Ring-Closing Alkyne Metathesis. Application to the Total Synthesis of Sophorolipid Lactone

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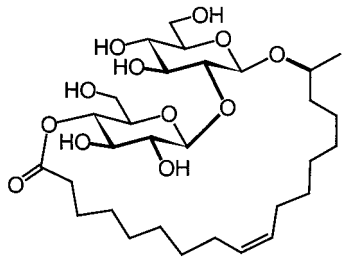
The first total synthesis of a major component of the microbial biosurfactant sophorolipid has been achieved. This approach to the 26-membered macrolide **1** containing a *Z*-configured alkene group in its lipidic tether spanning the sophorose backbone is based on a ring-closing metathesis reaction of diyne **21** catalyzed by Mo[N(t-Bu)(Ar)]$_3$ (**5**; Ar = 3,5-dimethylphenyl) activated in situ by CH_2Cl_2, followed by Lindlar reduction of the resulting cycloalkyne **22**. The two β-glycosidic linkages of compound **21** were installed by means of the glucal epoxide method and a modified Koenigs−Knorr reaction promoted by AgOTf/lutidine, respectively.

Introduction

The yeast *Candida bombicola* is able to grow even on pure hydrocarbons as the only carbon source. It emulsifies hydrophobic culture media by the production of extracellular biosurfactants called sophorolipids (SL) that can be obtained in large amounts by fermentation under optimized conditions.[1] These glycolipids are of growing commercial interest as biodegradable emulsifiers with low critical micelle concentrations that can be easily produced from cheap raw materials as diverse as *n*-alkanes, vegetable oils, carbohydrates, and even industrial waste products (yields of 70−135 g of SL per liter of the fermentation broth can be routinely obtained).[2−4] Various applications of SL in the cosmetic industry, for pharmaceutical formulations, in food production, and even for technical purposes such as oil pollution abatement of seawater can be envisaged and have been claimed in the patent literature.[2−4]

Native SL is a rather complex mixture of up to 14 different compounds.[5] Although its composition and properties strongly depend on both the fermentation conditions and the carbon sources used as the culture medium, the sophorose glycoside **2**[6] and the 1′,4″-lactone **1** derived from it always constitute major components of this mixture.[7] All other constituents essentially differ from these parent compounds in the acylation pattern of the remaining −OH groups.[8]



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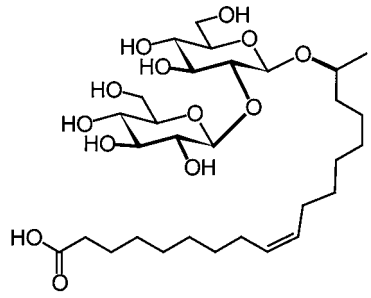

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Little is known about the (physico)chemical and, in particular, the biological properties of the individual compounds such as **1** and **2**, although this information may be crucial for future applications. While SL is generally considered to be a nontoxic biodetergent,[3e]

(1) (a) Gorin, P. A. J.; Spencer, J. F. T.; Tulloch, A. P. *Can. J. Chem.* **1961**, *39*, 846. (b) Tulloch, A. P.; Spencer, J. F. T.; Gorin, P. A. J. *Can. J. Chem.* **1962**, *40*, 1326.

(2) Review: Karanth, N. G. K.; Deo, P. G.; Veenanadig, N. K. *Curr. Sci.* **1999**, *77*, 116.

(3) See the following for leading references and literature cited therein: (a) Asmer, H.-J.; Lang, S.; Wagner, F.; Wray, V. *J. Am. Oil Chem. Soc.* **1988**, *65*, 1460. (b) Otto, R. T.; Daniel, H.-J.; Pekin, G.; Müller-Decker, K.; Fürstenberger, G.; Reuss, M.; Syldatk, C. *Appl. Microbiol. Biotechnol.* **1999**, *52*, 495. (c) Zhou, Q.-H.; Kosaric, N. *J. Am. Oil Chem. Soc.* **1995**, *72*, 67. (d) Daniel, H.-J.; Otto, R. T.; Binder, M.; Reuss, M.; Syldatk, C. *Appl. Microbiol. Biotechnol.* **1999**, *51*, 40. (e) Inoue, S.; Ito, S. *Biotechnol. Lett.* **1982**, *4*, 3. (f) Krivobok, S.; Guiraud, P.; Seigle-Murandi, F.; Steiman, R. *J. Agric. Food Chem.* **1994**, *42*, 1247. (g) Cooper, D. G.; Paddock, D. A. *Appl. Environ. Microbiol.* **1984**, *47*, 173.

(4) For a particularly efficient production see: Marchal, R.; Lemal, J.; Sulzer, C. U.S. Patent 5,616,479.

(5) For investigations into the composition of native SL and the determination of individual components see: (a) Davila, A. M.; Marchal, R.; Monin, N.; Vandecasteele, J. P. *J. Chromatogr.* **1993**, *648*, 139. (b) de Koster, C. G.; Heerma, W.; Pepermans, H. A. M.; Groenewegen, A.; Peters, H.; Haverkamp, J. *Anal. Biochem.* **1995**, *230*, 135.

(6) Sophorose is the trivial name for the disaccharide 2-*O*-(β-D-glucopyranosyl)-D-glucopyranose.

(7) Structure elucidation: Tulloch, A. P.; Hill, A.; Spencer, J. F. T. *Can. J. Chem.* **1968**, *46*, 3337. For a more recent NMR study confirming the earlier results, see ref 3a.

(8) (a) Derivatives of lactone **1** bearing acetyl groups at the 6′- and/or the 6″-OH of the sophorose backbone are particularly abundant in native SL. It is known, however, that they are converted into **1** upon enzymatic hydrolysis without concomitant opening of the lactone ring.[3a,b] (b) For a brief study of the inhibitory effects of lactone 6′,6″-diacetate on the growth of various yeasts see: Ito, S.; Kinta, M.; Inoue, S. *Agric. Biol. Chem.* **1980**, *44*, 2221.

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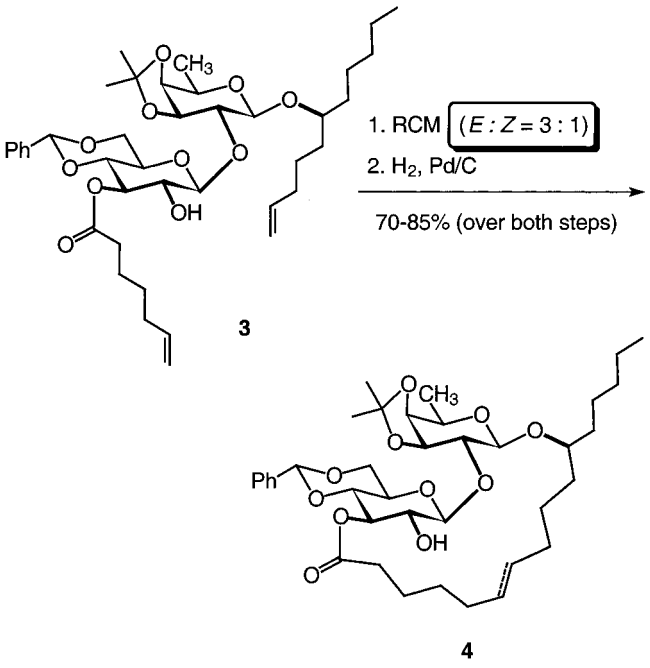
recent reports indicate that *purified* samples display significant cytotoxic effects (LC_{50} 15 mg L^{-1}) that are greater than those of the native product mixture.[3b] SL also inhibits the activity of phospholipid- and Ca^{2+}-dependent protein kinase[9] and can induce cell differentiation of the human promyelocytic leucemia cell lines HL 60 into monocytes.[9] Moreover, it is well-known that many glycolipids elicit a strong immune response in humans,[10] an aspect that has not been addressed with regard to SL. In view of these preliminary results, it is certainly called for to map the biological profile of the major constituents of SL in more detail prior to potential applications in food, cosmetics, or pharmaceutical formulations. Given the difficulties in obtaining analytically pure samples by conventional separation techniques, we were prompted to develop a concise preparative route to the parent sophorolipid lactone **1**, from which acid **2** can also be obtained upon simple hydrolysis. Rather than relying on a conservative macrolactonization strategy,[11] however, we considered the intricate structure of this target as a testing ground for probing new methodology. The results of this investigation are summarized below.

Results and Discussion

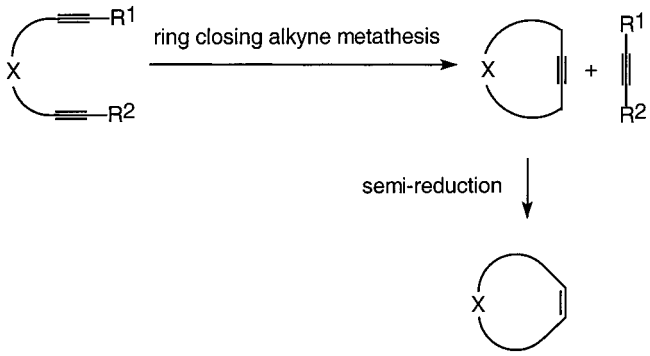
Strategy and Retrosynthetic Analysis. In recent work, we have outlined an efficient entry into bioactive resin glycosides produced by higher plants based on the excellent application profile of various ruthenium catalysts for ring-closing olefin metathesis (RCM).[12] One of the products formed by this route was the disaccharide lactone **4**, a key building block for the total synthesis of tricolorin A (Scheme 1). Although this compound bears considerable resemblance to sophorolipid lactone, suggesting that RCM could also be employed en route to **1**,[13,14] a more detailed assessment of the projected case calls for a revised strategy.

RCM of diene **3** invariably delivered lactone **4** as a mixture of stereoisomers (E:$Z \approx 3$:1) at the newly formed double bond independent of the catalyst used.[15] This outcome is characteristic for RCM-based macrocyclizations in which the (*E*)-alkene is (strongly) favored in most of the recorded cases.[13−16] In view of this compelling precedence, a stereoselective synthesis of **1** containing a *Z*-configured alkene moiety in its lipidic tether based on conventional RCM cannot be expected.

Scheme 1



Scheme 2



In contrast, ring-closing metathesis of diynes constitutes a more promising strategy that allows the stereochemical issue to be geared to the cyclization event. In combination with a Lindlar-type reduction of the resulting cycloalkynes, this method opens a convenient and stereoselective entry into macrocyclic (*Z*)-alkenes (Scheme 2)[17] and may therefore constitute the method of choice for the total synthesis of sophorolipid lactone **1**. Alkyne metathesis, however, is still in its infancy as compared with alkene metathesis, which over the past decade has evolved into a mature tool for advanced organic synthesis.[13,18] Although no application of alkyne metathesis to

(9) Isoda, H.; Kitamoto, D.; Shinmoto, H.; Matsumura, M.; Nakahara, T. *Biosci. Biotechn. Biochem*. **1997**, *61*, 609.

(10) For a general review on glycolipids see: Li, Y.-T.; Li, S.-C. *Adv. Carbohydr. Chem. Biochem*. **1982**, *40*, 235.

(11) A recent report on an enzyme-catalyzed macrocyclization of acid **2** did not afford lactone **1** but resulted in esterification with the primary alcohol groups of the sophorose, i.e., with either the 6′-OH or the 6″-OH position, respectively. Cf.: Bisht, K. S.; Gross, R. A.; Kaplan, D. L. *J. Org. Chem*. **1999**, *64*, 780.

(12) (a) Fürstner, A.; Müller, T. *J. Am. Chem. Soc*. **1999**, *121*, 7814. (b) Fürstner, A.; Müller, T. *J. Org. Chem*. **1998**, *63*, 424. (c) Lehmann, C. W.; Fürstner, A.; Müller, T. *Z. Kristallogr*. **2000**, *215*, 114.

(13) For the most recent review on alkene and alkyne metathesis see: Fürstner, A. *Angew. Chem*. **2000**, *112*, 3140; *Angew. Chem., Int. Ed*. **2000**, *39*, 3012.

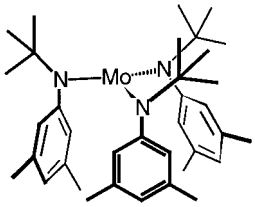
(14) (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Fürstner, A. *Top. Catal*. **1997**, *4*, 285. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2036. (d) Fürstner, A. *Top. Organomet. Chem*. **1998**, *1*, 37. (e) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Methathesis Polymerization*, 2nd ed.; Academic Press: New York, 1997.

(15) The choice of the catalyst had no appreciable effect on the *E*:*Z* ratio, although their structures are substantially different; the following three RCM catalysts have been employed en route to **4**. (a) $Cl_2(PCy_3)_2Ru{=}CHCH{=}CPh_2$: Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc*. **1993**, *115*, 9858. (b) (*p*-cymene)$(PCy_3)RuCl_2$/*hν*: Fürstner, A.; Ackermann, L. *Chem. Commun*. **1999**, 95. (c) [(*p*-cymene)-$(PCy_3)RuCl(=C=C=CPh_2)]^+PF_6^-$: Fürstner, A.; Picquet, M.; Bruneau, C.; Dixneuf, P. H. *Chem. Commun*. **1998**, 1315. Fürstner, A.; Liebl, M.; Lehmann, C. W.; Picquet, M.; Kunz, R.; Bruneau, C.; Touchard, D.; Dixneuf, P. H. *Chem. Eur. J*. **2000**, *6*, 1847.

(16) Further examples of RCM-based macrocyclizations from our laboratory in which the *E* isomer largely dominates or is even the only product formed: (a) Fürstner, A.; Grabowski, J.; Lehmann, C. W. *J. Org. Chem*. **1999**, *64*, 8275. (b) Fürstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem*. **1999**, *64*, 2361. (c) Fürstner, A.; Seidel, G.; Kindler, N. *Tetrahedron* **1999**, *55*, 8215. (d) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc*. **1997**, *119*, 9130. (e) Fürstner, A.; Langemann, K. *J. Org. Chem*. **1996**, *61*, 3942. (f) Fürstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem*., in press.

(17) Fürstner, A.; Seidel, G. *Angew. Chem*. **1998**, *110*, 1758; *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 1734.

a target as densely functionalized as **1** has been reported to date, the known examples[19−24] are highly promising and encouraged us to implement this emerging methodology into the present study. Among the catalysts presently available, a molybdenum species formed in situ from Mo[N(t-Bu)(Ar)]$_3$ (**5**; Ar = 3,5-dimethylphenyl) and CH_2Cl_2 seems to be the most promising with regard to efficiency and tolerance toward polar functional groups in the substrate.[20,21,25]



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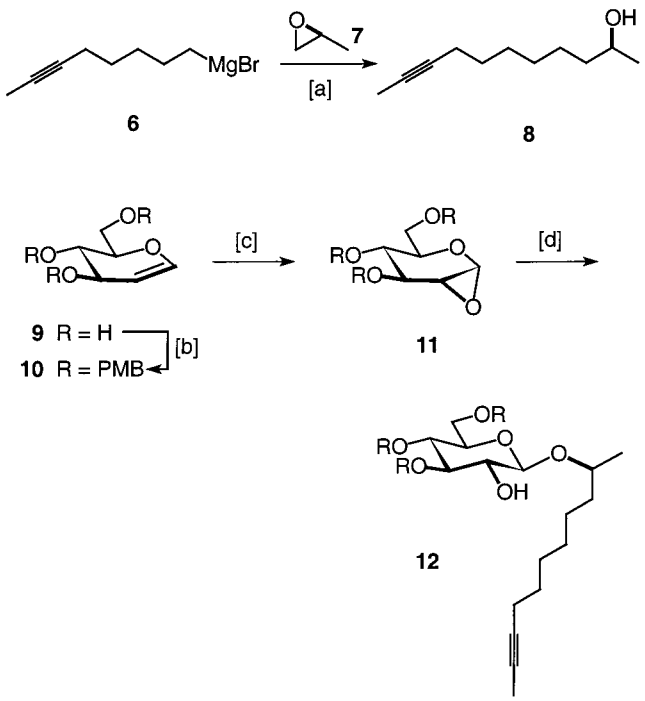
Another important issue en route to **1** concerns the choice of the proper protecting groups. They must be cleaved in the final step of the sequence without compromising the integrity of the unsaturated lactone ring. This precludes basic (saponification) as well as acidic conditions (acyl migration), while hydrogenolysis is obviously incompatible with the double bond in the octadecenoic acid tether. With these stringent criteria in mind, we have designed a synthesis that converges to *p*-methoxybenzyl (PMB) ethers as the only residual protecting groups for the −OH functions in the penultimate step. The oxidative conditions used for their deprotection should be tolerated by the sensitive target.[26]

Total Synthesis of Sophorolipid Lactone. Our synthesis of sophorolipid lactone **1** requires enantiomerically pure alcohol **8** (ee ≥ 99.5%) for the first glycosylation step, which was conveniently obtained by a Cu(I)-catalyzed ring-opening reaction of (*S*)-propenoxide **7**[27] with the Grignard reagent **6** derived from 1-bromo-6-octyne in THF according to a procedure previously reported by our laboratory.[28] The other starting material is commercially available D-glucal **9** that was protected as tri-*O*-PMB ether **10** under conventional conditions (Scheme 3). These two components were then glycosylated using Danishefsky's glycal epoxide methodology.[29] Thus, substrate **10** was treated with a slight excess of dimethyldioxirane in CH_2Cl_2 at −25 °C,[30] all volatiles were stripped off in vacuo, and the resulting epoxide **11** was reacted with alcohol **8** in THF in the presence of $ZnCl_2$ (2 equiv) as the Lewis-acidic promoter. Although this reaction afforded the desired *β*-configured product **12** in only 42% isolated yield, other conceivable approaches to this building block bearing an unprotected −OH group at C-2 require more steps.[31,32]

Scheme 3[a]



[a] Legend: [a] CuCl(COD) (10 mol %), THF, −78 °C → room temperature, 63%; [b] *p*-MeOC$_6$H$_4$CH$_2$Cl, NaH, (*n*-Bu)$_4$NI cat., DMF, 0 °C → room temperature, 76%; [c] dimethyldioxirane, CH_2Cl_2, −25 °C; [d] alcohol **8**, $ZnCl_2$, THF, −78 °C → room temperature, 42%.

The assembly of the second sugar building block (Scheme 4) starts with a routine transacetalization of *p*-methoxybenzaldehyde dimethylacetal with D-glucose in the presence of *p*-TsOH·H_2O as the catalyst, delivering the fairly sensitive 4,6-*O*-*p*-methoxybenzylidene acetal **13** on a multigram scale.[33] Peracetylation followed by selective deprotection of the anomeric center of product **14** using benzylamine as the nucleophile delivers the reducing sugar **15** in good yield. To preserve its labile acetal function, this compound was converted into glycosyl bromide **16** under essentially neutral conditions using Br_2 activated by P(OPh)$_3$ in CH_2Cl_2 as the reagent of choice.[34] Product **16** was stable enough to be purified by

(18) For a short review on alkyne metathesis see: Bunz, U. H. F.; Kloppenburg, L. *Angew. Chem., Int. Ed.* **1999**, *38*, 478. A more detailed and updated discussion is found in ref 13.

(19) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108.

(20) Fürstner, A.; Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc.* **1999**, *121*, 9453.

(21) Fürstner, A.; Grela, K. *Angew. Chem.* **2000**, *112*, 1292; *Angew. Chem., Int. Ed.* **2000**, *39*, 1234.

(22) Fürstner, A.; Rumbo, A. *J. Org. Chem.* **2000**, *65*, 2608.

(23) Fürstner, A.; Dierkes, T. *Org. Lett.* **2000**, *2*, 2463.

(24) Fürstner, A.; Seidel, G. *J. Organomet. Chem.* **2000**, *606*, 75.

(25) (a) Complex **5** is prepared as described in: Laplaza, C. E.; Odom, A. L.; Davis, W. M.; Cummins, C. C.; Protasiewicz, J. D. *J. Am. Chem. Soc.* **1995**, *117*, 4999. (b) See also: Cummins, C. C. *Chem. Commun.* **1998**, 1777.

(26) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1991.

(27) (*S*)-**7** is commercially available or can be conveniently prepared on a large scale in optically active form using Jacobsen's excellent resolution method, cf.: (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (b) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 6776.

(28) (a) Fürstner, A.; Konetzki, I. *J. Org. Chem.* **1998**, *63*, 3072. (b) Fürstner, A.; Konetzki, I. *Tetrahedron* **1996**, *52*, 15071.

(29) (a) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661. (b) Review: Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380.

(30) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.

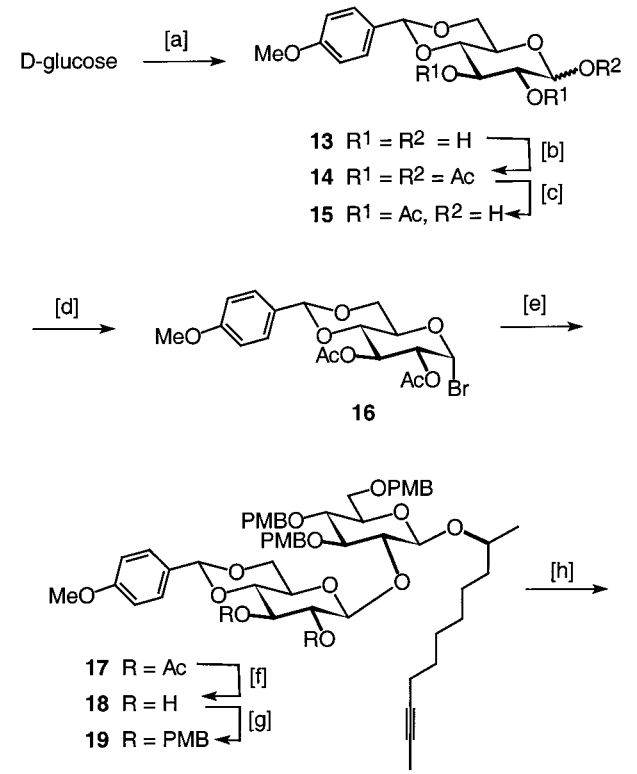
(31) Compound **12** can also be prepared via an ortho ester as the key intermediate by essentially following the approach used for the synthesis of caloporoside described in ref 28. Although the yields of all six individual steps are good to excellent, the overall efficiency is not higher than that of the glycal epoxidation route described herein.

(32) For a discussion of our strategic goals see: Fürstner, A. *Synlett* **1999**, 1523.

(33) Prepared in analogy to the procedure described by: Barili, P. L.; Berti, G.; Catelani, G.; Cini, C.; D'Andrea, F.; Mastrorilli, E. *Carbohydr. Res.* **1995**, *278*, 43.

(34) (a) Mani, N. S.; Kanakamma, P. P. *Synth. Commun.* **1992**, *22*, 2175. (b) See also: Spencer, R. P.; Cavallaro, C. L.; Schwartz, J. *J. Org. Chem.* **1999**, *64*, 3987.

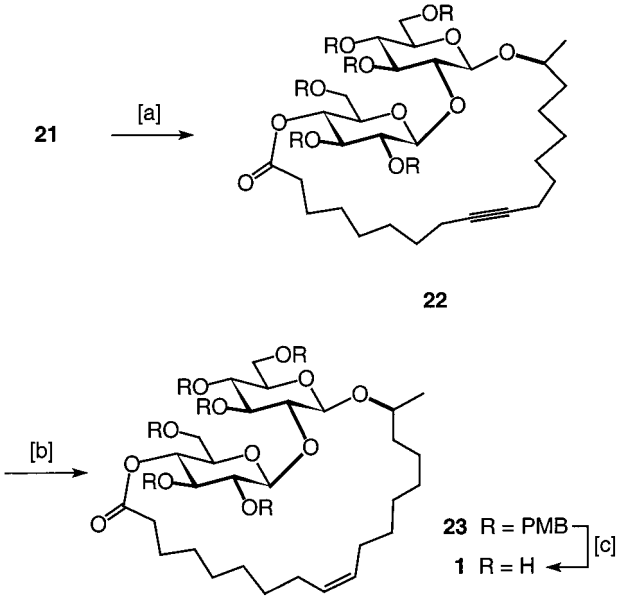
Scheme 4[a]



[a] Legend: [a] *p*-$MeOC_6H_4CH(OMe)_2$, *p*-TsOH·H_2O cat., DMF, 51%; [b] Ac_2O, pyridine, room temperature, 95%; [c] benzylamine, THF, room temperature, 76%; [d] Br_2, $P(OPh)_3$, CH_2Cl_2/pyridine, 0 °C → room temperature, 60%; [e] alcohol **12**, AgOTf, 2,6-di-*tert*-butylpyridine, MS 4 Å, −5 °C, 89%; [f] NaOMe, MeOH, room temperature, 99%; [g] *p*-$MeOC_6H_4CH_2Cl$, NaH, (*n*-Bu)$_4$NI cat., DMF, 0 °C → room temperature, 91%; [h] $NaBH_3CN$ (10 equiv), F_3CCOOH (25 equiv), MS 4 Å, DMF, 0 °C → room temperature, 88%; [i] 9-undecynoic acid, DCC, DMAP cat., 93%.

flash chromatography prior to use in the subsequent glycosylation reaction, which was carried out under slightly modified Koenigs−Knorr conditions.[35] Specifically, reaction of this bromide with alcohol **12** promoted by an excess of AgOTf (1.8 equiv)[36] and lutidine (3.2 equiv) in CH_2Cl_2 at −5 °C in the presence of molecular sieves yielded the desired sophorose glycoside **17** in a respectable 89% yield. Promoters other than AgOTf gave largely inferior results.[37] After having served the purpose of guiding the glycosylation in a β-selective way, the acetyl groups were cleaved off under standard conditions and the resulting diol **18** was converted into the corresponding PMB ether derivative **19** on treatment with NaH and *p*-methoxybenzyl chloride in the presence of catalytic amounts of *n*-Bu_4NI. Reductive cleavage of the 4,6-*O*-*p*-methoxybenzylidene acetal in **19** by means of a large excess of $NaBH_3CN$ and F_3CCOOH took the expected regioselective course,[38] delivering the desired product **20** in 88% yield together with trace amounts of the wrong regioisomer having a free 6″-OH group (<5%); this byproduct was readily removed by flash chromatography. Esterification of pure **20** with 9-undecynoic acid[19] in the presence of DCC and DMAP afforded compound **21**, thereby setting the stage for the crucial diyne metathesis reaction.

Scheme 5[a]



[a] Legend: [a] Mo[N(t-Bu)(Ar)]$_3$ (Ar = 3,5-dimethylphenyl), **5** (10 mol %), CH_2Cl_2/toluene, 80 °C, 78%; [b] H_2 (1 atm), Lindlar catalyst (Pd, 5% w/w, on $CaCO_3$ poisoned with Pb), quinoline, CH_2Cl_2, room temperature, quantitative; [c] DDQ, CH_2Cl_2/MeOH (18/1), room temperature, 8 h, 93% (containing only trace impurities; analytically pure sample after preparative HPLC: 64%).

Gratifyingly, this key transformation performed very well using a catalyst formed in situ from Mo[N(t-Bu)(Ar)]$_3$ (**5**; Ar = 3,5-dimethylphenyl) and CH_2Cl_2 in toluene at 80 °C as previously described (Scheme 5).[20] The desired cycloalkyne **22** was obtained in 78% yield, thus providing further evidence that alkyne metathesis is a reliable

(35) Reviews: (a) Paulsen, H. *Angew. Chem.* **1982**, *94*, 184; *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155. (b) Schmidt, R. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 6, p 33. (c) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503.

(36) Hanessian, S.; Banoub, J. *Carbohydr. Res.* **1977**, *53*, C13. In this procedure, the use of AgOTf in combination with tetramethylurea is recommended; in our hands, however, tetramethylurea gave rather low yields of the expected disaccharide, whereas lutidine as the base led to excellent and reproducible results.

(37) The use of Ag_2CO_3 or $AgNO_3$ deposited on silica/alumina led to marginal conversions only.

(38) (a) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371. (b) Garegg, P. J. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997; p 53.

and efficient reaction even if applied to fairly elaborate natural products. The fact that neither the acid-labile PMB ethers nor the glycosidic linkages were damaged by the Lewis acidic metal center of the catalyst adds two more important examples to the rapidly growing list of functional groups that are compatible with this system.

Cycloalkyne **22** exhibits *two* sets of signals in the high field (600 MHz) NMR spectra recorded at ambient temperature. Extensive investigations, however, have shown beyond doubt that the connectivities of both components are identical. Therefore, this phenomenon is due to rotamers and is by no means caused by the presence of isomeric products formed prior or during alkyne metathesis. Similarly, two components are found in the NMR spectra of the Lindlar reduction product **23**, whereas the deprotected sophorolipid lactone **1** itself gives only the expected single set of resonances. An unambiguous assignment of all signals to the individual rotamers has been achieved by means of 1D and 2D correlation experiments, the results of which are summarized in the Supporting Information.

Lindlar hydrogenation of cycloalkyne **22** under standard conditions in CH_2Cl_2 as the reaction medium proceeded uneventfully, delivering fully protected sophorolipid lactone **23**. In line with our expectations, the final deprotection of this compound using an excess of DDQ in CH_2Cl_2/H_2O (18:1)[39] afforded the targeted product **1**. In view of the amphiphilic character of this compound, however, its purification was somewhat delicate. Although the material collected after conventional flash chromatography (93%) was essentially pure, it did not give correct combustion analyses. Therefore, a sample was subjected to preparative HPLC; lactone **1** thus obtained in 64% yield fully meets all criteria of purity and integrity. In particular, its high-resolution NMR spectra (600 MHz) are perfectly in agreement with the proposed structure (cf. Experimental Section).

Conclusions. This work completes the first total synthesis of a major component of the microbial biosurfactant sophorolipid and constitutes the first application of ring-closing alkyne metathesis[17] to the carbohydrate series. Together with previous syntheses reported from our laboratory dealing with alkaloids,[19,22] prostaglandins,[21] acetogenins,[23] and perfume ingredients,[19,24] this example further illustrates the wide scope of this transformation and the excellent compatibility of the available catalysts[17−20] with a host of polar functional groups, even if these are grouped in dense arrays. A comparison of our recent RCM approach to the glycolipidic segment **4** of tricolorin A (Scheme 1)[12] with this synthesis of glycolipid **1** shows that "conventional" RCM and the emerging alkyne metathesis are essentially equipotent in preparative terms, with the latter offering the additional advantage of providing a *stereoselective* entry into macrocyclic products.[13] Further applications corroborating these advantageous features are underway and will be reported in due course.

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Supporting Information Available: Text giving full experimental details, appropriate characterization of all new compounds, and an unambiguous assignment of the NMR signals of all disaccharidic products described. This material is available free of charge via the Internet at http://pubs.acs.org.

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