Total Syntheses and Biological Assessment of Macrocyclic Glycolipids

Alois Fürstner[a]

Keywords: Carbohydrates / Glycosides / Macrolides / Metathesis / Natural products

Novel strategies for the synthesis of structurally complex macrocyclic glycolipids are outlined which have opened concise and highly flexible entries into various resin glycosides and sugar-based macrodiolides. The key design elements consist of either a ring-closing alkene (RCM) or alkyne metathesis (RCAM) event or a newly developed template-directed dilactonization reaction. The performance and excellent application profile of these transformations are illustrated by the total syntheses of tricolorin A and G, woodrosin I, sophorolipid lactone, cycloviracin B_1, glucolipsin A, and various analogues thereof. A brief survey of the biological activities exerted by these amphiphilic natural products is provided.

1. Introduction

Despite the considerable advances in carbohydrate chemistry achieved in recent years, the total synthesis of bioactive glycoconjugates is still far from routine.[1,2] The structural complexity of such molecular hybrids provides a strong stimulus and unique opportunity for the development of new synthetic strategies and constitutes a rigorous testing ground for the efficacy of modern glycosidation reactions.[3,4] Compounds **1**−**6** (Scheme 1 and 2) bear witness to this notion. The preparative challenges posed by these intricate glycolipids, together with their promising biological activities, have rendered them target molecules of considerable interest in our quest for a synthesis-driven evaluation of bioactive natural products.[5,6] Outlined below is a summary of our efforts in this field together with a preliminary survey of the biological effects exerted by amphiphilic secondary metabolites of these types.

[a] Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, 45470 Mülheim/Ruhr, Germany
Fax: (internat.) + 49-(0)208-306-2994
Email: fuerstner@mpi-muelheim.mpg.de

2. Resin Glycosides

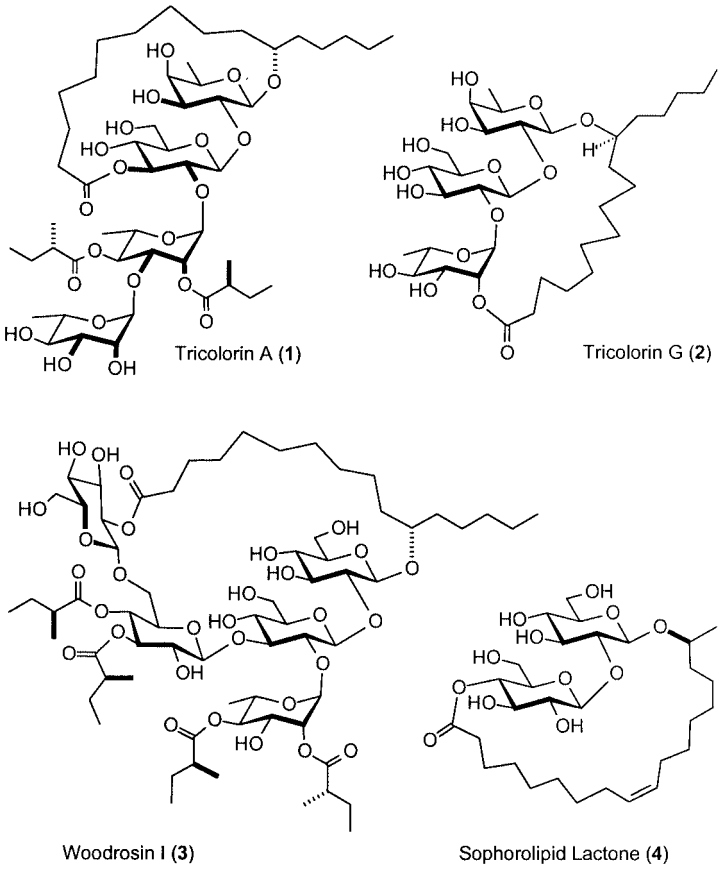
2.1. Tricolorin A and G

Plants belonging to the Morning Glory family (*Convolvulaceae*) are rich sources of alkaloids and resin glycosides and have been extensively used in traditional medicine as herbal remedies for various diseases. Although chemical investigations on their glycosidic components were initiated as early as the middle of the 19th century, it was not until the advent of modern spectroscopic techniques that the amazing structures of the resin glycosides produced by *Convolvulaceae* could be elucidated. Resin glycosides, in general, are conjugates between complex oligosaccharide entities and (11*S*)-hydroxyhexadecanoic acid (“jalapinolic acid”) as the common aglycon in virtually all members of this series.[7] The latter is frequently tied back to form a characteristic macrolactone ring spanning two or more sugar units of the backbone. Further carboxylic acids may complement the peripheral acylation pattern.

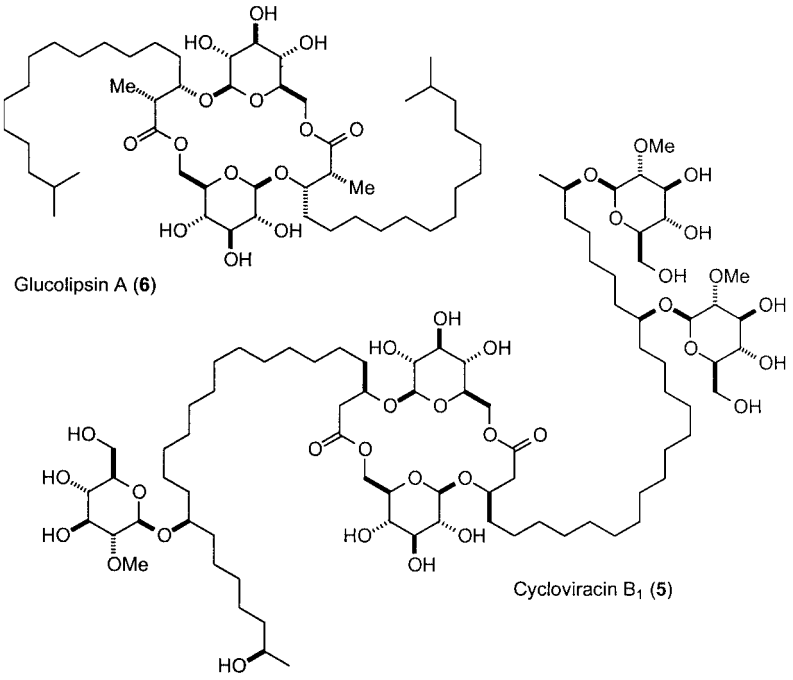
Tricolorin A (**1**) and G (**2**) are prototype members of this sort of amphiphilic glycoconjugate.[8] They have been isolated as the allelochemical principles of *Ipomoea tricolor*

Alois Fürstner (1962) studied chemistry at the Technical University of Graz, Austria, where he got his Ph.D. in 1987 (Prof. H. Weidmann). After postdoctoral studies with the late Prof. W. Oppolzer in Geneva, he finished his Habilitation in Graz (1992) before joining the Max-Planck-Institut für Kohlenforschung in 1993 as a group leader. Since 1998, he is Director at that Institute and is also affiliated with the University of Dortmund. He has received several awards for his work on organometallic chemistry, homogeneous catalysis, and the synthesis of bioactive target molecules, including the Leibniz award of the German Science Foundation (1999), the Thieme-IUPAC prize (2000), and the Arthur C. Cope Scholar Award of the ACS (2002).

MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.



Scheme 1. Glycolipids containing a macrolactone substructure



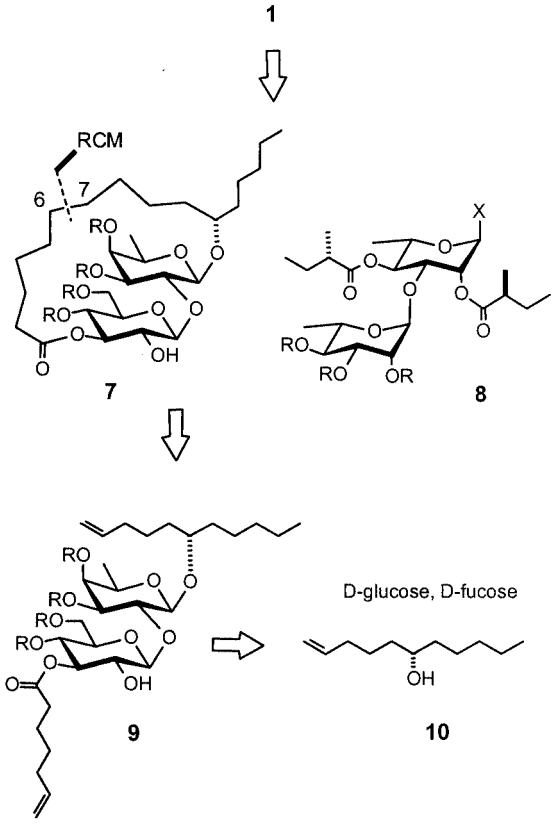
Scheme 2. Glycolipids with macrodilactone (macrodiolide) substructures

Cav., a plant used in traditional agriculture in Mexico as a cover crop to protect sugar cane against invasive weeds. Its molecular mechanism of action probably involves the inhibition of the H^+-ATPase of the plasma membrane, an enzyme that plays a crucial role in plant-cell physiology;[9] moreover, **1** acts as a natural uncoupler of photophosphorylation in spinach chloroplasts.[10] This compound also displays general cytotoxicity against several cancer cell lines ($ED_{50} \approx 2.2$ μg·mL^{-1} against human breast cancer and P-388 cells) and is able to antagonize phorbol ester binding to protein kinase C (PKC, $IC_{50} \approx 43$ μM).[8–10]

Although only very limited information is available concerning possible structure-activity relationships, it is known that the intact macrocyclic lactone ring of **1** is essential for effective plant growth inhibition.[10] This structural element, however, poses a major challenge in preparative terms. While two previous syntheses of tricolorin A have managed to close this ring by conventional macrolactonization techniques,[11–13] it is fairly obvious that such an approach will hardly allow the formation of a wider range of structural analogues because each new compound ultimately requires an independent multistep synthesis. Therefore we have explored an alternative entry into this challenging target by taking advantage of the favorable profile and inherent flexibility of ring-closing metathesis (RCM)[14] for the formation of large rings.[15,16]

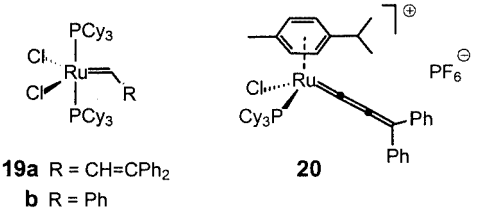
Previous investigations from this laboratory have shown that the efficiency of macrocyclizations by RCM using the standard ruthenium catalysts is strongly affected by heteroelements in the proximity of the reacting alkenes.[17–19] Such donor sites can attenuate the reactivity of the emerging Lewis-acidic carbene species by formation of stable chelate complexes. Any such complications should be minimized, however, if the ring of **1** is forged at a remote site, such as the C6–C7 bond (Scheme 3). The required cyclization precursor **9** can be readily assembled by established glycosidation methods from D-glucose, D-fucose and (6*S*)-undecen-1-ol (**10**) as the key building blocks. The latter is available in optically pure form (*ee* ≥ 99%) on a multigram scale by a ligand-controlled addition of dipentylzinc to 5-hexenal.[20,21] In the forward sense, a few routine protecting-group manipulations and standard glycosidations allowed the assembly of compound **14** from precursors **11** and **12** (Scheme 4). Its vicinal diol entity can then be regioselectively acylated due to the inherently higher reactivity of its 3′′-OH group. This not only readily provides diene **15b** (*n* = 3) as the key intermediate for the total synthesis of tricolorin A, but also allows for a convenient introduction of other residues at that site, which can then be processed in the same way to provide analogues of **1** that differ from the parent compound in ring size and hence lipophilicity. This possibility has been exemplified by the synthesis of compound **17**, which is missing two of the CH_2 groups in the macrocyclic loop, and compound **18**, featuring a considerably expanded lactone moiety.[15,16]

In line with our expectations, all RCM reactions proceeded smoothly using either the classical Grubbs carbene complex **19**[22] or the recently developed cationic ruthenium



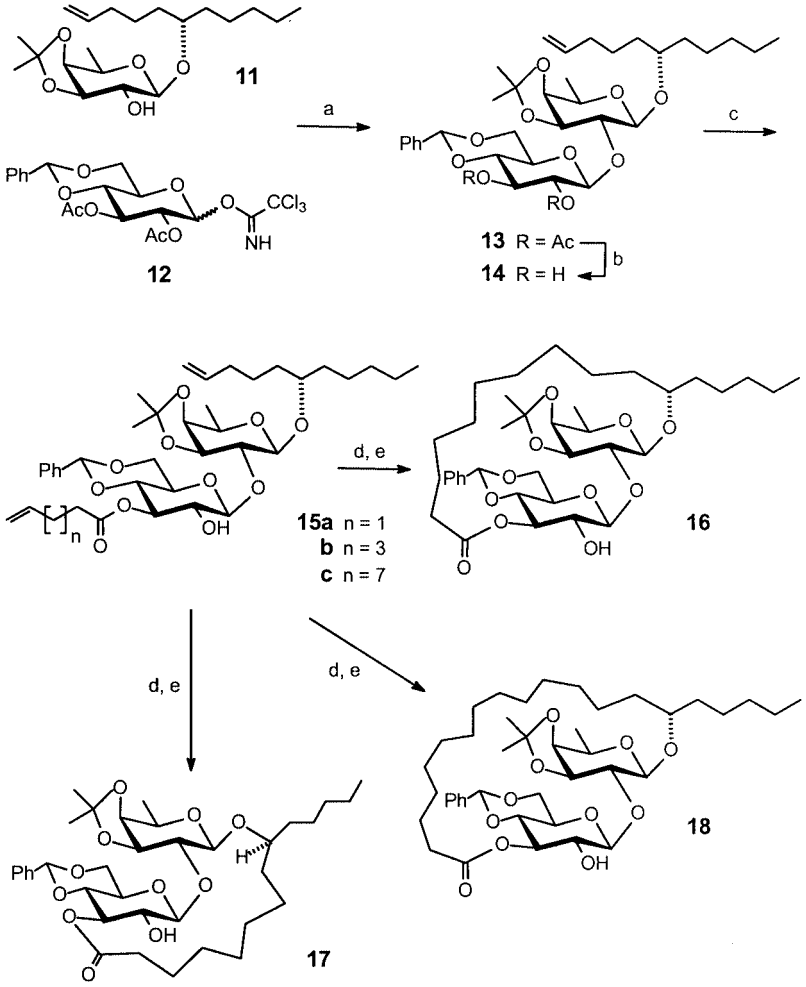
Scheme 3. Retrosynthetic analysis of tricolorin A (**1**)

allenylidene complex **20**[23] as the precatalysts. The fact that neither the free hydroxyl groups nor any other functionality of substrates **15a–c** interfere with RCM illustrates the excellent selectivity profile of catalysts of this type.



Standard hydrogenation of the cycloalkene formed by RCM (*E*/*Z* mixture) afforded disaccharide **16**, which can be elaborated into tricolorin A (**1**) by glycosidation with acceptor **8** according to literature procedures.[11,12] Compound **16** is also the first crystallographically characterized resin glycoside derivative.[24] Although five independent molecules are found in the unit cell, their superposition shows that even the conformation of the macrocyclic motif is surprisingly well preserved (Figure 1).

Compound **14** is not only the key intermediate en route to tricolorin A (**1**) and analogues thereof, but also opens access to tricolorin G (**2**) in which jalapinolic acid spans a trisaccharidic backbone (Scheme 5). For this purpose, a properly functionalized rhamnose unit must be attached to the *less* reactive C2′′ hydroxyl group of diol **14** prior to the



Scheme 4. Key steps of the total synthesis of tricolorin A and analogues: a) $BF_3{\cdot}Et_2O$ cat., −20 °C, CH_2Cl_2/*n*-hexane, 82%; b) KOMe cat., MeOH, 71%; c) DCC, DMAP, CH_2Cl_2, **15a**: 4-pentenoic acid, 80%; **15b**: 6-heptenoic acid, 71%; **15c**: 10-undecenoic acid, 67%; d) catalyst **19a**, CH_2Cl_2, reflux; e) H_2 (1 atm), Pd/C, EtOH, **16**: 77% (over both steps); **17**: 76% (over both steps); **18**: 76% (over both steps)

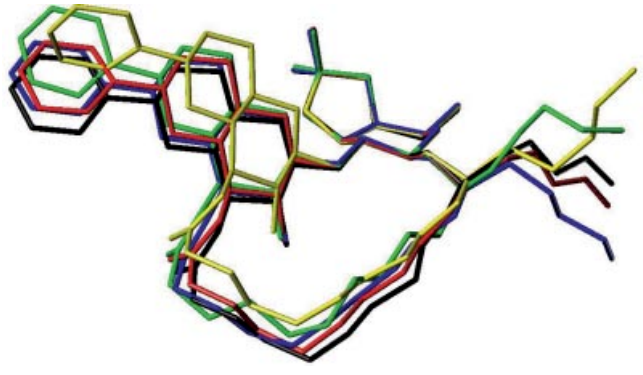
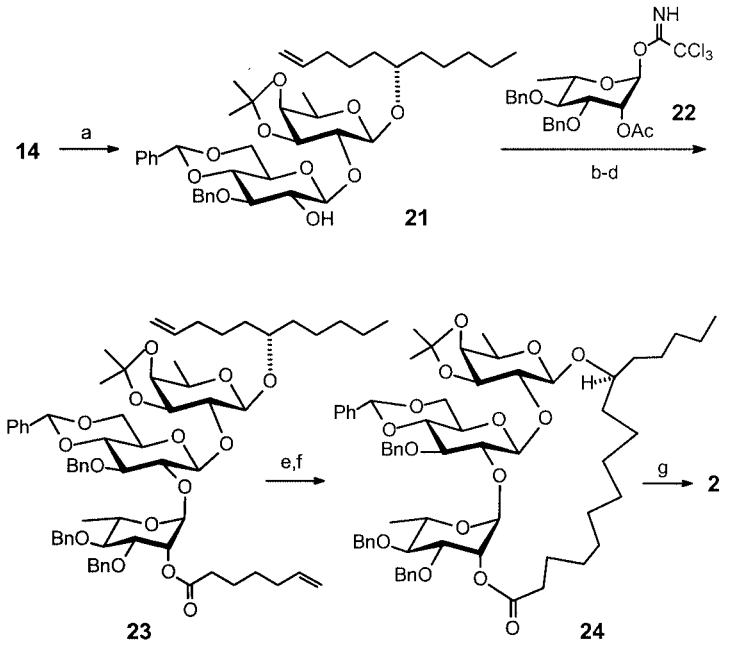


Figure 1. Superposition of the five crystallographically independent molecules of **16**; the superposition has been calculated by fitting the oxygen atoms of the fucose moiety

crucial RCM reaction. This regiochemistry was ensured by blocking the more reactive site as a benzyl ether followed by reaction of the resulting product **21** with trichloroacetimidate **22** in the presence of $BF_3{\cdot}Et_2O$ as the catalyst. Exchange of the acetyl group on the rhamnose entity for the corresponding 6-heptenoic acid ester delivered the required diene **23** as the substrate for the subsequent RCM reaction, which was again highly productive. Saturation of the cycloalkene formed gave product **24**, which was deprotected to complete the first total synthesis of tricolorin G (**2**). Once again, the flexibility of the chosen approach allowed us to form analogues of this intricate target without undue preparative efforts.[16]

2.2. Woodrosin I

Woodrosin I (**3**) is an ether-insoluble glycolipid isolated from the stems of *Ipomoea tuberosa* L. [*Merremia tuberosa* (L.) Rendle], commonly called "Woodrose" after the shape of its dried calyx.[25] This particular compound is certainly the structurally most demanding resin glycoside to be conquered by total synthesis so far.[26−28] Particular challenges arise from the impressively large macrolide ring spanning four glucose units, the complementary acylation pattern at its periphery, which seriously restricts the choice of temporary protecting groups, as well as the branched pentasaccharide backbone entailing severe steric hindrance at vicinal positions.



Scheme 5. Total synthesis of tricolorin G (**2**): a) (i) $(Bu_3Sn)_2O$, toluene, reflux, 6 h; (ii) Bu_4NI, BnBr, 2.5 h, 57% (+ 18% of the regioisomer); b) donor **22**, $BF_3{\cdot}Et_2O$ cat., CH_2Cl_2/*n*-hexane, −20 °C, 53%; c) KOMe, MeOH, room temp.; d) 6-heptenoic acid, DCC, DMAP cat., CH_2Cl_2, 84% (over both steps); e) catalyst **19a**, CH_2Cl_2, reflux, 22 h; f) H_2 (1 atm), $[RhCl(PPh_3)_3]$ cat., EtOH, 93% (over both steps); g) (i) F_3CCOOH, CH_2Cl_2, 3 h; (ii) H_2 (1 atm), Pd/C, MeOH, F_3CCOOH cat., 49%

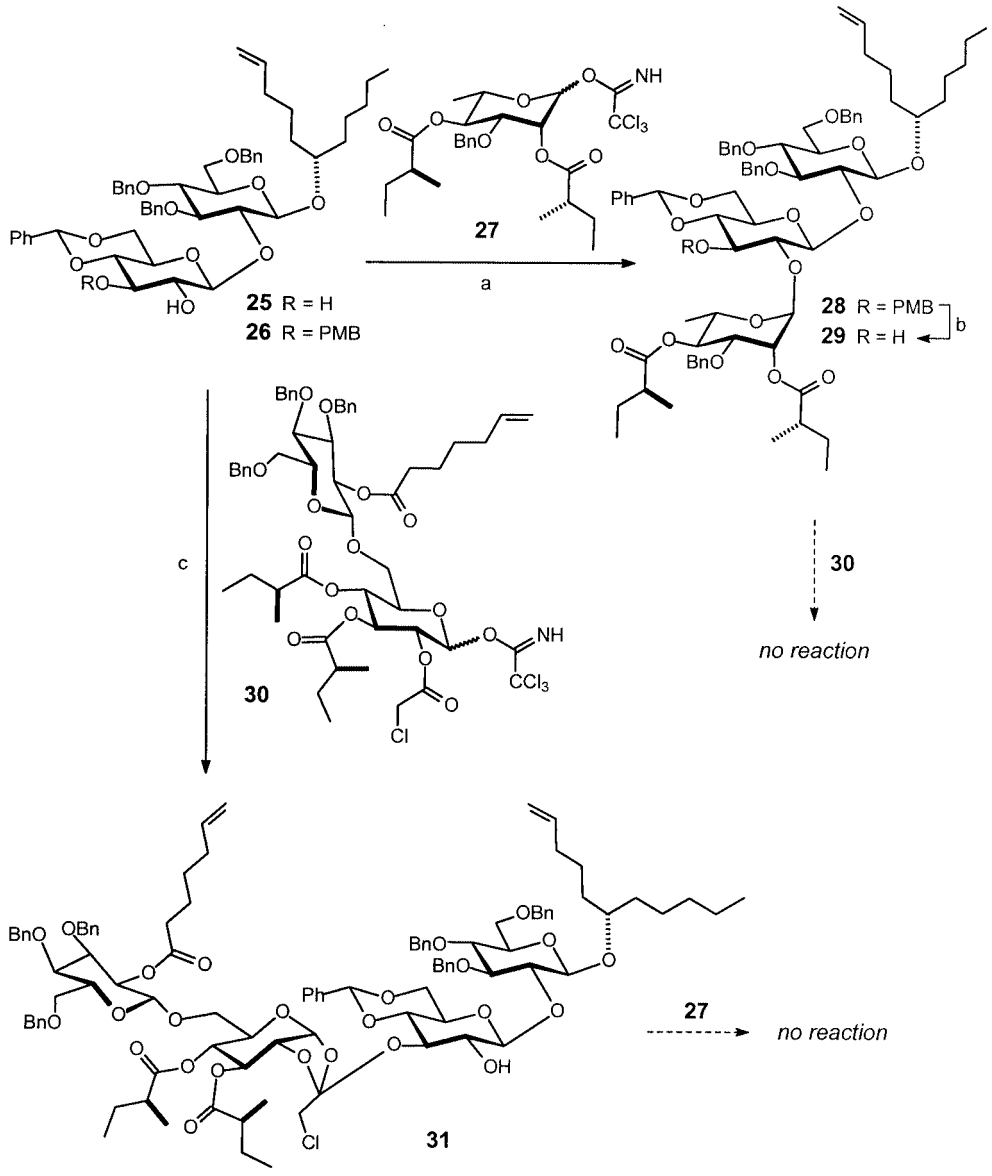
While the experiences gained in the tricolorin project gave reason to believe that the formation of the macrocycle by RCM should be straightforward when carried out at a remote site within the hydrocarbon chain of **3**, the actual synthesis highlights the notion that the assembly of complex oligosaccharidic frameworks is far from routine and still bears considerable risks despite the arsenal of glycosidation methods available to the practitioner.[3,4] Several noteworthy aspects are addressed below.

First and foremost, the formation of the oligosaccharide backbone of **3** posed considerable problems because of the severe steric hindrance at the branching site (Scheme 6). While it was easy to attach the rhamnose unit **27** to the 2′′-OH group of compound **26**, no way was found to introduce the then missing disaccharide entity **30**[27] to the adjacent position, despite a considerable number of attempts. This inherent lack of reactivity is obviously due to the very crowded situation in **29**, rendering the -OH group virtually inaccessible. Even glycosyl donors less complex than **30** could not be coupled to that site.[27]

We therefore inversed the order of events; this route, though ultimately successful, was severely complicated by the escapade of one of the protecting groups. Thus, treatment of substrate **25** with trichloroacetimidate **30** in the presence of catalytic amounts of TMSOTf in CH_2Cl_2 resulted in a *regioselective* reaction of the glycosyl acceptor's vicinal diol unit; surprisingly, however, the reaction exclusively delivered the orthoester **31** by participation of the adjacent chloroacetyl moiety rather than the expected β-glycoside.[28] Once more, all attempts to access the now remaining hydroxyl group at O2′′ and attach the missing rhamnose moiety to this site were in vain and only led to a rapid destruction of this elaborate compound. This lack of reactivity is again ascribed to a severe steric shielding of the hydroxyl group in the bay region of the orthoester.[28]

Despite this pitfall, the total synthesis of woodrosin was pursued further in the hope of rectifying the connectivity pattern at a later stage. Inspection of models suggested that the trajectory of a glycosyl donor towards the hidden 2′′-OH group might be less narrow *after* closing the macrocyclic ring. Therefore the completion of the sugar backbone was postponed until after the RCM reaction. Driven by this hope, diene **31** was treated with catalytic amounts of the ruthenium indenylidene complex **32**[29] recently developed in this laboratory as a readily accessible alternative to the classical Grubbs catalyst **19**. This resulted in an exceptionally efficient ring closure, delivering cycloalkene **33** in 94% isolated yield (*E*:*Z* ≈ 9:1; Scheme 7).

With this product in hand, the introduction of the missing rhamnose moiety was re-investigated. The lability of donor **27** in the presence of a Lewis acid, however, made it necessary to apply an "inverse glycosylation procedure".[30] Specifically, alcohol **33** was premixed with catalytic amounts of TMSOTf in rigorously anhydrous Et_2O prior to the slow addition of compound **27**. The outcome of this key experiment surpassed our expectations. Not only was it possible to attach the missing rhamnose unit to the oligosaccharide backbone, but the compromising orthoester junction was found to *rearrange concomitantly* to the required β-glycosidic linkage. By optimizing the pre-mixing and addition times it was possible to isolate product **34** in 60% yield. In view of the delicacy of this transformation,



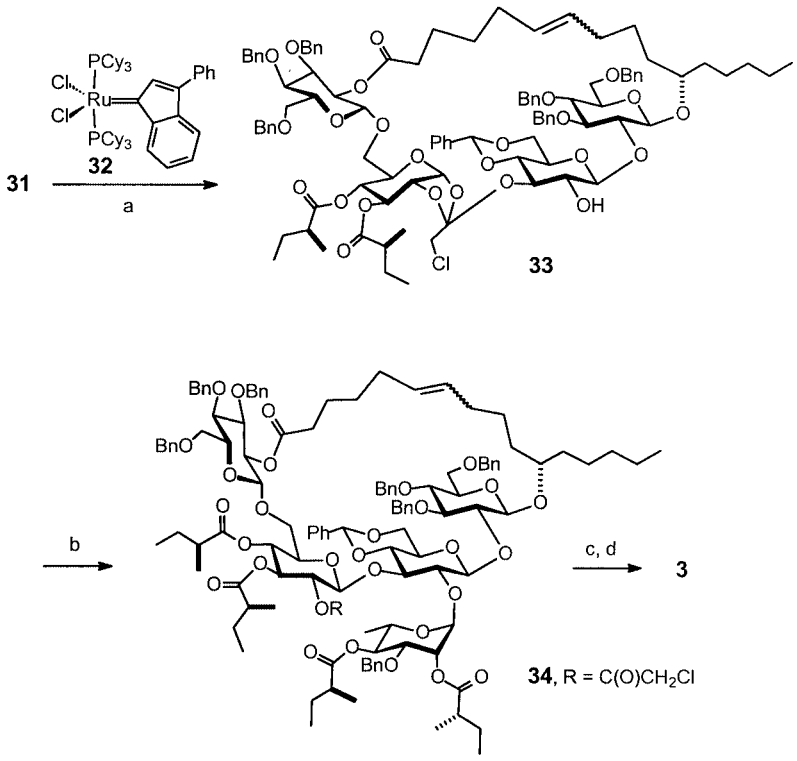
Scheme 6. Towards the oligosaccharidic perimeter of woodrosin I: a) donor **27**, TMSOTf cat., Et_2O/THF, −20 °C, 62%; b) DDQ, CH_2Cl_2/H_2O, 71%; c) donor **30**, TMSOTf cat., CH_2Cl_2, 84%

and the lability of the reaction partners, this result showcases the power of the trichloroacetimidate method[4] and, at the same time, represents one of the most advanced applications of Kochetkov's orthoester protocol reported to date.[31] Product **34** was then elaborated into woodrosin I (**3**) without incident.[26−28]

2.3. Sophorolipid Lactone

Although most resin glycosides have been isolated from higher plants, scattered reports on the production of related glycolipids by bacteria, fungi and yeasts can be found throughout the literature, some of which contain fatty acid components other than jalapinolic acid as the aglycon. The most prominent example is the yeast *Candida bombicola*, which is able to grow even on pure hydrocarbons.[32,33] It emulsifies such hydrophobic culture media by the production of extracellular biosurfactants called sophorolipids (SL) that can be obtained in large amounts by fermentation. These glycolipids are of growing commercial interest as biodegradable emulsifiers for applications in the cosmetic industry, pharmaceutical formulations, food production and even various technical purposes.

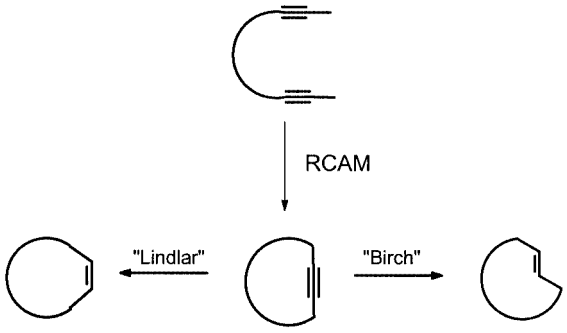
Native SL is a rather complex mixture of up to 14 different compounds, the ratio of which strongly depends on the chosen fermentation conditions; the sophorose 1′,4′′-lactone **4**, however, is invariably a major component of this mixture. While the synthesis of its disaccharide backbone comprising two glucose units is rather straightforward as compared to the assembly of the oligosaccharide perimeter of woodrosin I, the challenge of any synthesis of **4** lies in



Scheme 7. Completion of the total synthesis of woodrosin I: a) complex **32** cat., CH_2Cl_2, reflux, 94%; b) donor **27**, TMSOTf cat., Et_2O, 0 °C, 60%; c) hydrazinium acetate, DMF, −10 → 0 °C; d) H_2, Pd/C, MeOH, 84% (over both steps)

the *stereoselective* formation of the (*Z*)-alkene entity embedded into its macrolactone ring.

As can be seen from the examples discussed above, RCM tends to favor the formation of the corresponding (*E*)-isomers and is likely inappropriate for the present case.[14] Therefore, this compound provides an excellent opportunity to probe the efficiency of the newly developed ring-closing *alkyne* metathesis reaction (RCAM), since the resulting cycloalkyne can be stereoselectively reduced to the required (*Z*)-alkene by a Lindlar hydrogenation (Scheme 8).[34]



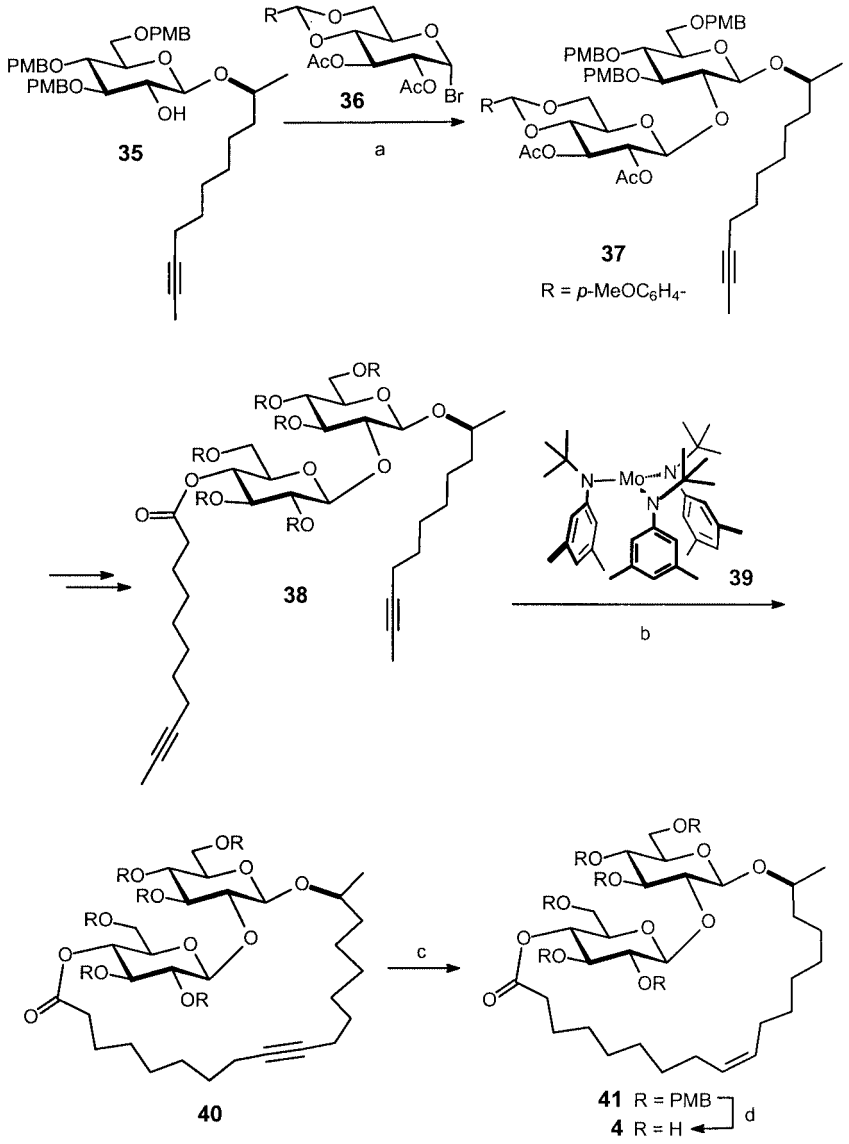
Scheme 8. Principle of ring-closing alkyne metathesis (RCAM) followed by stereoselective semi-reduction

Although RCAM in general is still in its childhood, this transformation worked exquisitely well when applied to diyne **38** which derives from glucopyranosyl bromide **36** and the β-glucoside **35** as shown in Scheme 9.[35] Specifically, reaction of compound **38** with a catalyst formed in situ from $Mo[N(tBu)(Ar)]_3$ (Ar = 3,5-dimethylphenyl) **39** and CH_2Cl_2 in toluene at 80 °C, as described previously,[36] afforded the desired cycloalkyne **40** in 78% yield. This outcome lends credence to the notion that alkyne metathesis is a reliable and efficient tool even in complex settings: neither the acid-labile PMB ethers nor the glycosidic linkages were damaged by the Lewis acidic metal center of the catalyst nor did they interfere with its performance; this adds two important examples to the rapidly growing list of functional groups that are compatible with this system. Lindlar hydrogenation of **40** followed by an exhaustive oxidative cleavage of the PMB-ether groups in **41** with DDQ completed the first total synthesis of this amphiphilic glycolipid.[35]

3. Glycolipidic Macrodiolides

3.1. Cycloviracin B_1

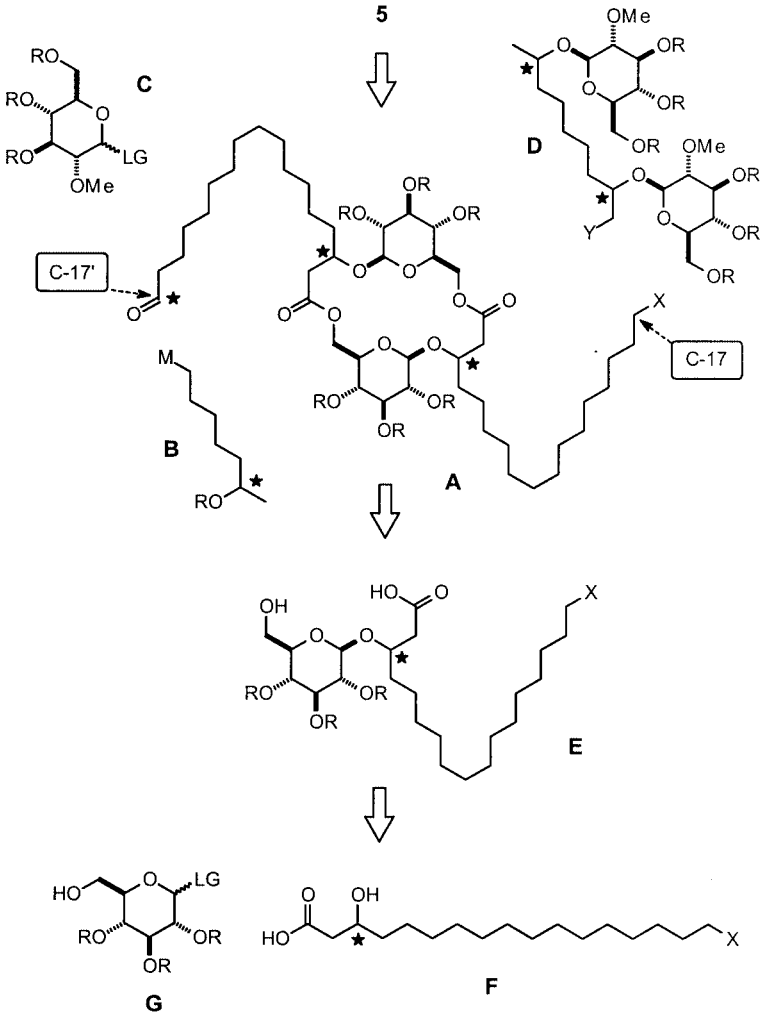
The paucity of effective medication against viral infections together with the increasing resistance towards approved drugs render the search, optimization and clinical development of novel antiviral agents highly desirable. The macrodiolide derivative cycloviracin B_1 (**5**) might constitute a promising new lead in this regard because of the selective



Scheme 9. Total synthesis of sophorolipid lactone (**4**) by RCAM: a) AgOTf, 2,6-di-*tert*-butylpyridine, MS 4 Å, −5 °C, 89%; b) complex **39** (10 mol %), CH_2Cl_2/toluene, 80 °C, 78%; c) H_2 (1 atm), Lindlar catalyst, quinoline, CH_2Cl_2, quant.; d) DDQ, aq. CH_2Cl_2, 93%

antiviral effect exerted by this complex glycoconjugate.[37] An imperative prelude to any further assessment of its biological properties and to a synthesis-driven mapping of its pharmacophore, however, is the unambiguous determination of the absolute configuration of the six chiral centers residing on its alkyl chains, which was unknown at the outset of our synthesis project.[38−40]

In view of the size and complexity of this target, however, it was clear that only a highly convergent and inherently flexible approach might allow us to reach this objective. The key design element of this plan exploits the hidden symmetry of **5** (Scheme 10). The fact that the individual subunits of its macrodiolide core are indistinguishable by NMR spectroscopy at 600 MHz is best explained by assuming a C_2-symmetric core structure. This then suggests to implement a two-directional synthesis strategy[41] en route to **5** to minimize the preparative efforts and to ensure maximum flexibility during fragment coupling. Given the different length of its two lateral chains and their discrete hydroxylation patterns, however, this plan bears a considerable risk for the final assembly stages. While established methodology should allow the control of the configuration of the -OH group at C-17′ generated by coupling of fragments **A** and **B** (M = metal), the formation of the C−C bond at the symmetry related C-17/C-18 position joining segments **A** and **D** is highly problematic. Any attempt to convert fragment **D** into a carbon nucleophile (Y = metal) must result in reductive elimination with loss of the adjacent glycoside;[42] the inverse maneuver implying the conversion of the entire lactide **A** into a suitable nucleophile (X = metal) is similarly endangered by the presence of electrophilic and C−H acidic sites in this molecule. More specifically, deprotonation α to the lactones (i.e. at C-2 and/or C-2′) would engender the opening of the macrocycle by expul-

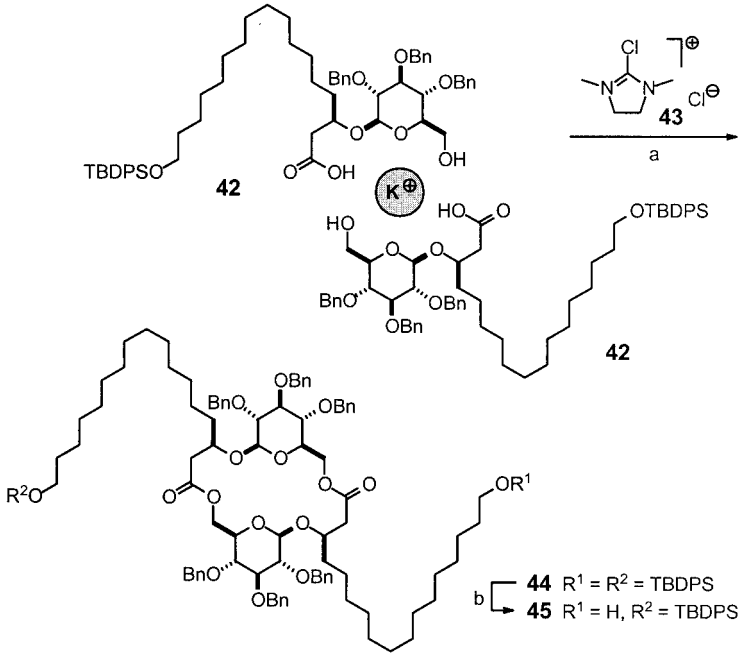


Scheme 10. Retrosynthetic analysis of cycloviracin B_1 (**5**)

sion of the adjacent sugar and formation of an α,β-unsaturated ester. Only a highly stabilized nucleophile X, if any, might kinetically resist these self-destructive pathways.

Despite these risks and uncertainties, the major design features of this retrosynthetic plan have been successfully put into practice. Particularly noteworthy is the fact that the central macrodiolide motif has been assembled in a highly efficient manner. Guided by the perception that the specific array of O atoms in the core region endows the molecule with some degree of ionophoric character, a template-directed cyclodimerization reaction of hydroxyacid **42** was developed that allowed us to construct this macrocyclic skeleton **44** in a single operation in 71% isolated yield when carried out in the presence of admixed potassium ions for the preorganization of two monomer units in a favorable head-to-tail arrangement (Scheme 11).[38,40,43] The commercial 2-chloro-1,3-dimethylimidazolinium chloride **43** turned out to be the activating agent of choice in this particular transformation.[44,45] As an additional bonus of the simplicity and flexibility of this approach, it was possible to prepare all conceivable stereoisomers without undue preparative efforts, which, in turn, allowed us to assign the absolute stereochemistry at the branching points of **5** as 3*R*,3′*R*.

The next critical phase of this total synthesis project comprised the delicate fragment coupling between this core segment and the glycosylated building block **47** to complete one of the alkyl chains of the natural product (Scheme 12). As discussed above, the success of this transformation depends critically on the ability to convert the intact macrodiolide ring into a suitable C-nucleophile. Importantly, this reactive intermediate must be kinetically resistant to a possible intramolecular attack onto its own lactone groups as well as to a destructive deprotonation of the C−H acidic sites adjacent to these lactones. Moreover, its reaction with aldehyde **47** must not entail any racemization of the chiral center α to the carbonyl. Because only a highly stabilized and weakly basic nucleophile might meet these stringent criteria, recourse was taken to a Julia olefination in the powerful modification developed by Kocienski.[46] It was expected that the somewhat higher kinetic acidity together with the better accessibility of the terminal tetrazolyl sulfone in **46**



Scheme 11. Preparation of the core segment of cycloviracin B_1 by a template-directed macrodilactonization reaction: a) compound **43**, DMAP, KH, CH_2Cl_2, 71%; b) (i) TBAF, THF, 92%; (ii) TBDPSCl, Et_3N, CH_2Cl_2, 85%

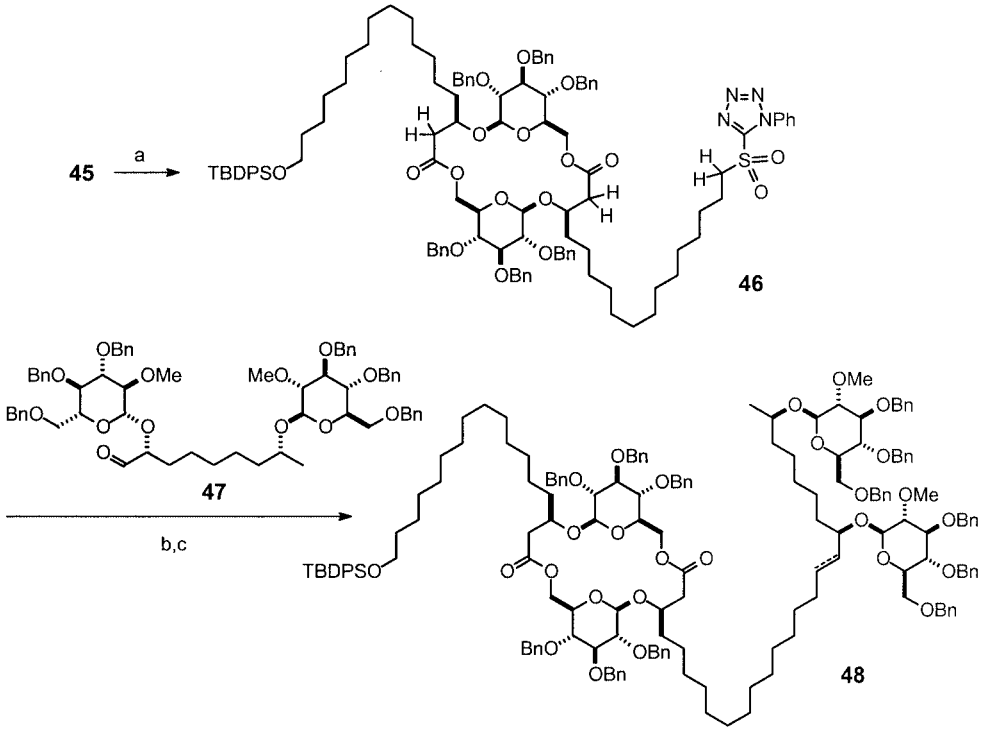
should allow for a selective deprotonation by means of a sterically encumbered base without damaging the ester moieties or the residual C−H acidic groups on the lactide ring. Gratifyingly, these expectations were fully met by the experiment. Thus, treatment of compound **46** with LiHMDS in DME at low temperature followed by addition of aldehyde **47** afforded the desired alkene in 61% yield (*E:Z* ≈ 1:1) which was subsequently hydrogenated under standard conditions to give product **48**.[39,40] We are unaware of any precedence for Julia-type olefination reactions involving sulfones bearing similarly base-labile and electrophilic motifs as those present in compound **46**.

Having secured good access to this elaborate construct, the stage was set for the introduction of the missing second alkyl side chain and hence the completion of the total synthesis. This was conveniently achieved by deprotection of the remaining silyl ether in **48** followed by oxidation of the resulting alcohol with PCC to afford the rather labile aldehyde **49**, which reacted smoothly with the highly functionalized diorganozinc reagent **50**[47] in the presence of a catalyst formed in situ from [Ti(O*i*Pr)$_4$] and bistriflate **51** as the controller ligand[20] to give alcohol **52** in 81% yield as a single diastereomer. Beyond doubt, this transformation constitutes one of the most advanced applications of ligand controlled dialkylzinc addition reactions to aldehydes known to date and bears witness to the maturity of this method.[21] Subsequent β-selective glucosidation of **52** with trichloroacetimidate **53** followed by an exhaustive hydrogenolysis of all residual benzyl ether protecting groups provided the (3*R*,19*S*,25*R*,3′*R*,17′*S*,23′*R*)-configured product **5** which was shown to be identical in all respects to the natural cycloviracin B_1.[38−40]

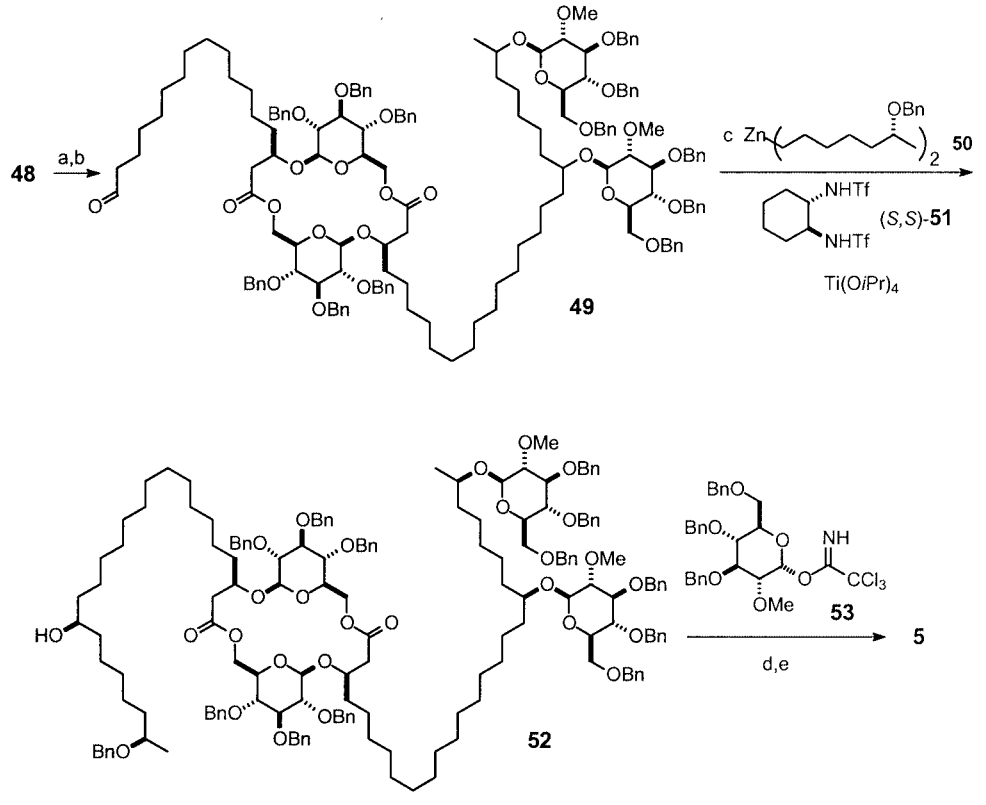
3.2. Glucolipsin A

The blueprint of the synthesis of cycloviracin B_1 outlined above can be easily adapted to the synthesis of the related macrodiolide glucolipsin A (**6**), a glucokinase inhibitor produced by *Streptomyces purpurogeniscleroticus* and *Nocardia vaccinii* strains.[48] While spectroscopic investigations had unraveled the symmetric structure of **6** and showed the presence of two β-glucose entities within its macrocyclic core, the absolute stereochemistry of the peripheral chiral centers remained elusive. This crucial aspect was unambiguously clarified by preparing all possible C_2-symmetric isomers and comparing their data with those of the natural product (Scheme 14).[49] It was again the efficiency and flexibility of the chosen approach which brought this complete set of compounds within reach.

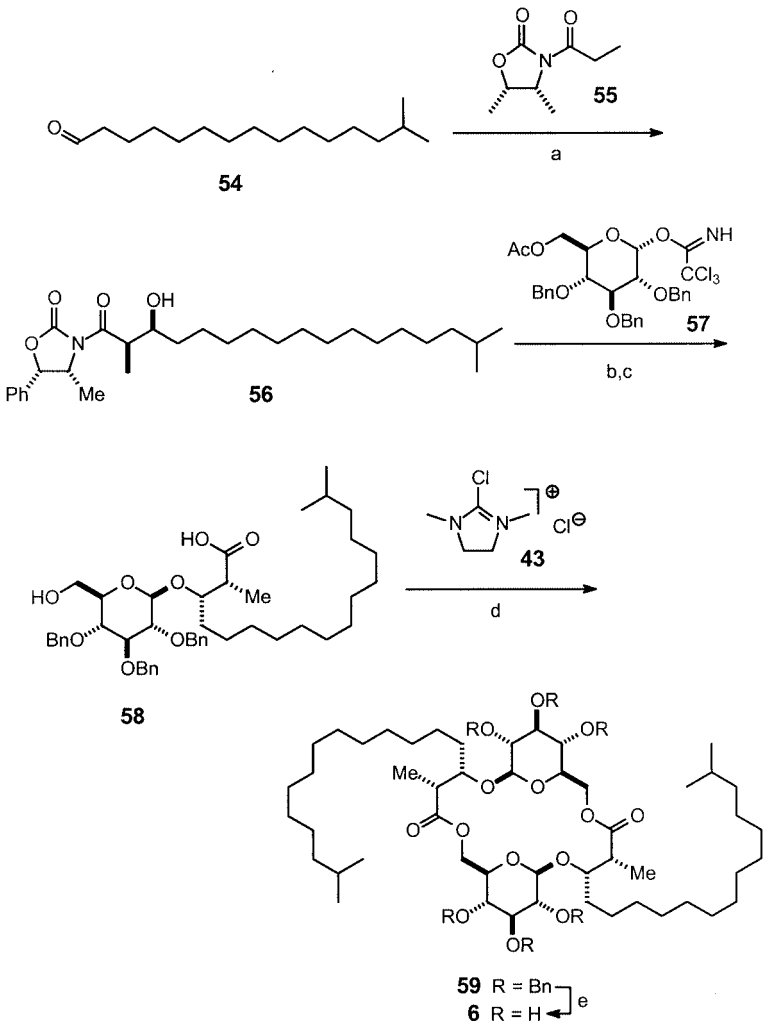
The required *syn*- and *anti*-configured aldol subunits were prepared by auxiliary guided reactions using the Evans[50] and Masamune−Abiko methodology,[51] respectively. A representative example is shown in Scheme 14, providing the (2*R*,3*S*)-configured product **56**, which turned out to be the correct building block for the synthesis of glucolipsin. Subsequent glycosidation with trichloroacetimidate **57** followed by hydrolytic cleavage of the auxiliary delivered the required hydroxy acid **58**, which was subjected to the macro-dilactonization protocol[38] mediated by 2-chloro-1,3-dimethylimidazolinium chloride (**43**) in the presence of admixed potassium cations. Exhaustive cleavage of the benzyl ether groups in the resulting macrodiolide **59** completed the synthesis of **6**.[49] Surprisingly, however, this study revealed that the fatty acid moiety of glucolipsin A comprises a *syn*-aldol with a (3*S*)-configured stereocenter,



Scheme 12. Fragment coupling by a Julia−Kocienski olefination: a) (i) 1-phenyl-5-mercaptotetrazole, DIAD, PPh_3, THF, 91%; (ii) $(NH_4)_6Mo_7O_{24}(H_2O)_7$, EtOH/$CH_2Cl_2$, 67%; b) (i) LiHMDS, DME, −78 °C, then **47**, 61%; (ii) H_2 (1 atm), Pd/C, EtOAc, 72%



Scheme 13. Completion of the total synthesis of cycloviracin B_1 (**5**): a) TBAF, THF, 95%; b) PCC, CH_2Cl_2, 83%; c) [Ti(O*i*Pr)$_4$], ligand **51** cat., reagent **50**, 81%; d) donor **53**, TMSOTf cat., CH_2Cl_2/MeCN, 87%; e) H_2 (1 atm), Pd/C, EtOH/EtOAc, 88%



Scheme 14. Total synthesis of glucolipsin A: a) nBu$_2$BOTf, Et$_3$N, CH$_2$Cl$_2$, 63%; b) donor **57**, TMSOTf cat., MeCN, 45%; c) LiOH, H$_2$O$_2$, aq. THF, 79%; d) reagent **43**, KH, DMAP, CH$_2$Cl$_2$, 54%; e) H$_2$ (1 atm), Pd(OH)$_2$ cat., MeOH, quant.

opposite to the (3*R*)-configured motif found in the otherwise closely related cycloviracin **5**.

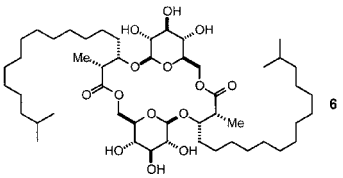
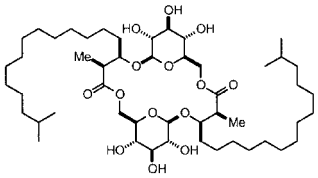
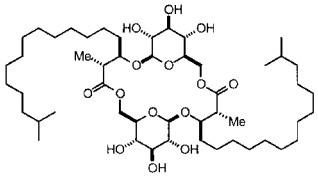
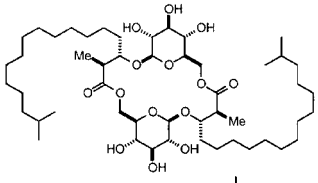
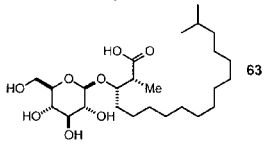
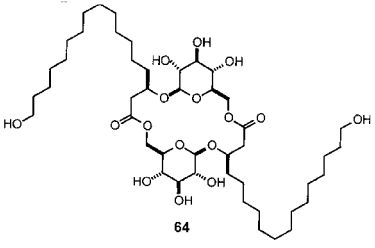
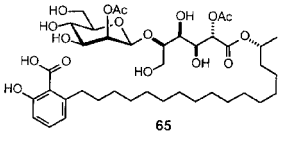
4. Biochemical and Biological Investigations

While scattered reports on the biological activities exerted by glycolipids of the type discussed in this review are available in the literature, a more comprehensive picture is still elusive. Therefore, the samples made available through the total synthesis projects pursued in this laboratory were used to gather additional information. Although a more extensive assessment is still in progress, some promising data have already been obtained.

The most striking aspect is our recent discovery that glucolipsin **6** and analogues **60**−**62** inhibit the dual specific phosphatase Cdc25A with IC$_{50}$ values in the low micromolar range, while being hardly active against the tyrosine phosphatase PTP1B in vitro.[49] To the best of our knowledge, glycolipids have not been identified as phosphatase inhibitors before.[52] The family of Cdc25 dual specific protein phosphatases is critically involved in cell cycle control. Their physiological substrates are cyclin-dependent kinases which trigger key transitions in the process of eukaryotic cellular division.[53] Therefore the homologous Cdc25 enzymes exert crucial regulatory functions at the crossroads between cellular proliferation, cell cycle arrest, and apoptosis. Their oncogenic properties, together with the fact that Cdc25A and B are overexpressed in many human tumors, render these isoenzymes molecular targets of utmost interest in the quest for anticancer drugs.

As can be seen from Table 1, the IC$_{50}$ values for the four diastereomers are identical within the error limit, indicating that the configuration of the stereocenters in the core region is not important for Cdc25A inhibition. The β-hydroxyacid **63**, which represents the monomeric building block present in **6**, is less selective and inhibits Cdc25A as well as PTP1B, although with significantly different potency. The fact that compound **64** as well as cycloviracin B$_1$ (**5**), which lack the methyl branch in the β-hydroxyacid segment but contain polar head groups in their lipidic appendices, are virtually inactive in this assay provides a first glimpse of possible

Table 1. Inhibition of Cdc25A and PTP1B by glucolipsin and analogues (n.i.: less than 50% inhibition at 50 μM)

Compound	Cdc25A (IC_{50})	PTP1B (IC_{50})
 **6**	2.2±1.1 μM	n.i.
 **60**	2.6±1.3 μM	n.i.
 **61**	2.6±1.3 μM	n.i.
 **62**	2.3±1.1 μM	n.i.
 **63**	1.6±1.3 μM	15±7 μM
 **64**	n.i.	n.i.
 **65**	5.5±2.8 μM	1.6±0.8 μM
Woodrosin I (**3**)	7±1.1 μM	n.i.
Sophorolipid lactone (**4**)	45±22 μM	n.i.
Tricolorin G (**2**)	n.i.	n.i.
Cycloviracin B_1 (**5**)	n.i.	n.i.

structure-activity relationships in this series. Moreover, woodrosin I (**3**) and caloporoside (**65**), yet another glycolipid previously conquered by total synthesis in our laboratory,[54] were also found to be phosphatase inhibitors, while sophorolipid lactone **4** and tricolorin G **2** elicited no response.

In addition to the enzymatic assays discussed above, the cytotoxicity and antiviral activity of selected glycolipids have been determined.[40] Our data confirm a specific antiviral activity for cycloviracin B_1 (i.e. the minimal antivirally effective concentration is ≥ fivefold lower than the minimal cytotoxic contentration), whereas none of its immediate precursors was found to exhibit similar effects. This includes compound **64**, representing the intact macrodiolide core of **5**, which is rather cytotoxic but not antivirally active at subtoxic concentrations. A herpes simplex virus-1 strain *resistant* to acyclovir (strain TK^- KOS ACV^r) shows the highest sensitivity against **5** in an assay using cultured human embryonic lung (HEL) cells. While woodrosin I (**3**) is effective at similar concentrations, its cytotoxicity is more pronounced than that of cycloviracin B_1. Selected data are compiled in Table 2. Compound **5** has also been evaluated, but found to be inactive at subtoxic concentrations, against Coxsackie B4 virus, respiratory syncytial virus, parainfluenza type 3 virus, reovirus type 1, Sindbis virus, and Punta Toro virus.[40]

5. Conclusions

While total synthesis in general has reached a truly impressive level of sophistication and can bring almost any target into reach,[55] this field of research faces increasing skepticism as to its contributions to the overall advancement of science.[56] Since this criticism has to be taken seriously, it seems appropriate to ask ourselves what we have learned during the synthetic endeavors described above. A lasting legacy of a total synthesis can consist of new reactions or reactivity patterns discovered in response to the chosen target. Though incremental, several aspects of the projects summarized in this feature article may fall into this category.

There is no doubt that these examples bear witness to the truly spectacular application profile of modern metathesis chemistry.[14] The ease with which the ruthenium carbene complexes **19** and **32** allowed the macrolide rings of tricolorin A (**1**), tricolorin G (**2**), or woodrosin I (**3**) to be formed constitutes an instructive counterpoint to the subtle difficulties encountered in the assembly of the carbohydrate perimeters of these targets. It is now widely recognized that RCM rivals all established methods for the synthesis of large rings. This transformation has evolved within a few years into a very reliable tool that can be safely implemented even into complex settings. Chemists have gained enough confidence in this reaction to subject elaborate and highly valuable materials to it, with the author of this review being no exception to the rule.[57] Although several issues related to RCM still remain to be solved, the strategic advantages of this transformation in general, together with the remarkable compatibility of the available catalysts, will

Table 2. Cytotoxicity and antiviral activity of various glycolipids in HEL cell cultures

Compound	Minimum Cytotoxic Concentration[a] ($\mu g \cdot mL^{-1}$)	Minimum Virus Inhibitory Concentration[b] ($\mu g.mL^{-1}$)				
		HSV-1 (KOS strain)	HSV-2 (G strain)	Vaccinia virus	Vesicular stomatitis virus	HSV-1 (TK^- KOS ACV^r strain)[c]
5	>200	24	120	24	>200	6.4
64	≥16	>16	>16	>16	>16	>16
3	≥8	4.8	≥6.4	4.8	>8	4.8

[a] Required to cause a microscopically detectable alteration of normal cell morphology. [b] Required to reduce virus-reduced cytopathogenicity by 50%. [c] TK^-: thymidine kinase deficient; ACV^r: resistant to acyclovir.

continue to shape modern organic chemistry. Particularly noteworthy is the inherent flexibility of this method which is exemplified, for example, by the ease with which several analogues of tricolorin A and G differing from the parent compounds in ring size, and hence lipophilicity, could be accessed by simple permutations of the acylation pattern of a common synthetic intermediate.

The syntheses outlined above illustrate yet another important aspect of RCM which is of even greater heuristic value. The tricolorins as well as woodrosin have been deliberately disconnected within the hydrocarbon chains at sites *remote* from the functional groups. This must be seen in the context of established retrosynthetic analyses which are uniformly guided by the polarity induced by the substituents of a given target and therefore invariably opt for disconnections at, or *close* to, the functional groups. Therefore one must conclude that RCM is complementary to the existing arsenal and exerts a significant impact on basic concepts of retrosynthetic logic.[58]

Though much less established, the metathesis of *alkynes* in general, and the only recently discovered ring-closing metathesis of diynes (RCAM)[34] in particular, also hold great promise for target-oriented synthesis, not least because of the exceedingly high tolerance of the available catalysts. The approach to sophorolipid lactone, together with several other applications from this laboratory,[59,60] bear witness to this notion and may encourage more extensive uses of this versatile methodology in advanced organic synthesis.

The projects outlined above also highlight the reliability of yet other organometallic bond-forming reactions. This includes the venerable aldol reaction, the Kocienski modification of the Julia olefination, and the ligand-controlled dialkylzinc additions to aldehydes. It is believed that the examples of these transformations shown in Schemes 12 and 13, respectively, involving *highly functionalized* nucleophiles are amongst the most advanced cases reported to date.

Furthermore, a comment on the carbohydrate chemistry exercised in these projects is appropriate. Despite the substantial methodological advances in glycosylation chemistry achieved in recent years, our programs showed that the assembly of sophisticated oligosaccharides is still far from routine. While each synthesis described above substantiates this aspect, the woodrosin I project stands out in this regard. Although we lay no claim to the uniqueness of the trichloroacetimidate method[4] for reaching this particular target, this reaction has repeatedly served our purposes very well and the examples summarized above certainly attest to the performance, reliability and maturity of this transformation. Furthermore, some noteworthy, but largely unexplored, aspects of this method became apparent during our projects: thus, it has been shown that (vicinal) diols can be regioselectively glycosylated without recourse to protecting group chemistry, and that this glycosidation strategy can be executed in an iterative, yet fully selective, way using 1,ω-unprotected sugars entities.[27]

Finally, the evaluation of the biochemical and biological properties of the glycoconjugates prepared during our program and the immediate precursors thereof has been rewarding. They have led to the discovery that glycolipids are promising antiviral agents and act as phosphatase inhibitors that display considerable selectivity for the dual specific phosphatase Cdc25A, with IC_{50} values in the low micromolar range.[61] Further studies along these lines are in progress and will be reported in due course.

Acknowledgments

I would like to express my sincere thanks to all my co-workers engaged in our program on glycolipids in the past for their commitment, intellectual input and careful experimental work. Their names appear in the references. I also thank Prof. H. Waldmann and Doz. H. Prinz, MPI für Molekulare Physiologie, Dortmund, and Prof. E. DeClercq, University of Leuven, Belgium, for their cooperation in the biological assessments. Generous financial support by the Max-Planck Society, the Deutsche Forschungsgemeinschaft (Leibniz award program), the Fonds der Chemischen Industrie, the Merck Research Council, and the Cope Scholar Funds administered by the ACS is gratefully acknowledged.

[1] General treatise: *Glycoscience: Chemistry and Chemical Biology*, vol. III (Eds.: B. Fraser-Reid, K. Tatsuta, J. Thiem), Springer, Berlin, **2001**.

[2] For some selected reviews see: [2a] K. C. Nicolaou, H. J. Mitchell, *Angew. Chem. Int. Ed.* **2001**, *40*, 1576−1624; *Angew. Chem.* **2001**, *113*. [2b] S. J. Danishefsky, J. R. Allen, *Angew. Chem.* **2000**, *112*, 882−912; *Angew. Chem. Int. Ed.* **2000**, *39*, 836−863. [2c] H. Kunz, *Angew. Chem.* **1987**, *99*, 297−311; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 294.

[3] General reviews: [3a] H. Paulsen, *Angew. Chem.* **1982**, *94*, 184−201; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 155−173. [3b]

R. R. Schmidt, in *Comprehensive Organic Synthesis*, vol. 6 (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 33−61. [3c]K. Toshima, K. Tatsuta, *Chem. Rev.* **1993**, *93*, 1503−1531. [3d] B. G. Davis, *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137−2160. [3e] S. J. Danishefsky, M. T. Bilodeau, *Angew. Chem.* **1996**, *108*, 1483−1522; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1380−1419. [3f] *Preparative Carbohydrate Chemistry* (Ed.: S. Hanessian), Dekker, New York, **1997**.

[4] [4a] R. R. Schmidt, *Angew. Chem.* **1986**, *98*, 213−236; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212−235. [4b] R. R. Schmidt, W. Kinzy, *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21−123. [4c] R. R. Schmidt, K.-H. Jung, in *Preparative Carbohydrate Chemistry* (Ed.: S. Hanessian), Marcel Dekker, New York, **1997**, pp. 283−312.

[5] For syntheses of *marine* lipidic natural products from this laboratory see: [5a] A. Fürstner, K. Grela, C. Mathes, C. W. Lehmann, *J. Am. Chem. Soc.* **2000**, *122*, 11799−11805. [5b] A. Fürstner, K. Grela, *Angew. Chem.* **2000**, *112*, 1292−1294; *Angew. Chem. Int. Ed.* **2000**, *39*, 1234−1236. [5c] A. Fürstner, M. Schlede, *Adv. Synth. Catal.* **2002**, *344*, 657−665.

[6] For biological assessments of other types of natural products by our laboratory see: [6a] A. Fürstner, *Angew. Chem.* **2003**, *115*, 3706−3728; *Angew. Chem. Int. Ed.* **2003**, *42*, 3582−3603. [6b] A. Fürstner, J. Grabowski, C. W. Lehmann, T. Kataoka, K. Nagai, *ChemBioChem* **2001**, *2*, 60−68. [6c] A. Fürstner, E. J. Grabowski, *ChemBioChem* **2001**, *2*, 706−709.

[7] Short reviews: [7a] R. Pereda-Miranda, M. Bah, *Curr. Top. Med. Chem.* **2003**, *3*, 111−131. [7b] H. Wagner, *Nobel Symp.* **1974**, *25*, 235−240.

[8] [8a] R. Pereda-Miranda, R. Mata, A. L. Anaya, D. B. M. Wickramaratne, J. M. Pezzuto, A. D. Kinghorn, *J. Nat. Prod.* **1993**, *56*, 571−582. [8b] M. Bah, R. Pereda-Miranda, *Tetrahedron* **1996**, *52*, 13063−13080. [8c] M. Bah, R. Pereda-Miranda, *Tetrahedron* **1997**, *53*, 9007−9022.

[9] M. R. Calera, A. L. Anaya, M. Gavilanes-Ruiz, *J. Chem. Ecol.* **1995**, *21*, 289−297.

[10] L. Achnine, R. Pereda-Miranda, R. Iglesias-Prieto, R. Moreno-Sánchez, B. Lotina-Hennsen, *Physiol. Plant.* **1999**, *106*, 246−252.

[11] [11a] D. P. Larson, C. H. Heathcock, *J. Org. Chem.* **1996**, *61*, 5208−5209. [11b] D. P. Larson, C. H. Heathcock, *J. Org. Chem.* **1997**, *62*, 8406−8418.

[12] [12a] S.-F. Lu, Q. O′yang, Z.-W. Guo, B. Yu, Y.-Z. Hui, *Angew. Chem.* **1997**, *109*, 2442−2444; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2344−2346. [12b] S.-F. Lu, Q. O′yang, Z.-W. Guo, B. Yu, Y.-Z. Hui, *J. Org. Chem.* **1997**, *62*, 8400−8405.

[13] For the total synthesis of other resin glycosides see: [13a] Z.-H. Jiang, A. Geyer, R. R. Schmidt, *Angew. Chem.* **1995**, *107*, 2730−2734; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2520−2524. [13b] J. Furukawa, S. Kobayashi, M. Nomizu, N. Nishi, N. Sakairi, *Tetrahedron Lett.* **2000**, *41*, 3453−3457. [13c] J. Furukawa, N. Sakairi, *Trends Glycosci. Glycotechnol.* **2001**, *13*, 1−10.

[14] Recent reviews: [14a] T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18−29. [14b] A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140−3172; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012−3043. [14c] R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413−4450. [14d] M. Schuster, S. Blechert, *Angew. Chem.* **1997**, *109*, 2124−2144; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2037−2056. [14e] A. Fürstner, *Top. Catal.* **1997**, *4*, 285−299. [14f] S. K. Armstrong, *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388.

[15] A. Fürstner, T. Müller, *J. Org. Chem.* **1998**, *63*, 424−425.

[16] A. Fürstner, T. Müller, *J. Am. Chem. Soc.* **1999**, *121*, 7814−7821.

[17] A. Fürstner, K. Langemann, *J. Org. Chem.* **1996**, *61*, 3942−3943.

[18] A. Fürstner, K. Langemann, *Synthesis* **1997**, 792−803.

[19] A. Fürstner, O. R. Thiel, C. W. Lehmann, *Organometallics* **2002**, *21*, 331−335.

[20] H. Takahashi, T. Kawakita, M. Ohno, M. Yoshioka, S. Kobayashi, *Tetrahedron* **1992**, *48*, 5691−5700.

[21] Reviews: [21a] P. Knochel, in *Active Metals: Preparation, Characterization, Applications* (Ed.: A. Fürstner), VCH, Weinheim, **1996**, pp. 191−236. [21b]P. Knochel, *Synlett* **1995**, 393−403. [21c] R. Noyori, in *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons, New York, **1994**, pp. 255−297. [21d]K. Soai, S. Niwa, *Chem. Rev.* **1992**, *92*, 833−856.

[22] [22a] S. T. Nguyen, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1993**, *115*, 9858−9859. [22b] P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100−110.

[23] [23a] A. Fürstner, M. Picquet, C. Bruneau, P. H. Dixneuf, *Chem. Commun.* **1998**, 1315−1316. [23b] A. Fürstner, M. Liebl, C. W. Lehmann, M. Picquet, R. Kunz, C. Bruneau, D. Touchard, P. H. Dixneuf, *Chem. Eur. J.* **2000**, *6*, 1847−1857.

[24] C. W. Lehmann, A. Fürstner, T. Müller, *Z. Kristallogr.* **2000**, *215*, 114−117.

[25] M. Ono, K. Nakagawa, T. Kawasaki, K. Miyahara, *Chem. Pharm. Bull.* **1993**, *41*, 1925−1932.

[26] A. Fürstner, F. Jeanjean, P. Razon, *Angew. Chem.* **2002**, *114*, 2203−2206; *Angew. Chem. Int. Ed.* **2002**, *41*, 2097−2101.

[27] A. Fürstner, F. Jeanjean, P. Razon, C. Wirtz, R. Mynott, *Chem. Eur. J.* **2003**, *9*, 307−319.

[28] A. Fürstner, F. Jeanjean, P. Razon, C. Wirtz, R. Mynott, *Chem. Eur. J.* **2003**, *9*, 320−326.

[29] A. Fürstner, O. Guth, A. Düffels, G. Seidel, M. Liebl, B. Gabor, R. Mynott, *Chem. Eur. J.* **2001**, *7*, 4811−4820.

[30] R. R. Schmidt, A. Toepfer, *Tetrahedron Lett.* **1991**, *32*, 3353−3356.

[31] [31a] N. K. Kochetkov, A. J. Khorlin, A. F. Bochkov, *Tetrahedron* **1967**, *23*, 693−707. For some applications see, inter alia: [31b] D. R. Mootoo, P. Konradsson, B. Fraser-Reid, *J. Am. Chem. Soc.* **1989**, *111*, 8540−8542. [31c] T. Ogawa, T. Nukada, *Carbohydr. Res.* **1985**, *136*, 135−152. [31d] P. J. Garegg, I. Kvarnström, *Acta Chem. Scand., Ser. B* **1976**, *30*, 655−658. [31e] R. U. Lemieux, A. R. Morgan, *Can. J. Chem.* **1965**, *43*, 2199−2201. [31f] T. Ogawa, K. Beppu, S. Nakabayashi, *Carbohydr. Res.* **1981**, *93*, C6−C9.

[32] [32a] P. A. J. Gorin, J. F. T. Spencer, A. P. Tulloch, *Can. J. Chem.* **1961**, *39*, 846−855. [32b] A. P. Tulloch, J. F. T. Spencer, P. A. J. Gorin, *Can. J. Chem.* **1962**, *40*, 1326−1338. [32c] See the following for a recent study and literature cited therein: S. K. Singh, A. P. Felse, A. Nunez, T. A. Foglia, R. A. Gross, *J. Org. Chem.* **2003**, *68*, 5466−5477.

[33] [33a] N. G. K. Karanth, P. G. Deo, N. K. Veenanadig, *Curr. Sci.* **1999**, *77*, 116−126. [33b] D. G. Cooper, J. E. Zajic, *Adv. Appl. Microbiol.* **1980**, *26*, 229−253.

[34] A. Fürstner, G. Seidel, *Angew. Chem.* **1998**, *110*, 1758−1760; *Angew. Chem. Int. Ed.* **1998**, *37*, 1734−1736.

[35] A. Fürstner, K. Radkowski, J. Grabowski, C. Wirtz, R. Mynott, *J. Org. Chem.* **2000**, *65*, 8758−8762.

[36] [36a] A. Fürstner, C. Mathes, C. W. Lehmann, *J. Am. Chem. Soc.* **1999**, *121*, 9453−9454. [36b] A. Fürstner, C. Mathes, C. W. Lehmann, *Chem. Eur. J.* **2001**, *7*, 5299−5317.

[37] [37a] M. Tsunakawa, N. Komiyama, O. Tenmyo, K. Tomita, K. Kawano, C. Kotake, M. Konishi, T. Oki, *J. Antibiot.* **1992**, *45*, 1467−1471. [37b] M. Tsunakawa, C. Kotake, T. Yamasaki, T. Moriyama, M. Konishi, T. Oki, *J. Antibiot.* **1992**, *45*, 1472−1480.

[38] A. Fürstner, M. Albert, J. Mlynarski, M. Matheu, *J. Am. Chem. Soc.* **2002**, *124*, 1168−1169.

[39] A. Fürstner, J. Mlynarski, M. Albert, *J. Am. Chem. Soc.* **2002**, *124*, 10274−10275.

[40] A. Fürstner, M. Albert, J. Mlynarski, M. Matheu, E. DeClercq, *J. Am. Chem. Soc.* **2003**, *125*, 13132−13142.

[41] C. S. Poss, S. J. Schreiber, *Acc. Chem. Res.* **1994**, *27*, 9−17.

[42] For studies on reductive eliminations in sugar chemistry form this laboratory see: [42a] A. Fürstner, H. Weidmann, *J. Org. Chem.* **1989**, *54*, 2307−2311. [42b] A. Fürstner, J. Baumgartner, *Tetrahedron* **1993**, *49*, 8541−8560 and literature cited therein.

[43] This concept has also recently been used in a follow-up model study: V. Bailliez, R. M. de Figueiredo, A. Olesker, J. Cleophax, *Tetrahedron Lett.* **2003**, *44*, 9151−9153.

[44] [44a] T. Isobe, T. Ishikawa, *J. Org. Chem.* **1999**, *64*, 5832−5835. [44b] T. Isobe, T. Ishikawa, *J. Org. Chem.* **1999**, *64*, 6984−6988. [44c] T. Isobe, T. Ishikawa, *J. Org. Chem.* **1999**, *64*, 6989−6992.
[45] For an application of this reagent in organometallic chemistry see: A. Fürstner, G. Seidel, D. Kremzow, C. W. Lehmann, *Organometallics* **2003**, *22*, 907−909.
[46] [46a] P. R. Blakemore, W. J. Cole, P. J. Kocienski, A. Morley, *Synlett* **1998**, 26−28. [46b] Review: P. R. Blakemore, *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563−2585.
[47] Prepared by the method described in: M. J. Rozema, C. Eisenberg, H. Lütjens, R. Ostwald, K. Belyk, P. Knochel, *Tetrahedron Lett.* **1993**, *34*, 3115−3118.
[48] J. Qian-Cutrone, T. Ueki, S. Huang, K. A. Mookhtiar, R. Ezekiel, S. S. Kalinowski, K. S. Brown, J. Golik, S. Lowe, D. M. Pirnik, R. Hugill, J. A. Veitch, S. E. Klohr, J. L. Whitney, S. P. Manly, *J. Antibiot.* **1999**, *52*, 245−255.
[49] A. Fürstner, J. Ruiz-Caro, H. Prinz, H. Waldmann, *J. Org. Chem.*, **2004**, *69*, 459−467.
[50] [50a] D. A. Evans, M. D. Ennis, D. J. Mathre, *J. Am. Chem. Soc.* **1982**, *104*, 1737−1739. [50b] D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129.
[51] [51a] A. Abiko, J.-F. Liu, S. Masamune, *J. Org. Chem.* **1996**, *61*, 2590−2591. [51b] A. Abiko, J.-F. Liu, S. Masamune, *J. Am. Chem. Soc.* **1997**, *119*, 2586−2587. [51c] T. Inoue, J.-F. Liu, D. C. Buske, A. Abiko, *J. Org. Chem.* **2002**, *67*, 5250−5256.
[52] For comprehensive literature coverage see: [52a] M. A. Lyon, A. P. Ducruet, P. Wipf, J. S. Jazo, *Nat. Rev. Drug Discovery* **2002**, *1*, 961−976. [52b] D. Brohm, N. Philippe, S. Metzger, A. Bhargava, O. Müller, F. Lieb, H. Waldmann, *J. Am. Chem. Soc.* **2002**, *124*, 13171−13178.
[53] Reviews: [53a] K. Galaktionov, A. K. Lee, J. Eckstein, G. Draetta, J. Meckler, M. Loda, D. Beach, *Science* **1995**, *269*, 1575−1577. [53b] G. Draetta, J. Eckstein, *Biochim. Biophys. Acta* **1997**, *1332*, M53−M63. [53c] I. Nilsson, I. Hoffmann, *Prog. Cell Cycle Res.* **2000**, *4*, 107−114.
[54] [54a] A. Fürstner, I. Konetzki, *J. Org. Chem.* **1998**, *63*, 3072−3080. [54b] See also: A. Fürstner, I. Konetzki, *Tetrahedron* **1996**, *52*, 15071−15078.
[55] [55a] E. J. Corey, X.-M. Cheng, *The Logic of Chemical Synthesis*, Wiley, New York, **1989**. [55b]K. C. Nicolaou, D. Vourloumis, N. Winssinger, P. S. Baran, *Angew. Chem.* **2000**, *112*, 46−126; *Angew. Chem. Int. Ed.* **2000**, *39*, 44−122. [55c] K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis: Targets, Strategies, Methods*, Wiley-VCH, Weinheim, **1996** and literature cited therein.
[56] See for example: [56a] C. Djerassi, *Science* **1999**, *285*, 835. [56b] R. F. Service, *Science* **1999**, *285*, 184−187.
[57] For some additional examples see: [57a] A. Fürstner, N. Kindler, *Tetrahedron Lett.* **1996**, *37*, 7005−7008. [57b] A. Fürstner, K. Langemann, *J. Org. Chem.* **1996**, *61*, 8746−8749. [57c] A. Fürstner, K. Langemann, *J. Am. Chem. Soc.* **1997**, *119*, 9130−9136. [57d] A. Fürstner, T. Müller, *Synlett* **1997**, 1010−1012. [57e] A. Fürstner, T. Gastner, H. Weintritt, *J. Org. Chem.* **1999**, *64*, 2361−2366. [57f] A. Fürstner, G. Seidel, N. Kindler, *Tetrahedron* **1999**, *55*, 8215−8230. [57g] A. Fürstner, O. R. Thiel, N. Kindler, B. Bartkowska, *J. Org. Chem.* **2000**, *65*, 7990−7995. [57h] A. Fürstner, O. R. Thiel, L. Ackermann, *Org. Lett.* **2001**, *3*, 449−451. [57i] A. Fürstner, J. Grabowski, C. W. Lehmann, *J. Org. Chem.* **1999**, *64*, 8275−8280. [57j] A. Fürstner, O. R. Thiel, *J. Org. Chem.* **2000**, *65*, 1738−1742. [57k] A. Fürstner, K. Radkowski, *Chem. Commun.* **2001**, 671−672. [57l] A. Fürstner, T. Dierkes, O. R. Thiel, G. Blanda, *Chem. Eur. J.* **2001**, *7*, 5286−5298. [57m] A. Fürstner, O. R. Thiel, G. Blanda, *Org. Lett.* **2000**, *2*, 3731−3734. [57n] A. Fürstner, K. Radkowski, C. Wirtz, R. Goddard, C. W. Lehmann, R. Mynott, *J. Am. Chem. Soc.* **2002**, *124*, 7061−7069. [57o] A. Fürstner, C. Aïssa, R. Riveiros, J. Ragot, *Angew. Chem.* **2002**, *114*, 4958−4960; *Angew. Chem. Int. Ed.* **2002**, *41*, 4763−4766. [57p] A. Fürstner, A. Leitner, *Angew. Chem.* **2003**, *115*, 320−323; *Angew. Chem. Int. Ed.* **2003**, *42*, 308−311. [57q] C. Aïssa, R. Riveiros, J. Ragot, A. Fürstner, *J. Am. Chem. Soc.* **2003**, *125*, 15512−15520.
[58] A. Fürstner, *Synlett* **1999**, 1523−1533.
[59] [59a] A. Fürstner, O. Guth, A. Rumbo, G. Seidel, *J. Am. Chem. Soc.* **1999**, *121*, 11108−11113. [59b] A. Fürstner, A. Rumbo, *J. Org. Chem.* **2000**, *65*, 2608−2611. [59c] A. Fürstner, G. Seidel, *J. Organomet. Chem.* **2000**, *606*, 75−78. [59d] A. Fürstner, C. Mathes, K. Grela, *Chem. Commun.* **2001**, 1057−1059. [59e] A. Fürstner, T. Dierkes, *Org. Lett.* **2000**, *2*, 2463−2465. [59f] A. Fürstner, C. Mathes, *Org. Lett.* **2001**, *3*, 221−223. [59g] A. Fürstner, A.-S. Castanet, K. Radkowski, C. W. Lehmann, *J. Org. Chem.* **2003**, *68*, 1521−1528. [59h] D. Song, G. Blond, A. Fürstner, *Tetrahedron* **2003**, *59*, 6899−6904. [59i] A. Fürstner, D. De Souza, L. Parra-Rapado, J. T. Jensen, *Angew. Chem.* **2003**, *115*, 5516−5518; *Angew. Chem. Int. Ed.* **2003**, *42*, 5358−5360.
[60] B. Aguilera, L. B. Wolf, P. Nieczypor, F. P. T. J. Rutjes, H. S. Overkleft, J. C. M. van Hest, H. E. Schoemaker, B. Wang, J. C. Mol, A. Fürstner, M. Overhand, G. A. van der Marel, J. H. van Boom, *J. Org. Chem.* **2001**, *66*, 3584−3589.
[61] See also: A. Fürstner, F. Feyen, H. Prinz, H. Waldmann, *Angew. Chem.* **2003**, *115*, 5519−5522; *Angew. Chem. Int. Ed.* **2003**, *42*, 5361−5364.

Received November 16, 2003

