oxidant gave **41** which was converted to lactone **42** using Jones conditions followed by selective reduction of the conjugated double bond with zinc dust in acetic acid.[59] Subsequent transesterification with trimethylsilyl ethanol and acetylation of the released secondary hydroxyl group provided the necessary building block **43**.

Treatment of **43** with TASF and esterification of the resulting acid **44** with disaccharide **28** gave diene **45** ready for ring closure.[60] As expected, this transformation was again highly productive, as was the selective hydrogenation of the resulting *E*/*Z*-alkene mixture over Wilkinson's catalyst. Following the protocol outlined above, product **46** was then desilylated prior to acid-catalyzed removal of the isopropylidene acetal in **47**. Finally, aliquots of synthetic ipomoeassin E (**5**) thus obtained were effectively converted to ipomoeassin D (**4**) by the orthoester rearrangement process[52] described above.

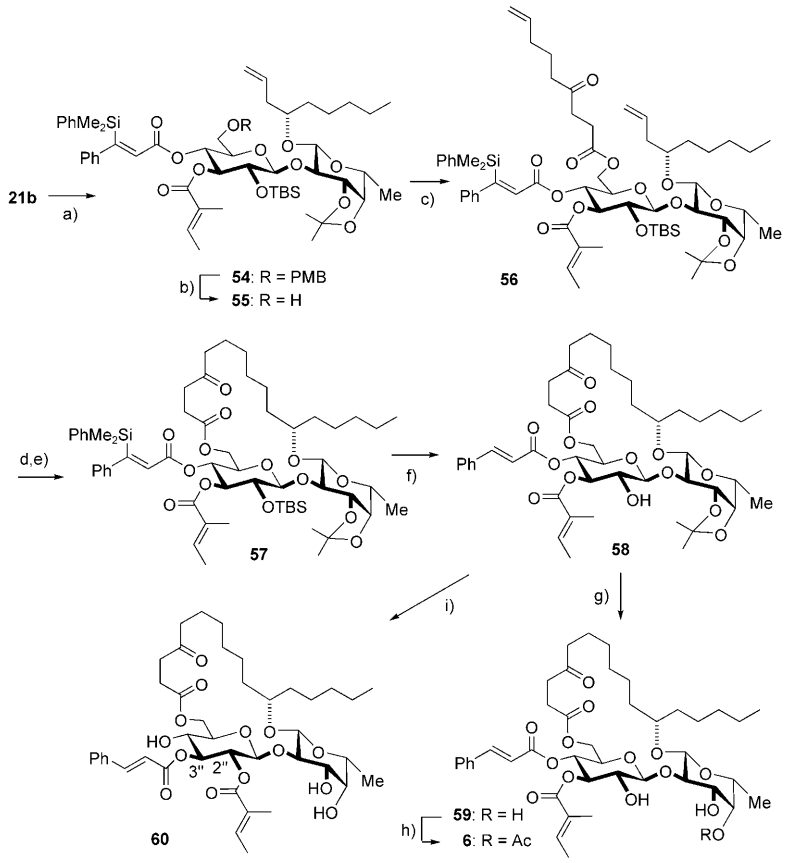
A striking and previously unrecognized spectral property of ipomoeassin E is the strong dependence of its proton NMR spectrum in C_6D_6 on the concentration and quality of the solvent (freshly distilled versus non-distilled). Figure 3 shows the remarkable shift and broadening of the signal attributed to H-3″ which is ascribed to a hydrogen-bonding event locking the alcoholic protons in its neighborhood.

Ipomoeassin C: When the alcohol formed upon opening of lactone **42** with trimethylsilyl ethanol is protected by a PMB group rather than an acetate, the very same sequence opens access to ipomoeassin C (**3**) (Scheme 9). Subsequent treat-



Scheme 9. Total synthesis of ipomoeassin C: a) HO$(CH_2)_2SiMe_3$, *p*TsOH·H_2O cat., CH_2Cl_2; b) PMBO(C=NH)CCl_3, TfOH cat., Et_2O, 0°C, 63% (over both steps); c) TASF, DMF, 76%; d) **28**, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, 73%; e) complex **30** (10 mol%), CH_2Cl_2, reflux, 88%; f) H_2 (1 atm), [RhCl(PPh$_3$)$_3$] (20%), EtOH, 86%; g) DDQ, CH_2Cl_2/H_2O; h) TASF, MeCN; i) TFA, CH_2Cl_2, j) $MeC(OEt)_3$, camphersulfonic acid cat, then aq. HOAc, 30% (over steps g–j).

ment of **48** with TASF and attachment of the released acid **49** to the common disaccharide platform **28** gave diene **50**. Its further elaboration by RCM and selective hydrogenation of the resulting cycloalkene mixture was uneventful. At this



Scheme 10. Total synthesis of ipomoeassin F and isomer: a) **26**, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, 71–83%; b) DDQ, CH_2Cl_2/H_2O, 75–84%; c) 4-oxo-8-nonenoic acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, 92–96%; d) complex **30** (20 mol%), CH_2Cl_2, reflux, 78–81%; e) H_2 (1 atm), [RhCl-$(PPh_3)_3$] (40 mol%), EtOH, 87–89%; f) TASF, MeCN, 43%; g) trifluoroacetic acid, CH_2Cl_2; h) $MeC(OEt)_3$, camphersulfonic acid cat., then aq. HOAc, 96% (overall); i) trifluoroacetic acid, CH_2Cl_2, 54% (cf. text).

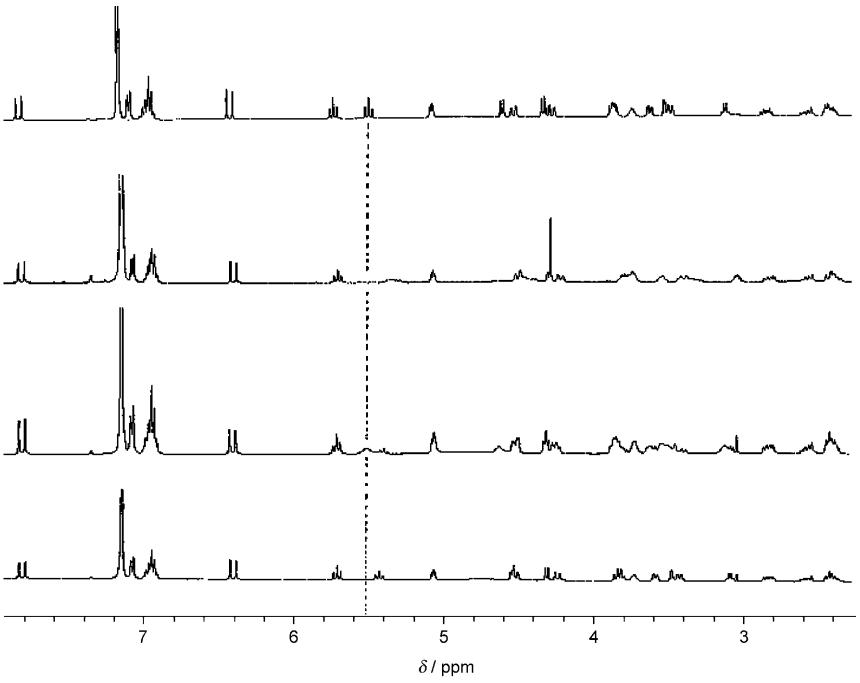


Figure 3. Concentration dependent ^1H NMR spectra of ipomoeassin E recorded in C_6D_6 (0.6 mL each). Top to bottom: 14 mg (commercial C_6D_6); 4 mg (commercial C_6D_6); 6 mg (distilled C_6D_6); 3 mg (distilled C_6D_6); "commercial" refers to the solvent provided in ampules by the supplier.

stage, the PMB ether in the tether of **51** was cleaved with DDQ[44] and the resulting product **52** transformed into the natural product by following the established route.

Ipomoeassin F and regioisomer: Ipomoeassin F (**6**) differs from its sister compound ipomoeassin A (**1**) only by the presence of two additional methylene units in the tail hanging off the fucoside anomeric center.[13] Although this formal homologation required the preparation of a different fucoside building block (**13b**, Scheme 2), no strategic changes were necessary en route to this promising target.

Even though not all individual steps shown in Scheme 10 were fully optimized, synthetic **6** was obtained in respectable overall yield. From the bioactivity standpoint, its progenitor compound **59** formed by cleavage of the isopropylidene group in **58** is also noteworthy. Though not a natural product itself, it constitutes a valuable probe for testing the subtle correlation between the presence of an acetyl group at 4′-OH and the cytotoxicity of the ipomoeassins, which the published data seem to imply (cf. Introduction).[12,15,23] Additional information should be obtained from the regioisomeric compound **60**, which was accidentally isolated during our initial attempts to drive the late-stage acetal cleavage by using higher concentrations of trifluoroacetic acid. Although these conditions ultimately lead to degradation, it was noticed that the process can be stopped at a stage where compound **60** has accumulated. A careful NMR analysis showed unambiguously that both ester groups on the glucose have migrated along the periphery. Therefore this isomer may provide further insights into the relationship be-

tween the lateral acylation pattern and the cytotoxicity of such resin glycosides.

Biological assessment: All natural products and the small assortment of non-natural analogues prepared during this campaign were assayed for cytotoxicity against HeLa cells and/or the mouse L-929 tumor cell line. Relevant results are compiled in Table 2 and compared with the published data for the A2780 human ovarian cancer cell line[12,13] and the human leukemic monocyte lymphoma U937 cell line, which had turned out to be the most sensitive amongst the tested cell lines.[23]

Table 2. Antitumor activity of the ipomoeassins and analogues, and comparison with published data for the A2780 and U937 cell lines.[12,13,23]

Compound	HeLa	L-929[a]	A2780	U937
1	64 nM	77.8 nM	0.5 μM	20.2 nM
2	2.5 μM		0.4 μM	134 nM
3	1.5 μM	> 1 μM	2.9 μM	
4	32 nM	135 nM	35 nM	7.9 nM
5	4.3 μM	> 1 μM	3.3 μM	163 nM
6		7.4 nM	36 nM	2.6 nM
38	7.0 μM	>1 μM		
59		290 nM		
60		580 nM		

[a] Values represent the average of two measurements, incubation time: 5 d, in-screen validation against known cytotoxic compounds.

Our assays confirmed previous observations that the antitumor activity of the individual ipomoeassin resin glycosides is very strongly correlated with their acylation and oxygenation pattern. In particular, acetylation of the axial 4′-OH group of the fucopyranose is highly beneficial, as evident from the comparison of the results obtained for the sister compounds **1**/**2**, **4**/**5**, and **6**/**59**. Thus, acetylation of this secondary alcohol upgrades the cytotoxicity of the compound by up to two orders of magnitude. Moreover, comparison of the pair **1** and **3** shows that hydroxylation of the C-5 position in the lipophilic tether is detrimental, even though acetylation of this site, as borne out in compound **4**, largely restores or even enhances the cytotoxicity. On the other hand, our synthetic analogue **38**, in which the carbonyl group of the tether has been removed, is largely inactive, showing that the ketone is essential. Likewise, our synthetic analogues **59** and **60** reveal that the exact location of the two unsaturated esters on the glucose ring has a strong influence on the bioactivity.

Ipomoeassin F (**6**) consistently turned out to be the most active member of this series, showing IC_{50} values in the low nanomolar range against all cell lines tested so far. As **6** incorporates only two more methylene groups in the alkyl chain than its shorter homologue **1**, it is evident that the lipophilicity/hydrophilicity balance is another subtle but critical parameter that deserves further careful inspection.

A cell cycle analysis showed that incubation of L-929 cells with those ipomoeassins that have IC_{50} values <1 μM invariably led to an accumulation of cells in the G_1 phase. For further statistical analysis, approximately 90 and 70% of all recorded events were gated after 24 and 48 h treatment, respectively, in order to generally exclude smaller cell debris (cf. Figure 4).

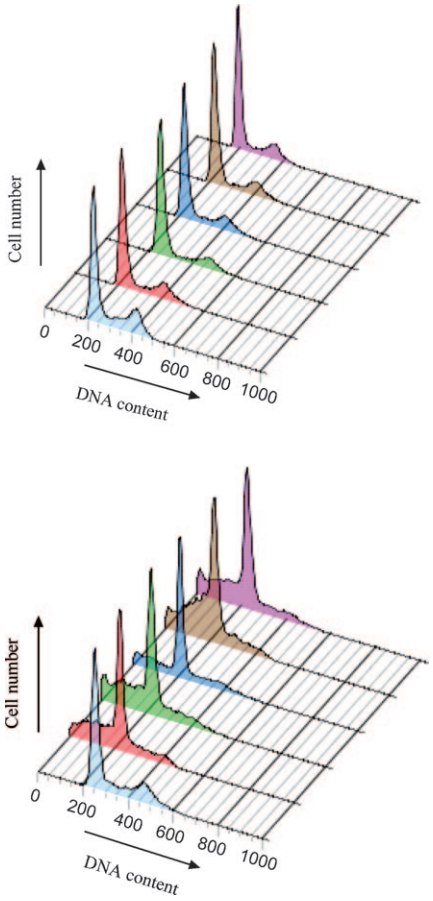


Figure 4. Influence of different ipomoeassins and ipomoeassin analogues on the cell cycle of mouse L-929 cells upon 24 h (top) and 48 h (bottom) treatment. Untreated cultures showed a high peak in the G_1 phase. In the presence of ipomoeassins (varying concentrations according to formerly determined IC_{50} values, see Table 2) cells further accumulated in the G_1 phase, also showing a sub-G_1 population after 48 h incubation. Color code: light blue: MeOH control (final concentration 0.5% *v*/*v*); red: **6** (50 ng mL^{-1}); green: **1** (0.5 μg mL^{-1}); blue: **59** (1 μg mL^{-1}); brown: **4** (1 μg mL^{-1}); purple: **60** (5 μg mL^{-1}).

In untreated cultures, however, most of the cells (ca. 60%) were in the G_1 phase, whereas approximately 25% were in the G_2/M phase. After 24 h treatment with ipomoeassins, the number of cells in the G_1 phase increased to about 73%, accompanied with a decreased number of L-929 mouse fibroblasts in the G_2/M phase (ca. 18%). Besides the observed G_1 arrest, it could be shown that after 48 h treatment a significant number of sub-G_1 cells (DNA content smaller than in G_1, cf. Figure 4) and of apoptotic cells was noticed. Only ca. 8% of the L-929 cells were in G_2/M, whereas the amount of cells in the S phase was still nearly unaffected (ca. 10%).

Experimental Section

All experimental details can be found in the Supporting Information. The details include compound characterization, bioassay and X-ray details.

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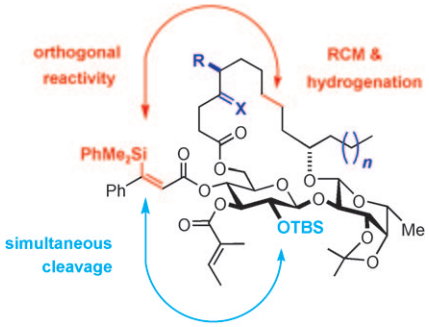
Multitasking: *C*-Silylation of the lateral ester constitutes the key strategic element of a total synthesis of all known ipomoeassin resin glycosides and a small collection of analogues. This uncommon protecting group manoeuvre precludes the lateral cinnamate from interfering with the RCM closure of the macrocycle and protects it against hydrogenation during the saturation of the cycloalkene.



Natural Products

*T. Nagano, J. Pospíšil, G. Chollet, S. Schulthoff, V. Hickmann, E. Moulin, J. Herrmann, R. Müller, A. Fürstner** ..... ▮▮▮▮–▮▮▮▮

Total Synthesis and Biological Evaluation of the Cytotoxic Resin Glycosides Ipomoeassin A–F and Analogues