Efficient Total Syntheses of Resin Glycosides and Analogues by Ring-Closing Olefin Metathesis

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Received April 26, 1999

Abstract: A highly efficient entry into the resin glycoside family of natural products is outlined which takes advantage of the inherently modular character of ring-closing metathesis (RCM) for the formation of their macrolactone substructures. Starting from only three well accessible sugar building blocks and (6*S*)-undec-1-en-6-ol (**7**) (prepared by enantioselective addition of dipentylzinc to hexenal in the presence of a catalyst formed from Ti(OiPr)$_4$ and bis-(*R,R*)-trifluoromethanesulfonamide (**9**)), it was possible to achieve total syntheses of tricolorin A (**1**), tricolorin G (**2**), and jalapinolic acid (**58**) as well as the synthesis of the disaccharidic unit **48** which constitutes a common structural motif of all simonin, operculin, tuguajalapin, orizabin, mammoside, quamoclin, and stoloniferin resin glycosides. Furthermore, various analogues of these naturally occurring glycolipids have been obtained in a straightforward manner from the same set of substrates. This highlights the flexibility of the chosen approach and opens the door for a synthesis-driven mapping of the structure/activity profile of this structurally demanding class of oligosaccharides. The macrocyclization reactions via RCM have been performed using carbene **22** introduced by Grubbs, the cationic allenylidene complex **23**, or the particularly convenient precatalyst [(*p*-cymene)RuCl$_2$(PCy$_3$)] **24**. All these ruthenium-based systems catalyze the ring closure of the highly functionalized diene substrates with comparable efficiency and turned out to be compatible with an array of functional groups including unprotected secondary hydroxyl functions.

Introduction

Chemical investigations on resin glycosides were initiated as early as the middle of the 19th century.[1] Until the advent of modern spectroscopy, however, it was impossible for chemists to deduce the amazingly complex but aesthetically most appealing structures of the individual members of this family of glycolipids. All of them contain jalapinolic acid (11(*S*)-hydroxyhexadecanoic acid) as the aglycon which is usually tied back to form a macrolactone ring spanning two or more units of their saccharide backbones.[2−11] In addition to this very characteristic structural motif, resin glycosides are rich in deoxy sugars, particularly D-fucose, L-rhamnose, and D-quinovose, with L-Rha*p*-(1→2)-D-Fuc, L-Rha*p*-L-Rha and D-Glc*p*-(1→2)-D-Fuc representing highly conserved disaccharidic subunits.

Although the biological properties of resin glycosides have not yet been fully assessed, a closer look into this class of natural products seems highly promising in view of the existing data on the use of glycolipids in general for the treatment of severe immune disorders.[12] The fact that many of them are isolated from plants which are essential ingredients of traditional

(1) (a) Johnston, J. F. W. *Philos. Trans*. **1840**, 342. (b) Kayser, G. A. *Justus Liebigs Ann. Chem*. **1844**, *51*, 81. (c) Mayer, W. *Justus Liebigs Ann. Chem*. **1855**, *95*, 129. (d) Power, F. B.; Rogerson, H. *J. Chem. Soc. Trans*. **1912**, *101*, 1. (e) Mannich, C.; Schumann, P. *Arch. Pharm. Ber. Dtsch. Pharm. Ges*. **1938**, *276*, 221.

(2) Tricolorin family: (a) Pereda-Miranda, R.; Mata, R.; Anaya, A. L.; Wickramaratne, M.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod*. **1993**, *56*, 571. (b) Bah, M.; Pereda-Miranda, R. *Tetrahedron* **1996**, *52*, 13063. (c) Bah, M.; Pereda-Miranda, R. *Tetrahedron* **1997**, *53*, 9007.

(3) Simonins: Noda, N.; Yoda, S.; Kawasaki, T.; Miyahara, Y. *Chem. Pharm. Bull*. **1992**, *40*, 3163.

(4) Orizabins: Noda, N.; Ono, M.; Miyahara, K.; Kawasaki, T.; Okabe, M. *Tetrahedron* **1987**, *43*, 3889.

(5) Multifidins: Ono, N.; Honda, F.; Karahashi, A.; Kawasaki, T.; Miyahara, K. *Chem. Pharm. Bull*. **1997**, *45*, 1955.

(6) Stoloniferins: (a) Noda, N.; Takahashi, N.; Miyahara, K.; Yang, C.-R. *Phytochemistry* **1998**, *48*, 837. (b) Noda, N.; Takahashi, N.; Kawasaki, T.; Miyahara, K.; Yang, C.-R. *Phytochemistry* **1994**, *36*, 365.

(7) Operculins: (a) Ono, M.; Nishi, M.; Kawasaki, T.; Miyahara, K. *Chem. Pharm. Bull*. **1990**, *38*, 2986. (b) Ono, M.; Fukunaga, T.; Kawasaki, T.; Miyahara, K. *Chem. Pharm. Bull*. **1990**, *38*, 2650.

(8) Tuguajalapins: Noda, N.; Tsuji, K.; Miyahara, K.; Yang, C.-R. *Chem. Pharm. Bull*. **1994**, *42*, 2011.

(9) Mammosides: (a) Kitagawa, I.; Ohashi, K.; Baek, N. I.; Sakagami, M.; Yoshikawa, M.; Shibuya, H. *Chem. Pharm. Bull*. **1997**, *45*, 786. (b) Kitagawa, I.; Baek, N. I.; Ohashi, K.; Sakagami, M.; Yoshikawa, M.; Shibuya, H. *Chem. Pharm. Bull*. **1989**, *37*, 1131.

(10) Quamoclins: Ono, M.; Kuwabata, K.; Kawasaki, T.; Miyahara, K. *Chem. Pharm. Bull*. **1992**, *40*, 2674.

(11) For yet other families of resin glycosides see the following for leading references: (a) MacLeod, J. K.; Ward, A.; Oelrichs, P. B. *J. Nat. Prod*. **1997**, *60*, 467. (b) Kitagawa, I.; Baek, N. I.; Kawashima, K.; Yokokawa, Y.; Yoshikawa, M.; Ohashi, K.; Shibuya, H. *Chem. Pharm. Bull*. **1996**, *44*, 1680. (c) Noda, N.; Tsuji, K.; Kawasaki, T.; Miyahara, K.; Hanazono, H.; Yang, C.-R. *Chem. Pharm. Bull*. **1995**, *43*, 1061. (d) Noda, N.; Kobayashi, H.; Miyahara, K.; Kawasaki, T. *Chem. Pharm. Bull*. **1988**, *36*, 920. (e) Kitagawa, I.; Baek, N. I.; Yokokawa, Y.; Yoshikawa, M.; Ohashi, K.; Shibuya, H. *Chem. Pharm. Bull*. **1996**, *44*, 1693. (f) Fang, Y.-W.; Chai, W.-R.; Chen, S.-M.; He, Y.-Z.; Zhao, L.; Peng, J.-H.; Huang, H.-W.; Xin, B. *Carbohydr. Res*. **1993**, *245*, 259.

(12) Although most resin glycosides have been isolated from plants (*Convolvulaceae*), scattered reports on the isolation of related glycolipids from bacteria, fungi, and yeasts can be found in the literature, some of which contain fatty acid components other than jalapinolic acid as the aglycon. For an extensive compilation of relevant literature on the isolation, structure, and biological properties of such glycolipids see the following for leading references: (a) Bisht, K. S.; Gross, R. A.; Kaplan, D. L. *J. Org. Chem*. **1999**, *64*, 780. (b) See also: Legler, G. *Phytochemistry* **1965**, *4*, 29. (c) Wagner, H.; Kazmaier, P. *Tetrahedron Lett*. **1971**, *12*, 3233. (d) Kawasaki, T.; Okabe, H.; Nakatsuka, I. *Chem. Pharm. Bull*. **1971**, *19*, 1144 and literature cited therein. (e) Key, B. A.; Gray, G. W.; Wilkinson, S. G. *Biochem. J*. **1970**, *13*, 593. (f) Hirayama, T.; Kato, I. *FEBS Lett*. **1982**, *139*, 81. (g) Weber, L.; Stach, J.; Haufe, G.; Hommel, R.; Kleber, H.-P. *Carbohydr. Res*. **1990**, *206*, 13. (h) Asmer, H. J.; Lang, S.; Wagner, F.; Wray, V. *J. Am. Oil Soc*. **1988**, *65*, 1460.

medicine recipies provides additional support for this notion. As a prototype example one may quote the use of *Ipomoea batatas* in Brazilian folk medicine.[3] This plant, which has subsequently been introduced as a health food in Japan, is a rich source of various resin glycosides such as simonin I (**3**) and analogues.[3] Even more interesting are recent reports on the significant cytotoxic activity of tricolorin A (**1**) against cultured P-388 and human breast cancer cell lines.[2] This particular resin glycoside and congeners (e.g., tricolorin G (**2**)) also constitute the allelochemical principle of *Ipomoea tricolor*, a plant serving in traditional agriculture in Mexico as a cover crop for the protection of sugar cane.[2]

Tricolorin A (**1**)

Tricolorin G (**2**)

Simonin I (**3**)
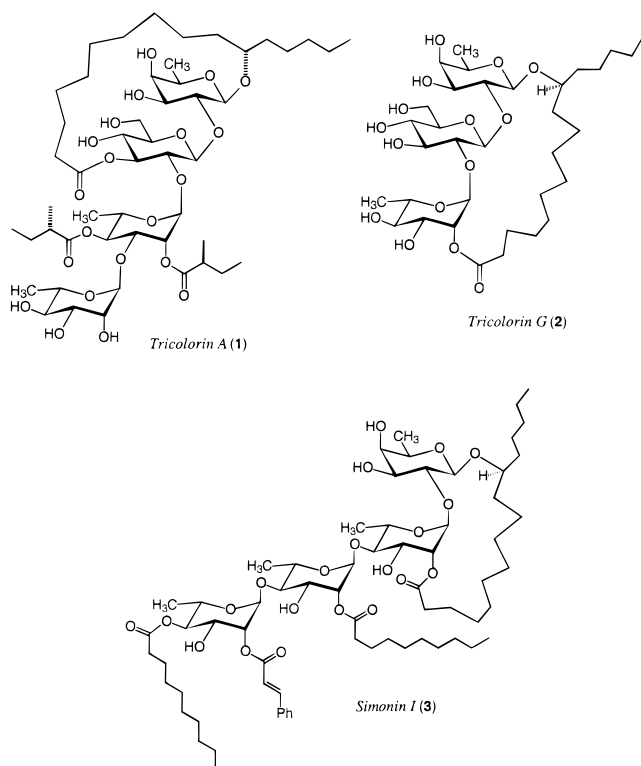
To probe these promising and diverse biological effects of resin glycosides in more detail, a synthesis-driven mapping of their structure/activity profile is called for. Because of the difficulties posed by the intricate structures of these glycolipids, however, very little work has been devoted to this area. The major challenge resides in the regioselective formation of their macrolide entities which have been cyclized in all of the syntheses published so far by conventional macrolactonization procedures.[13-15] It is clear, however, that this approach will hardly allow the formation of a wide range of structural analogues, because each new compound ultimately requires an independent multistep synthesis. Therefore, we have explored an alternative entry into this challenging family of natural products by taking advantage of the favorable profile of ring-closing metathesis (RCM) for the formation of large rings.[16] We now disclose our endeavors in this field, which led to the

total synthesis of several naturally occurring resin glycosides and provide at the same time access to a panel of advanced structural analogues due to the inherent flexibility of the chosen approach.

Results and Discussion

Total Synthesis of Tricolorin A. Our previous investigations on RCM have uncovered the essential requirements for productive macrocyclizations and have revealed the remarkable scope of this method.[17-19] From these data we concluded that the presence of polar "relay" substituents, their affinity toward the catalytically active metal species, the proper distance of these polar groups to the alkene moieties, and low steric hindrance close to the double bonds constitute decisive parameters for the productive formation of a large ring via RCM.[18]

We reasoned that all of these criteria can be met en route to **1**, provided that the large ring is closed within the lipidic disaccharide unit **4** at (or near) the site indicated in Scheme 1. The required cyclization precursor, i.e., diene **6**, can be assembled via established glycosidation strategies from D-glucose, D-fucose, and (6*S*)-undec-1-en-6-ol (**7**); the latter should be readily accessible via asymmetric synthesis. A convenient approach to the L-Rha*p*-(1→3)-L-Rha building block **5** necessary for the formation of tricolorin A as well as the assembly of **4** and **5** to the final target have already been described in the literature.[13,14]

This retrosynthetic analysis was reduced to practice as shown in Schemes 2 and 3. Thus, an enantioselective addition of dipentylzinc to 5-hexenal (**8**) in the presence of a catalyst formed in situ from Ti(O-*i*Pr)$_4$ and bis-(*R,R*)-trifluoromethanesulfon-amide (**9**)[20] provided (*S*)-**7** in good yield and in excellent enantiomeric purity (ee ≥ 99%) on a multigram scale. Its glycosylation with tri-*O*-acetyl-α-D-fucopyranosyl bromide (**10**)[21] in the presence of AgNO$_3$ on silica/alumina as the promotor[22] gave compound **11** in 69% yield, which was deacetylated (**11** → **12**) and subsequently converted into the isopropylidene acetal **13** under standard conditions.

(17) For recent reviews on RCM see the following for leading references: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Fürstner, A. *Top. Catal*. **1997**, *4*, 285. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2036. (d) Fürstner, A. *Top. Organomet. Chem*. **1998**, *1*, 37.
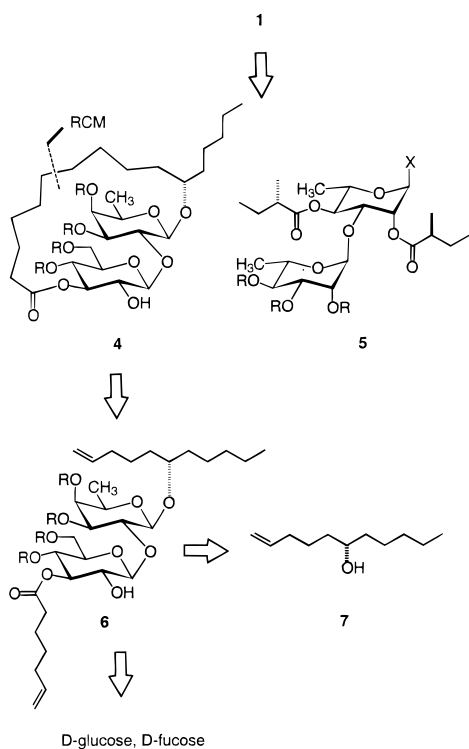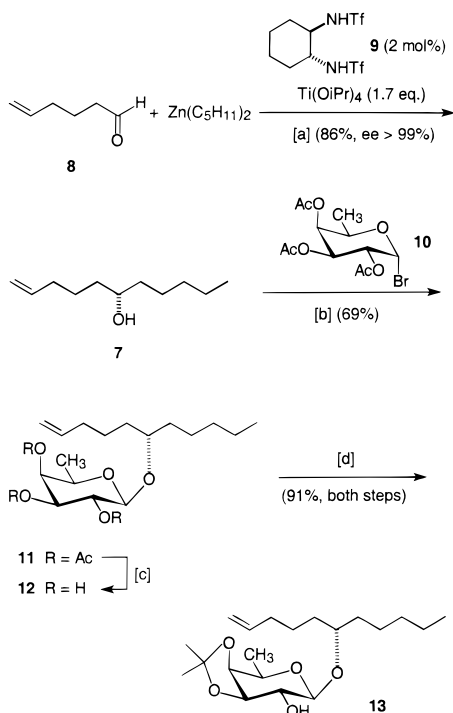
(18) For RCM-based macrocycle syntheses from our laboratory see: (a) Fürstner, A.; Langemann, K. *J. Org. Chem*. **1996**, *61*, 3942. (b) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792−803. (c) Fürstner, A.; Kindler, N. *Tetrahedron Lett*. **1996**, *37*, 7005. (d) Fürstner, A.; Langemann, K. *J. Org. Chem*. **1996**, *61*, 8746. (e) Fürstner, A.; Müller, T. *Synlett* **1997**, 1010. (f) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc*. **1997**, *119*, 9130. (g) Fürstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem*. **1999**, *64*, 2361. (h) Fürstner, A.; Seidel, G.; Kindler, N. *Tetrahedron* **1999**, *55*, 8215.

(19) For RCM-based total syntheses of natural products from other groups see the following for leading references: (a) Nicolaou, K. C.; King, N. B.; He, Y. *Top. Organomet. Chem*. **1998**, *1*, 73. (b) Hoveyda, A. H. *Top. Organomet. Chem*. **1998**, *1*, 105. (c) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc*. **1996**, *118*, 9606. (d) Bertinato, P.; Sorensen, E. J.; Meng, D.; Danishefsky, S. J. *J. Org. Chem*. **1996**, *61*, 8000. (e) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc*. **1999**, *121*, 866. (f) Magnier, E.; Langlois, Y. *Tetrahedron Lett*. **1998**, 837. (g) Kim, S. H.; Figueroa, I.; Fuchs, P. L. *Tetrahedron Lett*. **1997**, *38*, 2601. (h) Irie, O.; Samizu, K.; Henry, J. R.; Weinreb, S. M. *J. Org. Chem*. **1999**, *64*, 587. (i) Arakawa, K.; Eguchi, T.; Kakinuma, K. *J. Org. Chem*. **1998**, *63*, 4741. (j) May, S. A.; Grieco, P. A. *Chem. Commun*. **1998**, 1597.

(20) (a) Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691. (b) Knochel, P. In *Active Metals. Preparation, Characterization, Applications*; Fürstner, A., Ed.; VCH: Weinheim, 1996; p 191. (c) Knochel, P. *Synlett* **1995**, 393. (d) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; p 255.

(21) Prepared from D-fucose by acetylation (Ac$_2$O, DMAP, pyridine, 98%) and subsequent treatment with HBr (33% in HOAc) in Ac$_2$O/CH$_2$Cl$_2$ at 0 °C → room temperature; cf. Nicolaou, K. C.; Hummel, C. W.; Nakada, M.; Shibayama, K.; Pitsinos, E. N.; Saimoto, H.; Mizuno, Y.; Baldenius, K.-U.; Smith, A. L. *J. Am. Chem. Soc*. **1993**, *115*, 7625.

(13) (a) Larson, D. P.; Heathcock, C. H. *J. Org. Chem*. **1996**, *61*, 5208. (b) Larson, D. P.; Heathcock, C. H. *J. Org. Chem*. **1997**, *62*, 8406.

(14) (a) Lu, S.-F.; O'yang, Q.; Guo, Z.-W.; Yu, B.; Hui, Y.-Z. *Angew. Chem*. **1997**, *109*, 2442; *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2344. (b) Lu, S.-F.; O'yang, Q.; Guo, Z.-W.; Yu, B.; Hui, Y.-Z. *J. Org. Chem*. **1997**, *62*, 8400.

(15) Jiang, Z.-H.; Geyer, A.; Schmidt, R. R. *Angew. Chem*. **1995**, *107*, 2730; *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 2520.

(16) For a preliminary communication see: Fürstner, A.; Müller, T. *J. Org. Chem*. **1998**, *63*, 424.

Scheme 1

Scheme 2[a]

The other monosaccharide unit was obtained from 4,6-*O*-benzylidene-D-glucopyranose (**14**)[23] as outlined in Scheme 3. Peracetylation of **14** followed by deprotection of the anomeric

(22) Van Boeckel, C. A. A.; Beetz, T.; Kock-van Dalen, A. C.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 596.

(23) Barili, P. L.; Berti, G.; Catelani, G.; Cini, C.; D'Andrea, F.; Mastrorilli, E. *Carbohydr. Res.* **1995**, *278*, 43.

Scheme 3[a]
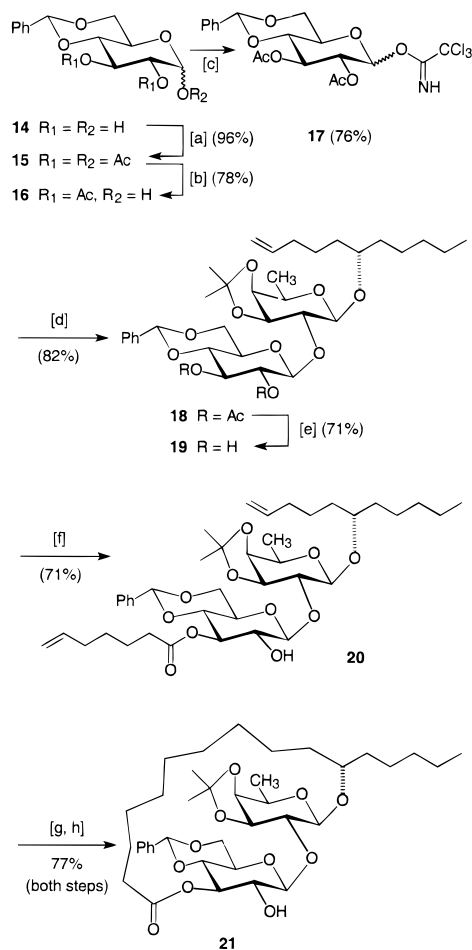
position of **15** using benzylamine gave compound **16**,[13] which readily afforded trichloroacetimidate **17** on treatment with Cl₃CCN and Cs₂CO₃ in CH₂Cl₂. Reaction of this glycosyl donor (α:β ≈ 2:1) with the fucose derivative **13** in CH₂Cl₂/hexane at −20 °C in the presence of catalytic amounts of BF₃·Et₂O cleanly provided the desired β-configurated disaccharide **18** in 82% yield.[24] Deprotection followed by acylation of the resulting diol **19** with 6-heptenoic acid in the presence of DCC and DMAP proceeded selectively at the O-3 position, thus affording ester **20** as the only product in 71% yield. The site of acylation was unambiguously assigned by NMR, and the reactivity pattern O-3 ≫ O-2 in diol **19** is in full accordance with Heathcock's observations in his macrolactonization approach toward tricolorin A.[13]

In line with our expectations, diene **20** cleanly cyclized to the desired 19-membered ring on reaction with the ruthenium carbene **22** (5 mol %)[25] in refluxing CH₂Cl₂. The fact that neither the free hydroxyl group nor any other functional group in the

(24) For pertinent reviews on the trichloroacetimidate method see: (a) Schmidt, R. R. *Angew. Chem.* **1986**, *98*, 213; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212. (b) Schmidt, R. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, p 33. (c) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21.

(25) (a) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858. (b) See also: Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem.* **1995**, *107*, 2179.

Syntheses of Resin Glycosides and Analogues

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Table 1. Screening of Different Ruthenium-Based Metathesis Precatalysts (5 mol % each) in the Cyclization of Diene **20** to Macrocycle **21**

entry	precatalyst	solvent	T (°C)	yield (%)[a]
1	**22**	CH_2Cl_2	40	77
2	**23**	toluene	80	85
3	**24**[b,c]	CH_2Cl_2	40	70

[a] After standard hydrogenation of the crude cycloalkene mixture over Pd/C in EtOH. [b] Formed in situ from [(p-cymene)RuCl$_2$]$_2$ (2.5 mol %) and PCy$_3$ (5 mol %). [c] The reaction is carried out under neon light; cf. ref 27a.

substrate interferes with RCM illustrates the excellent compatibility and selectivity of the Grubbs catalyst. Hydrogenation of the crude cycloalkene (*E/Z*-mixture) thus obtained over Pd/C afforded the desired disaccharide **21** in 77% yield over both steps. Since **21** has already been used as a key building block in previous studies on tricolorin A,[13,14] our RCM-based approach completes a formal total synthesis of this particular target. The molecular structure of product **21** was confirmed by X-ray analysis (for details see the Supporting Information).[26]

Evaluation of Other Metathesis Catalysts. Parallel to our studies on the application of RCM to natural product synthesis, we are engaged in a program on the development of new metathesis precatalysts. In this context, we identified compounds **23** and **24** (which can be formed in situ from commercially available [(p-cymene)RuCl$_2$]$_2$ and PCy$_3$) as very promising candidates which exhibit similar application profiles as the standard ruthenium carbene complex **22** introduced by Grubbs in a series of model studies.[27] They bear, however, the additional advantage of being particularly easy to make starting from commercially available reagents only.
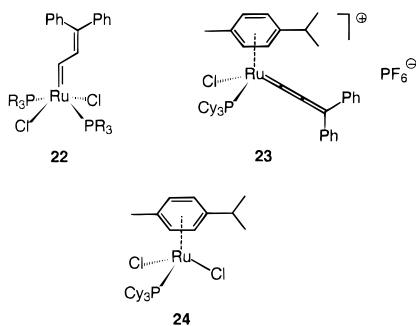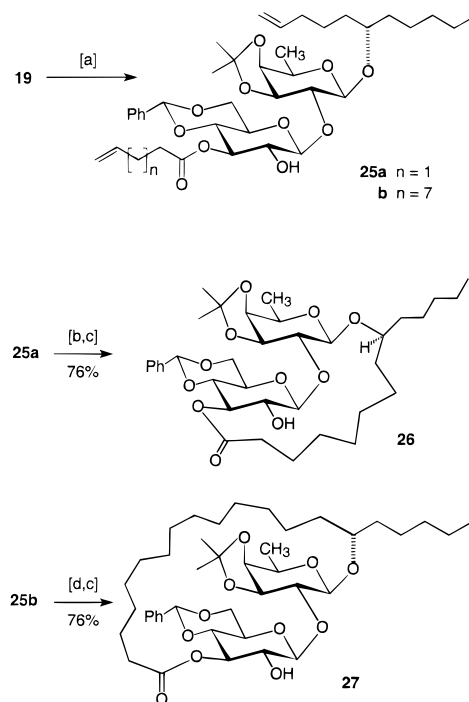

We were tempted to probe the performance of these new precatalysts in the cyclization of the highly functionalized diene **20**. Gratifyingly, both of them afford the desired macrocycle **21** (after hydrogenation of the crude cycloalkene mixture) in good to excellent yield (Table 1). This includes the most user-friendly, photochemically driven procedure for RCM outlined recently (entry 3) which uses only the commercially available ruthenium dimer [(p-cymene)RuCl$_2$]$_2$ as the precatalyst.[27a,28] These results corroborate our previous conclusions that the new ruthenium-based precatalysts compare well to the Grubbs carbene **22** in terms of yield, rate, compatibility with functional groups, and overall selectivity profile.

Tricolorin A Analogues. It should be emphasized that regio-selective esterifications of diol **19** with acids other than 6-hep-

Scheme 4[a]

[a] Conditions: [a] (**25a**): 4-pentenoic acid, DCC, DMAP (cat.), CH_2Cl_2, rt, 80%; (**25b**): 10-undecenoic acid, DCC, DMAP (cat.), CH_2Cl_2, rt, 67%; [b] **22** (20 mol %), CH_2Cl_2, reflux, 3 d; [c] H$_2$ (1 atm), Pd/C, EtOH; [d] **22** (10 mol %), CH_2Cl_2, reflux, 24 h.

tenoic acid followed by RCM of the resulting dienes allow a convenient entry into tricolorin A analogues differing from the parent compound in their lipophilic character. The biological response to such compounds may unravel as to which extent the proper balance between the hydrophilicity of the oligosaccharide segment and the lipophilicity of the macrolide entity accounts for the physiological activity of resin glycosides in general.

Therefore, we have prepared compound **26** missing two CH$_2$ units in the lactone ring as well as the significantly more lipophilic, ring-expanded analogue **27** (Scheme 4). Esterification of **19** with 4-pentenoic acid or 10-undecenoic acid delivers dienes **25a,b** which are converted into the 17-membered ring **26** and into the 23-membered macrolide **27**, respectively, upon exposure to catalyst **22** and subsequent hydrogenation of the resulting cycloalkenes (*E/Z*-mixtures) over Pd on charcoal.

Both macrocyclizations proceed well and deliver the desired products in respectable yields; it is, however, interesting to note that the *rate* of ring closure is significantly slower in the case of the pentenoic acid derivative **25a** and that a higher catalyst loading is required to achieve quantitative conversion. This behavior is very much in line with our rationale for RCM-based macrocyclizations outlined previously,[18] which emphasizes the importance of the *distance* between the polar groups and the alkenes to be metathesized. According to this model 4-pentenoates constitute borderline cases, because the reactivity of the emerging carbenes will be attenuated by the formation of six-membered chelate structures such as **A** (Scheme 5). It is the

(26) A full report on the X-ray structure of compound **21** can be found in Lehmann, C. W.; Rust, J.; Fürstner, A., Müller, T. *Z. Kristallogr.*, submitted for publication.

(27) (a) Fürstner, A.; Ackermann, L. *Chem. Commun.* **1999**, 95. (b) Fürstner, A.; Picquet, M.; Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **1998**, 1315. (c) See also: Fürstner, A.; Hill, A. F.; Liebl, M.; Winton-Ely, J. D. E. T. *Chem. Commun.* **1999**, 601.

(28) The precise mode of action of this photochemically driven catalyst system is yet unknown. Although precatalyst **24** is also effective in toluene, it is best employed in CH_2Cl_2; cf. ref 27a. As pointed out by one reviewer, one can speculate if CH_2Cl_2 is activated by the ruthenium complex, thus serving as the actual carbene source. See the following for a leading reference on the formation of ruthenium carbene complexes by oxidative insertion into *gem*-dihaloalkanes: Belderrain, T. R.; Grubbs, R. H. *Organometallics* **1997**, *16*, 4001.

Scheme 5
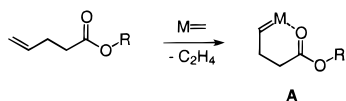
Scheme 6[a]
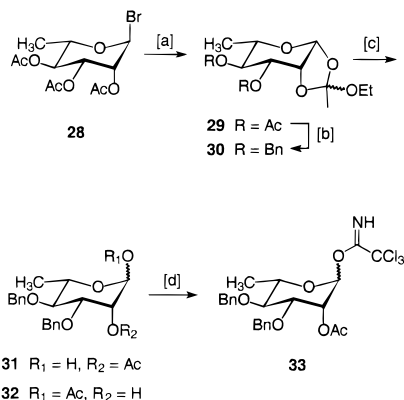
a Conditions: [a] *sym*-collidine, EtOH, Bu$_4$NI, 80 °C, 8 h, 66%; [b] BnBr, KOH, THF, reflux, 8 h, 78%; [c] HOAc/H$_2$O (4:1), rt, 16 h; [d] Cs$_2$CO$_3$, Cl$_3$CCN, CH$_2$Cl$_2$, rt, 14 h, 46%.

stability of such intermediates which decides if the macrocyclization reaction will proceed or if the catalyst is merely sequestered in an unproductive form.[18]

Total Synthesis of Tricolorin G. Not only is compound **19** the key intermediate en route to tricolorin A **1** and analogues thereof, but it also opens access to tricolorin G **2**, in which jalapinolic acid spans a trisaccharidic core. For this purpose, a properly functionalized rhamnose unit must be attached to the less reactive C-2″ hydroxyl group of diol **19** prior to the crucial RCM reaction.

The required rhamnosyl donor **33** is prepared as outlined in Scheme 6. Thus, reaction of 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl bromide (**28**)[29] with *sym*-collidine and EtOH delivers product **29** on a multigram scale, the acetyl groups of which can then be replaced by benzyl ethers. Hydrolysis of the ortho ester group in **30** with aqueous acetic acid leads to the formation of a mixture of acetates **31** and **32**.[30] These individual compounds, however, must not be separated because they converge into a single trichloroacetimidate, **33**, on exposure to Cl$_3$CCN and Cs$_2$CO$_3$ in CH$_2$Cl$_2$ as previously outlined for a related case in the glucose series.[31] This outcome reflects a rapid base-induced migration of the acetyl group, converting **32** into **31** prior to the formation of the trichloroacetimidate function.

In view of the reactivity pattern of diol **19** (vide supra), its more nucleophilic 3″-OH group must be blocked prior to the crucial glycosidation step. This was achieved by reacting it with (*n*-Bu$_3$Sn)$_2$O in toluene, followed by exposure of the resulting stannyl ether to (*n*-Bu)$_4$NI and benzyl bromide (Scheme 7).[32] Surprisingly, however, this benzylation turned out to be less selective than the acylations carried out within the syntheses of tricolorin A and analogues, affording a ~3.2:1 mixture of compounds **34** and **36**. Since these regioisomers can be readily separated by conventional flash chromatography, we did not

(29) Prepared from L-rhamnose by acetylation (Ac$_2$O, DMAP, pyridine, 98%) and subsequent treatment with HBr (33% in HOAc) in Ac$_2$O/CH$_2$Cl$_2$ at 0 °C → room temperature; cf. Experimental Section.

(30) The same sequence of reactions using D-glucose instead of L-rhamnose as the starting material was used during a recent total synthesis of caloporoside; cf. Fürstner, A.; Konetzki, I. *J. Org. Chem.* **1998**, *63*, 3072.

(31) Fürstner, A.; Konetzki, I. *Tetrahedron Lett.* **1998**, *39*, 5721.

(32) David, S. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997; p 69.

Scheme 7[a]
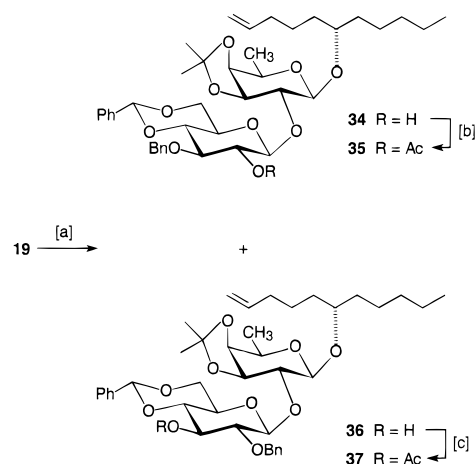
a Conditions: [a] (i) (Bu$_3$Sn)$_2$O, toluene, reflux, 6 h; (ii) Bu$_4$NI, BnBr, 2.5 h, **34** (57%) + **36** (18%); [b] Ac$_2$O, DMAP, CH$_2$Cl$_2$, rt, 92%; [c] Ac$_2$O, Et$_3$N, DMAP(cat.), CH$_2$Cl$_2$, 80%.

optimize this step any further. Reaction of aliquots of **34** and **36** with Ac$_2$O in CH$_2$Cl$_2$/DMAP gave acetates **35** and **37**; the detailed analysis of their 2D NMR spectra allowed an unequivocal differentiation between the regioisomers and confirmed that the major product formed in the benzylation reaction is the desired compound **34** necessary for the total synthesis of tricolorin G.

Reaction of alcohol **34** with trichloroacetimidate **33** catalyzed by BF$_3$·Et$_2$O in CH$_2$Cl$_2$/hexane affords trisaccharide **38** in reasonable yield (Scheme 8).[24] Replacement of the acetyl group by a 6-heptenoic acid ester delivers compound **40** without incident and sets the stage for the crucial ring closure reaction. Exposure of diene **40** to catalytic amounts of ruthenium carbene **22** in refluxing CH$_2$Cl$_2$ and subsequent hydrogenation of the resulting mixture of cycloalkenes in the presence of Wilkinson's catalyst afford fully protected tricolorin G (**41**) in remarkable 93% yield over both steps. Due to the lability of the glycosidic linkages in this compound, its deprotection turned out to be somewhat delicate and must be carried out under carefully controlled conditions. For this purpose, the acetal functions are cleaved by means of dilute trifluoroacetic acid in aqueous CH$_2$Cl$_2$ prior to removal of the residual benzyl groups with H$_2$ in the presence of Pd/C. Quite unexpectedly, we noticed that this final hydrogenolysis only goes to completion if trifluoroacetic acid is added to the methanolic medium. Because of the polarity of the resulting product **2**, the final purification has to be carried out by preparative HPLC, providing tricolorin G in 49% yield and completing the first total synthesis of this complex glycolipid. The analytical properties and in particular the 600 MHz NMR data of the synthetic material are in full agreement with those reported in the literature for the natural product.[2c]

Synthesis of Tricolorin G Analogues. Upon submitting the regioisomeric product **36** obtained in the monobenzylation step of diol **19** described above to the same sequence of reactions, we were able to obtain compound **46** which constitutes an analogue of tricolorin G differing from the natural product only in the site of attachment of the rhamnopyranose ring to the residual sugar backbone.

As shown in Scheme 9, this synthesis proceeds smoothly, with the formation of the macrocycle via RCM (**44** → **45**) again being a highly productive transformation. Very much in line with the experiences encountered during the total synthesis of **2**, the deprotection sequence requires carefully controlled reaction conditions due to the inherent lability of the deoxysugar

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Scheme 8[a]
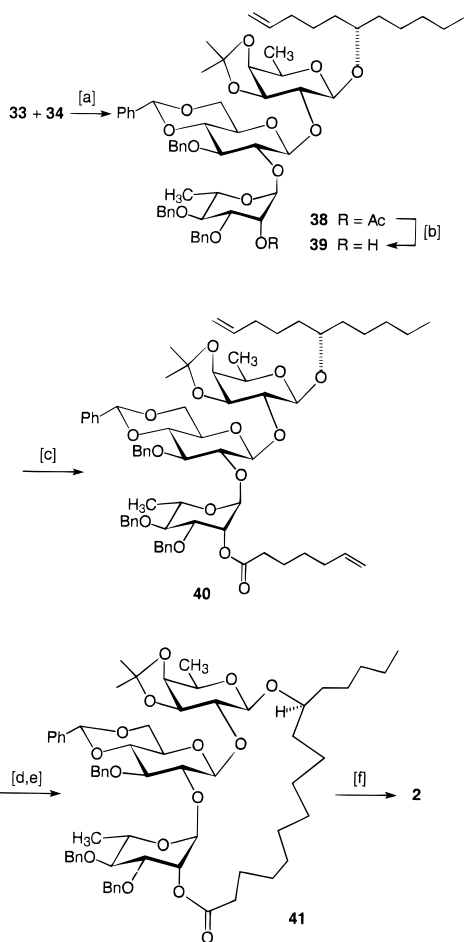
[a] Conditions: [a] BF$_3$·Et$_2$O (cat.), CH$_2$Cl$_2$/*n*-hexane, −20 °C, 1 h, 53%; [b] KOMe, MeOH, rt, 4 h; [c] 6-heptenoic Acid, DCC, DMAP (cat.), CH$_2$Cl$_2$, rt, 84% (over both steps); [d] **22** (10 mol %), CH$_2$Cl$_2$, reflux, 22 h; [e] H$_2$ (1 atm), RhCl(PPh$_3$)$_3$ (cat.), EtOH, 93% (over both steps); [f] (i) F$_3$CCOOH, CH$_2$Cl$_2$, rt, 3 h; (ii) H$_2$ (1 atm), Pd/C, MeOH, F$_3$CCOOH (cat.), 49%.

glycosidic linkages in compound **45**. Once again, traces of trifluoroacetic acid turned out to be necessary to guarantee complete debenzylation on exposure to H$_2$ and Pd/C in MeOH as the solvent. Under these conditions, however, a partial methanolysis of the lactone ring could not be avoided, providing methyl ester **47** as a minor byproduct in addition to the desired macrolide **46**.

The Common Disaccharide Core of the Simonin, Operculin, Tuguajalapin, Orizabin, Mammoside, Quamoclin, and Stoloniferin Family of Resin Glycosides. Despite the great overall diversity of naturally occurring resin glycosides, many of them share common structural motifs. As already mentioned in the Introduction, the disaccharide entity L-Rha*p*-(1→2)-D-Fuc (**48**) carrying a macrolactone ring derived from jalapinolic
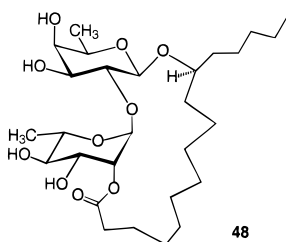
acid is prominently featured in a large subset comprising several

Scheme 9[a]
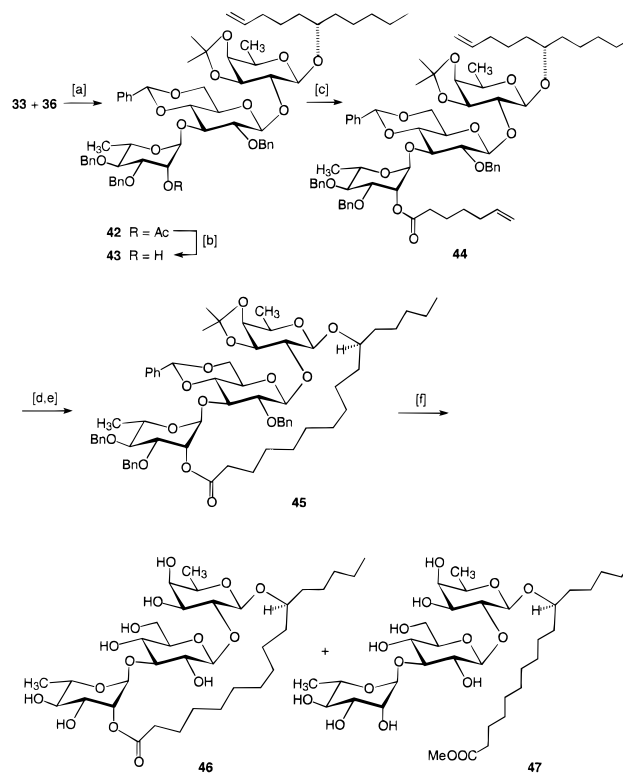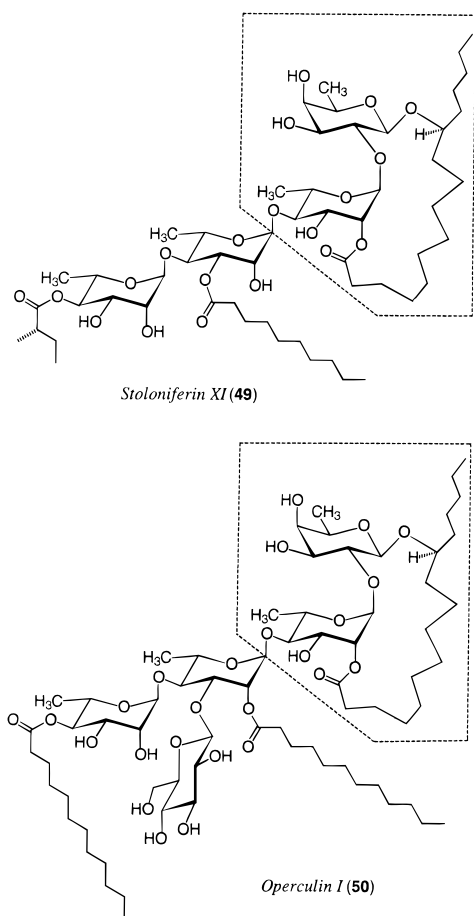

[a] Conditions: [a] BF$_3$·Et$_2$O (cat.), CH$_2$Cl$_2$/*n*-hexane, −20 °C, 1 h, 59%; [b] KOMe, MeOH, rt, 4 h; [c] 6-heptenoic Acid, DCC, DMAP (cat.), CH$_2$Cl$_2$, rt, 82% (over both steps); [d] **22** (10 mol %), CH$_2$Cl$_2$, reflux, 22 h; [e] H$_2$ (1 atm), RhCl(PPh$_3$)$_3$ (cat.), EtOH, 83% (over both steps); [f] (i) F$_3$CCOOH, CH$_2$Cl$_2$, rt, 3 h; (ii) H$_2$ (1 atm), Pd/C, MeOH, F$_3$CCOOH (cat.), 24 h, **46** (56%) + **47** (13%).

members of the simonin,[3] operculin,[7] tuguajalapin,[8] orizabin,[4] mammoside,[9] quamoclin,[10] and stoloniferin families.[6] Two prototype examples of these groups of natural products (i.e., **49** and **50**) are displayed in Scheme 10 in addition to simonin I (**3**) already mentioned in the Introduction. Since both building blocks necessary for the construction of this highly conserved structural motif **48** have already been used for the total syntheses of tricolorin A and G outlined above, we were prompted to extend our RCM approach to this particularly important structural subunit.

As shown in Scheme 11, glycosidation of D-fucopyranoside **13** with trichloroacetimidate **33** under standard conditions provides product **51** in 69% yield. Saponification of the acetyl residue and attachment of a 6-heptenoate moiety deliver substrate **53** required for the subsequent ring-closing metathesis reaction. Once again, this step proceeds cleanly in the presence of ruthenium carbene **22**; subsequent hydrogenation of the resulting *E/Z*-mixture of cycloalkenes in the presence of catalytic amounts of RhCl(PPh$_3$)$_3$ delivers product **54** in 78% yield over two steps. Gratifyingly, we noticed that hydrogenolysis of this product (1 atm of H$_2$, Pd/C) in HOAc/MeOH proceeds in a stepwise manner, with the benzyl group at O-4″ being significantly more labile. Therefore, it is possible to obtain the selectively deprotected compound **55** in good yield which is ideally suited for incorporation into all types of resin glycosides mentioned above.
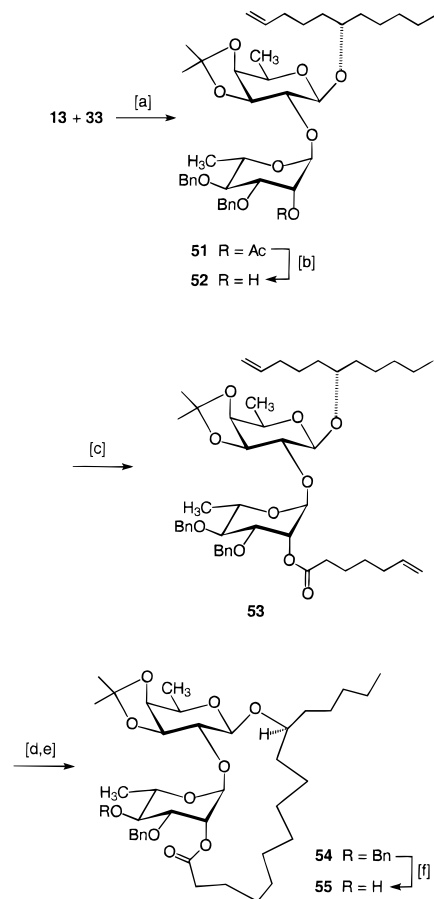
Synthesis of Jalapinolic Acid. In view of the efficiency by which jalapinolic acid lactones can be formed on various sugar templates (vide supra), it is not surprising to find that the parent jalapinolic acid (**58**) itself can also be obtained by a simple RCM approach (Scheme 12).

Scheme 10

Stoloniferin XI (49)

Operculin I (50)

Scheme 11[a]

[a] Conditions: [a] BF$_3$·Et$_2$O (cat.), CH$_2$Cl$_2$/n-hexane, −20 °C, 1.5 h, 69%; [b] KOMe, MeOH, rt, 3 h; [c] 6-heptenoic acid, DCC, DMAP (cat.), CH$_2$Cl$_2$, rt, 77% (over both steps); [d] **22** (10 mol %), CH$_2$Cl$_2$, reflux, 16 h; [e] H$_2$ (1 atm), RhCl(PPh$_3$)$_3$ (cat.), EtOH, rt, 78% (over both steps); [f] H$_2$ (1 atm), Pd/C, MeOH/HOAc (250:1), 2.5 d, 59%.

Scheme 12[a]

[a] Conditions: [a] 6-heptenoic acid, DCC, DMAP (cat.), CH$_2$Cl$_2$, rt, 89%; [d] **22** (5 mol %), CH$_2$Cl$_2$, reflux, 2.5 d; [e] H$_2$ (1 atm), Pd/C, EtOH, 8 h, rt, 43% (over both steps); [d] KOH, MeOH, reflux, 1.5 d, 87%.
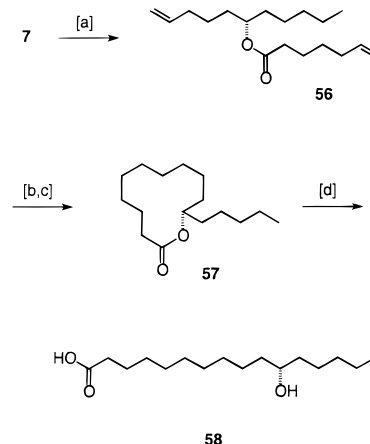
Thus, esterification of enantiomerically pure alcohol **7** with 6-heptenoic acid provides ester **56** which cyclizes under high dilution conditions on exposure to catalytic amounts of **22** or by means of the neon light driven protocol using **24** as the precatalyst (formed in situ from commercially available [(*p*-cymene)RuCl$_2$]$_2$ and PCy$_3$). Hydrogenation of the resulting macrocycle affords (11*S*)-jalapinolic acid lactone (**57**). The somewhat lower yield obtained in this case is mainly caused by difficulties in separating the cycloalkene mixture formed by RCM from traces of unreacted starting material. Saponification of **57** under fairly harsh conditions provides enantiomerically pure jalapinolic acid (**58**) in 87% yield.

Conclusions. As few as three well accessible sugar building blocks are necessary for the first total synthesis of the glycolipid tricolorin G (**2**), a formal total synthesis of its congener tricolorin A (**1**), and the preparation of the common core segment **55** found in the simonin, operculin, tuguajalapin, orizabin, mammoside, quamoclin, and stoloniferin families of resin glycosides. Moreover, various analogues of these bioactive natural products such as **26**, **27**, **46**, and **47** have been obtained in excellent yields from the very same starting materials. Finally, a short synthesis of jalapinolic acid (**58**) as the common lipophilic component of all resin glycosides is outlined based upon two metal-catalyzed C−C bond formations. This flexibility in synthetic planning results from the exceptional performance and the *inherently modular character of ring-closing metathesis* (RCM) for the formation of macrocyclic rings which constitutes the key step in all syntheses outlined in this paper. It is worth mentioning that the classical ruthenium carbene complex **22** introduced by Grubbs[25] and the more readily accessible "second-generation" precatalysts **23** and **24**[27] perform similarly well. The

ease by which these exceedingly useful reagents allow specific modifications to be made even on polyfunctional arrays highly recommends RCM as a *strategic* tool for the total synthesis of complex natural products as well as for applications to medicinal chemistry, where detailed structure/activity correlations require systematic variations of given lead structures. The results

summarized above confirm this notion,[33] because the syntheses of the same panel of compounds by more conventional methodology would require unreasonable efforts. Current work in our laboratory intends to corroborate this aspect and to expand the scope of metathetic transformations even further.[34]

Experimental Section

See the Supporting Information.

(33) The epothilone case constitutes a most notable precedent for this conclusion. For extensive reviews on how the SAR of this promising anticancer agent has been established using RCM-based synthesis strategies see ref 19a,d,j and the following for leading references: (a) Nicolaou; K. C.; Roschangar, F.; Vourloumis, D. *Angew. Chem., Int. Ed.* **1998**, *37*, 2014. (b) Nicolaou, K. C.; He, Y.; Roschanger, F.; King, N. P.; Vourloumis, D.; Li, T. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 84. (c) Nicolaou, K. C., Vallberg, H.; King, N. P.; Roschanger, F.; He, Y.; Vourloumis, D.; Nicolaou, C. G. *Chem. Eur. J.* **1997**, *3*, 1957. (d) Nicolaou, K. C.; Vourloumis, D.; Li, T.; Pastor, J.; Wissinger, N.; He, Y.; Ninkovic, S.; Sarabia, F.; Vallberg, H.; Roschanger, F.; King, N. P.; Finlay, M. R. V.; Giannakakou, P.; Verdier-Pinard, P.; Hamel, E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2097. (e) Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073. (f) Su, D.-S.; Balog, A.; Meng, D.; Bertinato, P.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L.; Horwitz, S. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2093 and literature cited therein.

Supporting Information Available: Full experimental section, compilation of the instrumentation used, details concerning the X-ray structure of compound **21**, list of IR data of all new compounds, and copies of the NMR spectra of keyintermediates and products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA991361L

(34) (a) For the first examples of ring-closing diyne metathesis see: Fürstner, A.; Seidel, G. *Angew. Chem.* **1998**, *110*, 1758; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1734. (b) For Pt(II)-catalyzed enyne metathesis reactions see: Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305. (c) For metathesis in supercritical carbon dioxide see: Fürstner, A.; Koch, D.; Langemann, K.; Leitner, W.; Six, C. *Angew. Chem.* **1997**, *109*, 2562; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2466.