Synthesis of the Spirofungin A Core via a Domino Strategy Consisting of Olefinic Ester Ring-Closing Metathesis and Iodospiroacetalization

Jochen Neumaier, Martin E. Maier*

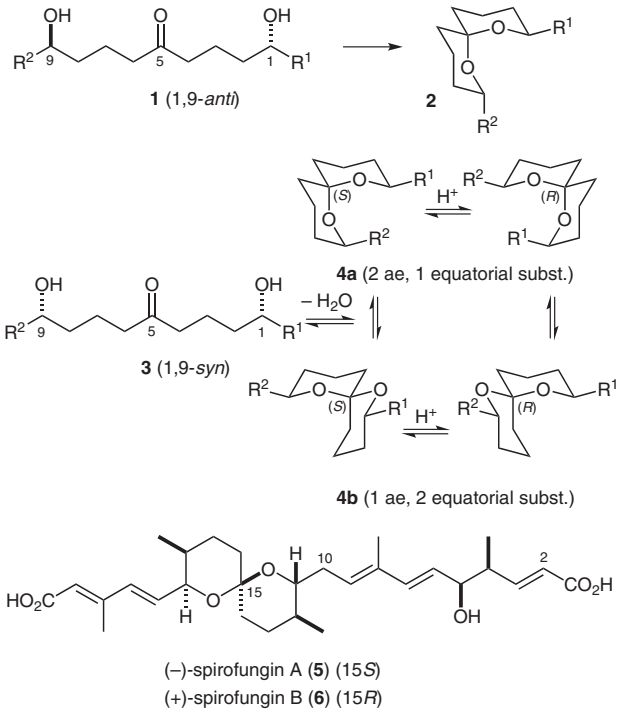
Institut für Organische Chemie, Universität Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany
Fax +49(7071)295137; E-mail: martin.e.maier@uni-tuebingen.de

Received 18 October 2010

Abstract: Olefination of ester **26** which was obtained from acid **20** and alkenol **25** using a reduced titanium ethylidene reagent led to cyclic enol ether **28** which could be cyclized by iodospiroacetalization to the spiroacetal core of the antifungal compound spirofungin A (**5**).

Key words: acetal, aldol reaction, natural product, ring-closing metathesis, spirofungin

The spiroacetal substructure can be found in many biologically active polyketides.[1] Natural products that contain a [6.6]-spiroacetal result from precursors featuring a 1,9-dihydroxynonan-5-one subunit, which in turn are easily accessible by the polyketide biosynthesis machinery.[2] The spiroacetal provides a unique shape serving as scaffold that positions side chains in a certain direction. Neglecting substituents between the 1,9-diol, the relative configuration at the two secondary alcohols determines the configuration of the spiroacetal.[1d,3] If the two hydroxy groups are *anti* like in dihydroxyketone **1** a spiroacetal **2** with two anomeric effects (ae) will result having both substituents in equatorial position (Scheme 1). On the other hand, if they are *syn* to each other the choice is between a spiroacetal with two anomeric effects and one substituent in axial orientation (acetals **4a**) and a spiroacetal with one anomeric effect and both substituents in equatorial position (acetals **4b**). If R^1 is different from R^2 in **4a** these acetals may exist as a mixture of two configurational isomers. This situation can be found, for example, in the spirofungins A (**5**) and B (**6**) which originate from strain *Streptomyces violaceusniger* Tü 4113.[4] They appear as a 1:4 (A/B) mixture of diastereomers at the spiroacetal center. Here the additional methyl groups on the pyran ring reduce the number of possible isomers from four to two. Besides the substituted spiroacetal the spirofungins contain two unsaturated side chains terminating in carboxylic groups. These compounds display good antifungal activity and inhibit the growth of several human cancer cell lines. The biological effects seem to be connected to selective inhibition of isoleucyl-tRNA synthase.[5,6] Up to now four total syntheses for spirofungins have been published.[5,7–9] In addition, several strategies leading to the spiroacetal core are known.[10] Furthermore, various derivatives of reveromycin A and spirofungin A have been prepared and evaluated for activity.[11] It turned out that the minor isomer, spirofungin A, is more active in the isoleucyl-tRNA assay.[11] Therefore, selective approaches to spirofungin A are in demand.

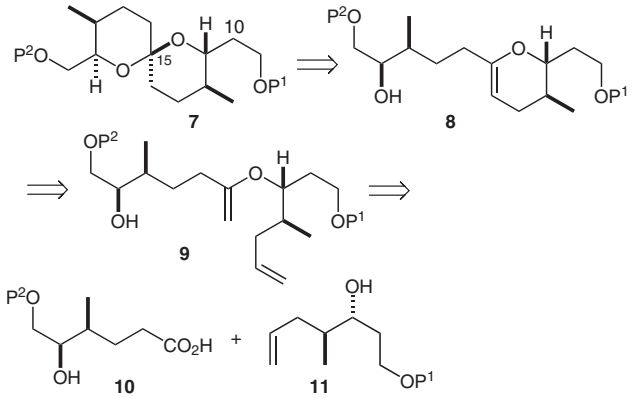


Scheme 1 Stereochemistry of [6.6]-spiroacetals and structure of spirofungin A (**5**) and B (**6**); for the determination of the configuration of the spiroacetal center, it is assumed that $R^1 > R^2$ (higher priority, CIP)

The wide occurrence of spiroacetals points to a privileged structure in biology.[12] Thus, having access to spiroacetal scaffolds should allow for the preparation of collections of interesting natural product analogues. The most common route to spiroacetals is the internal acetalization of dihydroxyketones. Other methods include hetero-Diels–Alder reactions of enones with methylene pyrans,[13] oxidative cyclization of alcohol containing pyrans,[14,15] reductive cyclization of cyano acetals,[10d] transformation of other acetals,[16] cyclization of hydroxyalkynones[17], gold(I)-mediated cyclization of alkynediols,[18] and spirocyclization of endocyclic enol ethers [4-(5,6-dihydro-4*H*-pyran-2-yl)butan-1-ols].[19] Various routes to such dihydropyrans exist, including ring-closing metathesis of olefinic vinyl ethers.[20,21] We were intrigued by the latter strategy[22] in the

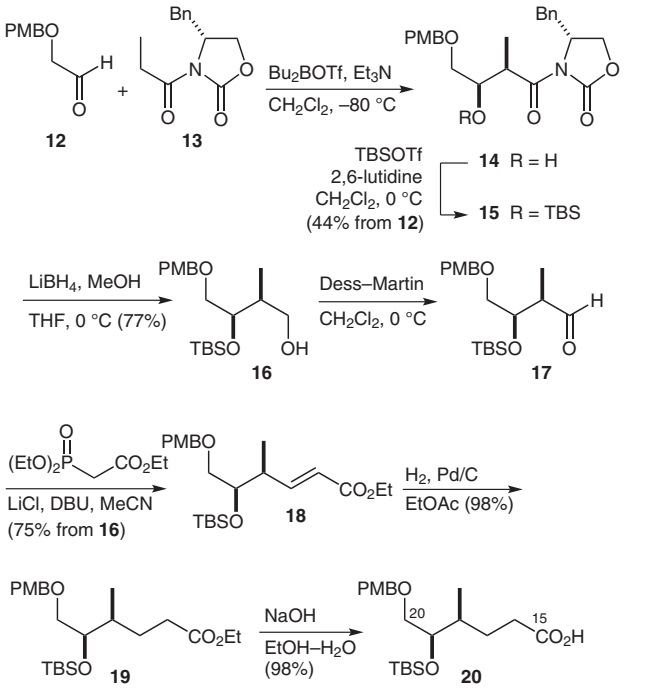
SYNLETT 2011, No. 2, pp 0187–0190
Advanced online publication: 23.12.2010
DOI: 10.1055/s-0030-1259287; Art ID: G29110ST

context of spirofungin synthesis since the corresponding substrates should be available by aldol or related strategies (Scheme 2). Accordingly, the spirocyclic core **7** can be traced back to enol ethers **8** and **9** which in turn lead to building blocks **10** and **11**.

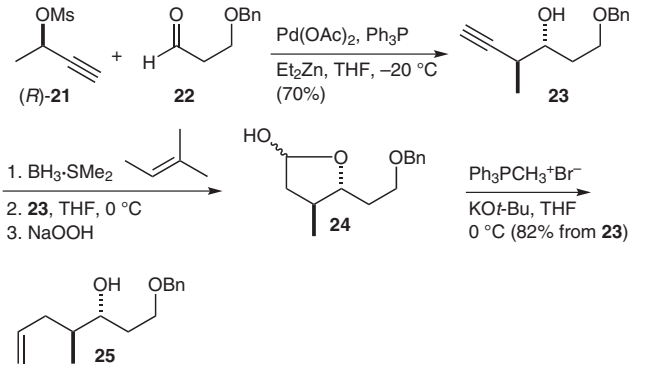


Scheme 2 Retrosynthetic analysis of the spiroacetal core of spirofungin A based on the domino sequence ester olefination, ring-closing metathesis and spiroacetalization

The synthesis of a carboxylic acid related to **10** started with the aldol reaction between *p*-methoxybenzyloxyacetaldehyde (**12**) and chiral propionate[23] **13**, derived from D-phenylalanine (Scheme 3).[24] We found the Evans aldol reaction[25] to be reproducible if aldehyde **12** is prepared from solketal according to the method of Langlois.[26] Silyl protection of aldol product **14** followed by reduction of **15** with $LiBH_4$ in THF delivered alcohol **16** in good overall yield. For chain extension, aldehyde **17**, obtained by Dess–Martin oxidation of alcohol **16**, was subjected to a Wittig–Horner reaction using the Roush conditions[27] (DBU, LiCl, MeCN) to provide enoate **18**. Catalytic hydrogenation of the double bond with Pd/C as catalyst in EtOAc led to ester **19** in almost quantitative yield. Base-induced saponification gave rise to acid **20** corresponding to the C15–C20 part of the spirofungins.



Scheme 3 Synthesis of carboxylic acid **20** via aldol reaction and chain extension

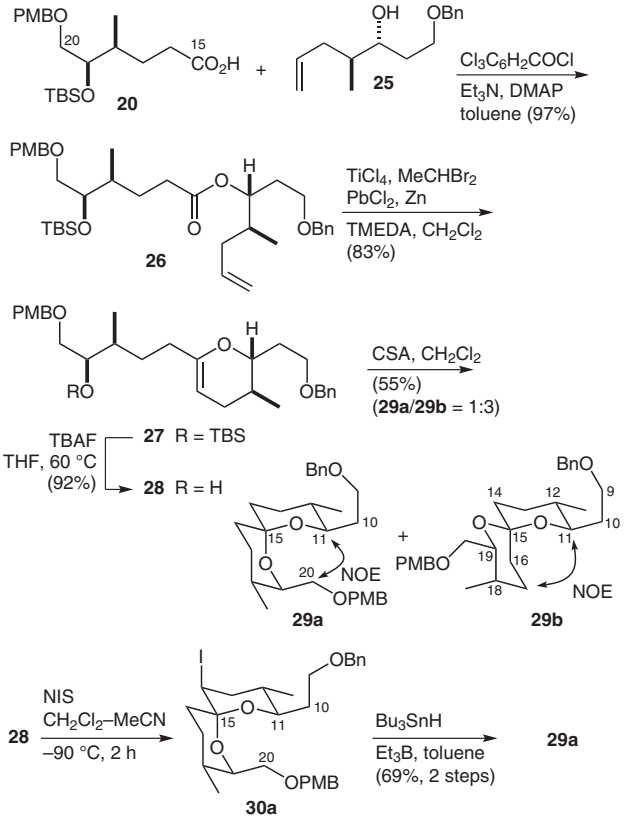


Scheme 4 Synthesis of alkenol **25** via Marshall–Tamaru reaction

The synthesis of alkenol **25** commenced with a Marshall–Tamaru reaction[28,29] between benzyloxypropanal[30] (**22**) and (*R*)-3-butyn-2-yl mesylate[31] **21** in the presence of $Pd(OAc)_2$, Ph_3P and diethylzinc (Scheme 4). After a reaction time of 72 hours at –20 °C alkynol **23** was obtained in 70% yield. Analysis by chiral GC–MS (Chirasil-β-Dex column) indicated a diastereomeric excess (de) of 95.1% and an enantiomeric excess (ee) of 94.6%. Via hydroboration of the triple bond with freshly prepared disiamylborane followed by oxidative workup, hemiacetal **24** was obtained as an anomeric mixture. Olefination of the crude hemiacetal by Wittig reaction furnished the desired alkenol **25** in good yield.

The two key fragments **20** and **25** were condensed under Yamaguchi conditions[32] resulting in olefinic ester **26** (Scheme 5). We initially tried to convert ester **26** into the corresponding acyclic enol ether using the Tebbe reagent[33] and then to perform a ring-closing metathesis. However, with substrate **26** this transformation was not successful.[34] The same negative result was obtained with the Tebbe–Petasis reagent (Cp_2TiMe_2).[35] Ultimately, olefination of the ester **26** and ring-closing metathesis could be achieved in one step using a reduced titanium alkylidene, generated from $TiCl_4$ (35 equiv), TMEDA (200 equiv), Zn dust (80 equiv), $PbCl_2$ (5 equiv) and 1,1-dibromoethane (40 equiv) in CH_2Cl_2 at 55 °C.[36] Pyran **27** could be obtained on gram scale in 83% yield. Due to its somewhat sensitive nature cyclic enol ether **27** was chromatographed on Al_2O_3 and NMR measurements were carried out in benzene-d_6. The secondary alcohol function was unveiled by treatment of silyl ether **27** with TBAF in THF. Spiroacetalization of enol ether **28** in the presence of CSA (2 equiv) delivered a mixture of the two diastereomeric acetals **29a** and **29b**. They could be separated by preparative TLC. The two spiroacetals could be differentiated based on their characteristic NMR data. In particular, the 11-H/20-H NOESY cross peak in **29a** is supportive for the assignment (Scheme 5). For **29b**, a 11-H/17-H NOESY

interaction could be observed. In addition, the spiroacetal carbon of **29a**, featuring two anomeric effects, appears at slightly higher field (δ = 96.8 ppm) as compared to the corresponding carbon atom in **29b** (δ = 97.4 ppm).[7] Selective formation of **29a**, corresponding to the core structure of spirofungin A was possible with *N*-iodosuccinimide (NIS, 1.5 equiv) in CH_2Cl_2–MeCN at –90 °C.[22] Formation of **30a** is the result of a *trans*-diaxial attack of electrophile and nucleophile to the glycal double bond.[37] The crude iodide **30a** was directly subjected to reductive dehalogenation using the combination of tributyltin hydride and triethylborane[38] providing the spiroacetal **29a** in 69% overall yield from substrate **28**.



Scheme 5 Condensation of acid **20** and alcohol **25** to olefinic ester **26** and its conversion into spiroacetal **29a**

In summary, we could demonstrate that unsaturated ester **26** could be converted in an efficient and highly stereoselective manner into spiroacetal **29a** which corresponds to the core structure of spirofungin A. One big advantage is the convergent nature of this strategy relying on relatively simple building blocks.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged. This work was carried out within the framework of COST action CM0804, Chemical Biology with Natural Products.

References and Notes

(1) For recent reviews, see: (a) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406. (b) Kiyota, H. *Top. Heterocycl. Chem.* **2006**, *5*, 65. (c) El Sous, M.; Ganame, D.; Zanatta, S.; Rizzacasa, M. A. *ARKIVOC* **2006**, *(vii)*, 105. (d) Booth, Y. K.; Kitching, W.; De Voss, J. *Nat. Prod. Rep.* **2009**, *26*, 490.

(2) (a) Young, J.; Taylor, R. E. *Nat. Prod. Rep.* **2008**, *25*, 651. (b) Frank, B.; Knauber, J.; Steinmetz, H.; Scharfe, M.; Blöcker, H.; Beyer, S.; Müller, R. *Chem. Biol.* **2007**, *14*, 221.

(3) Pothier, N.; Goldstein, S.; Deslongchamps, P. *Helv. Chim. Acta* **1992**, *75*, 604.

(4) Höltzel, A.; Kempter, C.; Metzger, J. W.; Jung, G.; Groth, I.; Fritz, T.; Fiedler, H.-P. *J. Antibiot.* **1998**, *51*, 699.

(5) Marjanovic, J.; Kozmin, S. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 8854; *Angew. Chem.* **2007**, *119*, 9010.

(6) See also: Miyamoto, Y.; Machida, K.; Mizunuma, M.; Emoto, Y.; Sato, N.; Miyahara, K.; Hirata, D.; Usui, T.; Takahashi, H.; Osada, H.; Miyakawa, T. *J. Biol. Chem.* **2002**, *277*, 28810.

(7) This paper reports on the synthesis and structural revision of spirofungin B: Zanatta, S. D.; White, J. M.; Rizzacasa, M. A. *Org. Lett.* **2004**, *6*, 1041.

(8) Shimizu, T.; Satoh, T.; Murakoshi, K.; Sodeoka, M. *Org. Lett.* **2005**, *7*, 5573.

(9) Crimmins, M. T.; O'Bryan, E. A. *Org. Lett.* **2010**, *12*, 4416.

(10) (a) Shimizu, Y.; Kiyota, H.; Oritani, T. *Tetrahedron Lett.* **2000**, *41*, 3141. (b) Shimizu, T.; Kusaka, J.; Ishiyama, H.; Nakata, T. *Tetrahedron Lett.* **2003**, *44*, 4965. (c) Dias, L. C.; De Oliveira, L. G. *Org. Lett.* **2004**, *6*, 2587. (d) La Cruz, T. E.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 1873.

(11) Shimizu, T.; Usui, T.; Fujikura, M.; Kawatani, M.; Satoh, T.; Machida, K.; Kanoh, N.; Woo, J.-T.; Osada, H.; Sodeoka, M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3756.

(12) Barun, O.; Kumar, K.; Sommer, S.; Langerak, A.; Mayer, T. U.; Müller, O.; Waldmann, H. *Eur. J. Org. Chem.* **2005**, 4773.

(13) El Sous, M.; Ganame, D.; Tregloan, P. A.; Rizzacasa, M. A. *Org. Lett.* **2004**, *6*, 3001.

(14) Dorta, R. L.; Martín, A.; Salazar, J. A.; Suárez, E.; Prangé, T. *J. Org. Chem.* **1998**, *63*, 2251.

(15) Wipf, P.; Uto, Y.; Yoshimura, S. *Chem. Eur. J.* **2002**, *8*, 1670.

(16) Shimizu, T.; Kobayashi, R.; Osako, K.; Osada, H.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6755.

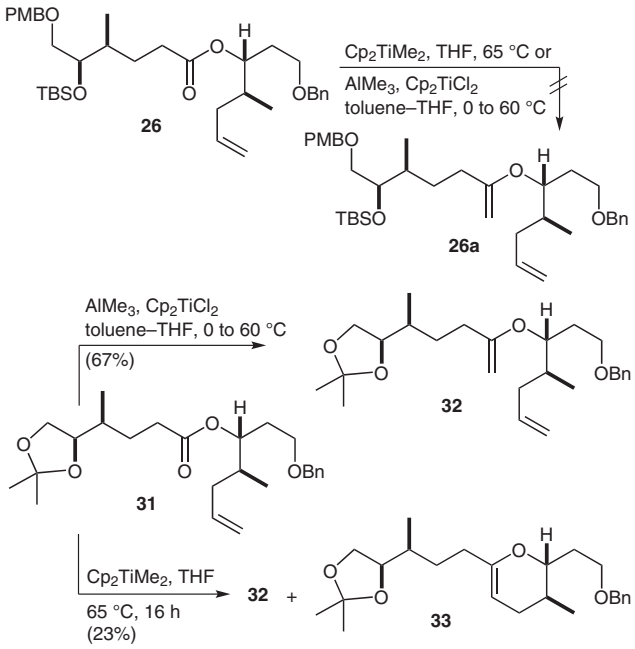
(17) (a) Hao, J.; Forsyth, C. J. *Tetrahedron Lett.* **2002**, *43*, 1. (b) Wang, C.; Forsyth, C. J. *Org. Lett.* **2006**, *8*, 2997.

(18) (a) Liu, B.; De Brabander, J. K. *Org. Lett.* **2006**, *8*, 4907. (b) Li, Y.; Zhou, F.; Forsyth, C. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 279; *Angew. Chem.* **2007**, *119*, 283. (c) Trost, B. M.; O'Boyle, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 16190. (d) Aponick, A.; Li, C.-Y.; Palmes, J. A. *Org. Lett.* **2009**, *11*, 121.

(19) (a) Diez-Martin, D.; Grice, P.; Kolb, H. C.; Ley, S. V.; Madin, A. *Tetrahedron Lett.* **1990**, *31*, 3445. (b) Uchiyama, M.; Oka, M.; Harai, S.; Ohta, A. *Tetrahedron Lett.* **2001**, *42*, 1931.

(20) (a) Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, *59*, 4029. (b) Fuwa, H.; Naito, S.; Goto, T.; Sasaki, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 4737; *Angew. Chem.* **2008**, *120*, 4815.

(21) (a) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565. (b) Iyer, K.; Rainier, J. D. *J. Am. Chem. Soc.* **2007**, *129*, 12604. (c) Zhang, Y.; Rainier, J. D. *Org. Lett.* **2009**, *11*, 237. (d) Rohanna, J. C.; Rainier, J. D. *Org. Lett.* **2009**, *11*, 493. (e) Postema, M. H. D.; Piper, J. L.; Komanduri, V.; Liu, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 2915; *Angew. Chem.* **2004**, *116*, 2975.
(22) A similar strategy has been used for the synthesis of the spiroacetal of spongistatin 1: Holson, E. B.; Roush, W. R. *Org. Lett.* **2002**, *4*, 3719.
(23) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77.
(24) Maier, M. E.; Ritschel, J. *ARKIVOC* **2008**, *(xiv)*, 314.
(25) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 83.
(26) Langlois, N.; Legeay, J.-C.; Retailleau, P. *Eur. J. Org. Chem.* **2008**, 5810.
(27) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
(28) Marshall, J. A.; Schaaf, G. M. *J. Org. Chem.* **2001**, *66*, 7825.
(29) Jägel, J.; Maier, M. E. *Synlett* **2006**, 693.
(30) See, for example: (a) Schomaker, J. M.; Pulgam, V. R.; Borhan, B. *J. Am. Chem. Soc.* **2004**, *126*, 13600. (b) Heumann, L. V.; Keck, G. E. *Org. Lett.* **2007**, *9*, 1951.
(31) Marshall, J. A.; Chobanian, H. *Org. Synth.* **2005**, *82*, 43.
(32) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(33) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (b) Cannizzo, L. F.; Grubbs, R. H. *J. Org. Chem.* **1985**, *50*, 2386. (c) Pine, S. H.; Kim, G.; Lee, V. *Org. Synth.* **1990**, *69*, 72; *Org. Synth., Coll. Vol. 8* **1993**, 512.
(34) In contrast to the negative result with ester **26**, the Tebbe olefination did work with substrate **31** featuring an acetal protecting group for the 1,2-diol subunit. With ester **31**, the Tebbe olefination only led to the acyclic enol ether **32** (Scheme 6), whereas the Tebbe–Petasis reagent produced a mixture of the open and closed enol ethers **32** and **33** (open/closed = 1:2); see also Supporting Information.



Scheme 6

(35) (a) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392. (b) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1995**, *36*, 2393.
(36) Majumder, U.; Rainier, J. D. *Tetrahedron Lett.* **2005**, *46*, 7209.
(37) (a) Tatsuta, K.; Fujimoto, K.; Kinoshita, M.; Umezawa, S. *Carbohydr. Res.* **1977**, *54*, 85. (b) Thiem, J.; Karl, H.; Schwentner, J. *Synthesis* **1978**, 696.
(38) Miura, K.; Ichinose, Y.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 143.