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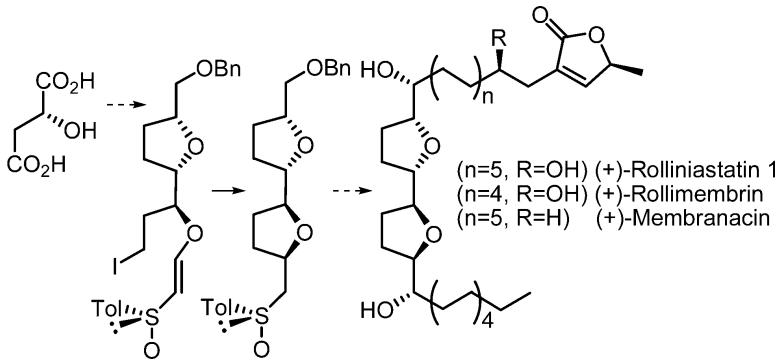

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Stereoselective Syntheses of Rolliniastatin 1, Rollimembrin, and Membranacin

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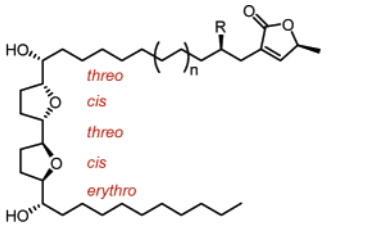
Abstract: A radical cyclization of β-alkoxyvinyl sulfoxides−Pummerer rearrangement−allylation protocol was successfully applied to the synthesis of the *threo*/*cis*/*threo*/*cis*/*erythro* bis-oxolane moiety in rolliniastatin 1 (**1**), rollimembrin (**2**), and membranacin (**3**).

Rolliniastatin 1 (**1**), rollimembrin (**2**), and membranacin (**3**) are Annonaceous acetogenins isolated from the seeds of *Rollinia mucosa* and *Rollinia membranacea* (Figure 1).[1] Annonaceous acetogenins are a large family of natural products that have been described as potent in vitro inhibitors of the mitochondrial respiratory chain complex I. Rolliniastatin 1 (**1**) (the murine P388 lymphocytic leukemia test (PS), 28% life extension at 0.25 mg/kg, and ED_{50} 4.5×10^{-5} μg/mL) and the more active rollimembrin (**2**) and membranacin (**3**) belong to the most potent subgroup featuring a dihydroxy bis-oxolane moiety with a *threo*/*cis*/*threo*/*cis*/*erythro* relative configuration.[2]

Compared to other Annonaceous acetogenins which are popular targets for total synthesis,[3] there has been limited synthetic activities toward this important subgroup: synthesis of **2** has not been reported yet, and we find in the literature only one synthesis of **1** by Koert[4] and a recent synthesis of **3**.[5]



1 (n=2, R=OH) (+)-Rolliniastatin 1
2 (n=1, R=OH) (+)-Rollimembrin
3 (n=2, R=H) (+)-Membranacin

Cytotoxic Annonaceous acetogenins
(*threo*/*cis*/*threo*/*cis*/*erythro*)
from seeds of *Rollinia mucosa* and *R. membranacea*

Figure 1. Rolliniastatin 1, rollimembrin, and membranacin.

Radical cyclization reactions of β-alkoxyacrylates and β-alkoxyvinyl ketones[6] are now well-known to produce *cis*-2,5-disubstituted oxolane and *cis*-2,6-disubstituted oxane rings. Recently, double stereocontrol in the radical cyclization of β-alkoxyvinyl sulfoxides was discussed in the preparation of oxolane products,[7] and we intended to examine the efficacy of these reactions in a stereocontrolled synthesis of **1**, **2**, and **3**.

[†] Seoul National University NS60.
[‡] Korea Institute of Science and Technology.

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(2) For further studies on the bioactivity of rolliniastatin 1 and related compounds, see: Royo, I.; DePedro, N.; Estornell, E.; Cortes, D.; Peláez, F.; Tormo, J. R. *Oncol. Res.* **2003**, *13*, 521−528.

(3) For more recent examples of synthetic efforts, see: (a) Nattrass, G. L.; Díez, E.; McLachlan, M. M.; Dixon, D. J.; Ley, S. V. *Angew. Chem., Int. Ed.* **2005**, *44*, 580−584. (b) Zhang, Q.; Lu, H.; Richard, C.; Curran, D. P. *J. Am. Chem. Soc.* **2004**, *126*, 36−37. (c) Crimmins, M. T.; She, J. *J. Am. Chem. Soc.* **2004**, *126*, 12790−12791. (d) Han, H.; Sinha, M. K.; D'Souza, L. J.; Keinan, E.; Sinha, S. C. *Chem.—Eur. J.* **2004**, *10*, 2149−2158. (e) Prestat, G.; Baylon, C.; Heck, M.-P.; Grasa, G. A.; Nolan, S. P.; Mioskowski, C. *J. Org. Chem.* **2004**, *69*, 5770−5773. (f) Cecil, A. R. L.; Hu, Y.; Vicent, M. J.; Duncan, R.; Brown, R. C. D. *J. Org. Chem.* **2004**, *69*, 3368−3374. (g) Zhu, L.; Mootoo, D. R. *J. Org. Chem.* **2004**, *69*, 3154−3157. (h) Yoshimitsu, T.; Makino, T.; Nagaoka, H. *J. Org. Chem.* **2004**, *69*, 1993−1998. (i) Strand, D.; Rein, T. *Org. Lett.* **2005**, *7*, 199−202. (j) Makabe, H.; Hattori, Y.; Kimura, Y.; Konno, H.; Abe, M.; Miyoshi, H.; Tanaka, A.; Oritani, T. *Tetrahedron* **2004**, *60*, 10651−10657. (k) Makabe, H.; Miyawaki, A.; Takahashi, R.; Hattori, Y.; Konno, H.; Abe, M.; Miyoshi, H. *Tetrahedron Lett.* **2004**, *45*, 973−977.

(4) Koert, U. *Tetrahedron Lett.* **1994**, *35*, 2517−2520.

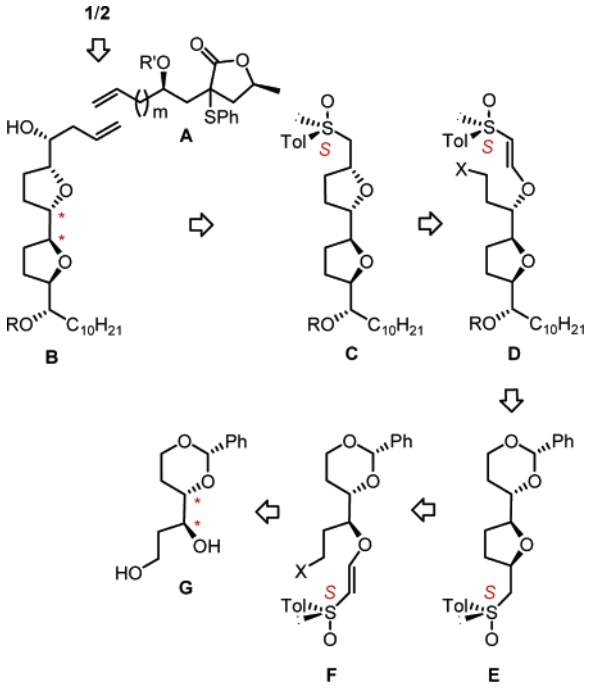
(5) Head, G. D.; Whittingham, W. G.; Brown, R. C. D. *Synlett* **2004**, 1437−1439.

(6) For selected examples of stereoselective radical cyclization reactions of β-alkoxyacrylates and β-alkoxyvinyl ketones in natural product syntheis, see: (a) Kang, E. J.; Cho, E. J.; Lee, Y. E.; Ji, M. K.; Shin, D. M.; Chung, Y. K.; Lee, E. *J. Am. Chem. Soc.* **2004**, *126*, 2680−2681. (b) Song, H. Y.; Joo, J. M.; Kang, J. W.; Kim, D.-S.; Jung, C.-K.; Kwak, H. S.; Park, J. H.; Lee, E.; Hong, C. Y.; Jeong, S.; Jeon, K.; Park, J. H. *J. Org. Chem.* **2003**, *68*, 8080−8087. (c) Jeong, E. J.; Kang, E. J.; Sung, L. T.; Hong, S. K.; Lee, E. *J. Am. Chem. Soc.* **2002**, *124*, 14655−14662. (d) Lee, E.; Choi, S. J.; Kim, H.; Han, H. O.; Kim, Y. K.; Min, S. J.; Son, S. H.; Lim, S. M.; Jang, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 176−178. (e) Lee, E.; Park, C. M.; Yun, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 8017−8018. For more examples on oxacycle synthesis via radical cyclization, read the following review. (f) Lee E. In *Radicals in Organic Synthesis, Vol. 2: Applications*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; pp 303−333.

(7) Keum, G.; Kang, S. B.; Kim, Y.; Lee, E. *Org. Lett.* **2004**, *6*, 1895−1897.

10.1021/ja0526867 CCC: $30.25

Scheme 1. Retrosynthetic Analysis 1



In retrosynthetic analysis, oxolanyl sulfoxide **E** was to be prepared from (*E*)-*β*-alkoxyvinyl (*S*)-sulfoxide precursor **F** (matched case)[7] via stereoselective radical cyclization. Bis-oxolane derivative **C** was envisaged to arise via a second stereoselective radical cyclization of (*E*)-*β*-alkoxyvinyl (*S*)-sulfoxide **D** (matched case), which may be obtained from intermediate **E**. Homoallylic alcohol **B** prepared from **C** may serve as a pivotal intermediate for **1** and **2** via cross metathesis reaction with terminal olefin **A** ($m = 7$ or 5) (Scheme 1).

Butane-1,4-diol (**4**) was monosilylated, and the corresponding aldehyde was converted into an unsaturated ester via modified Knoevenagel condensation[8] with monomethyl malonate. Sharpless asymmetric dihydroxylation[9] provided hydroxy lactone **5** (86% ee) in high yield. Lithium aluminum hydride reduction of **5**, benzylidene acetal formation, desilylation, and regioselective tosylation led to secondary alcohol **6**. Reaction of **6** with ethynyl *p*-tolyl (*S*)-sulfoxide (**7**)[10] in the presence of *N*-methylmorpholine followed by iodide substitution resulted in the formation of (*E*)-alkoxyvinyl (*S*)-sulfoxide **8**, which was purified by crystallization. When **8** was treated with tributylstannane in the presence of triethylborane at −20 °C in toluene, *cis*-2,5-disubstituted oxolanyl product **9** was obtained in 95% yield (d.r. = 88:1).[11] A pure sample of **9** was obtained in 93% yield after recrystallization, and the structure was confirmed by X-ray crystallographic studies (Figure 2). Radical cyclization of **8** in the presence of 1-ethylpiperidinium hypophosphite (EPHP) and triethylborane in ethanol at room temperature[12] also proceeded efficiently to yield **9** (d.r. = 26:1). Aldehyde **10** was then obtained from sulfoxide **9** via Pummerer rearrangement

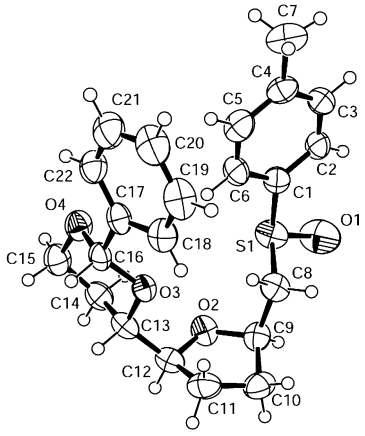
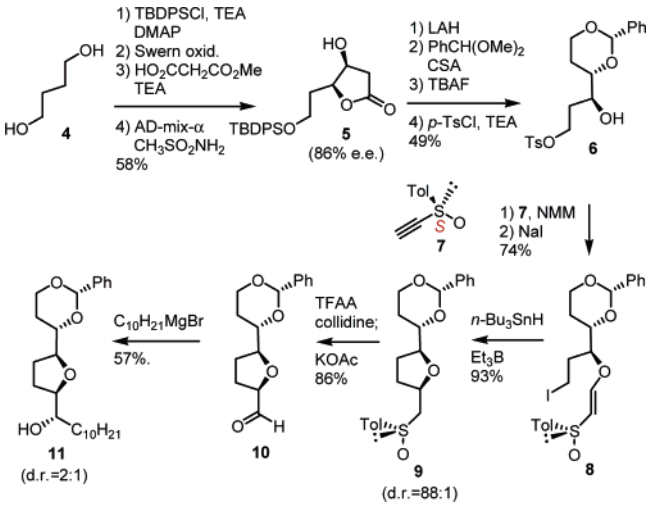


Figure 2. Crystal structure of **9**.

Scheme 2. Synthesis of Oxolane Intermediate **11**



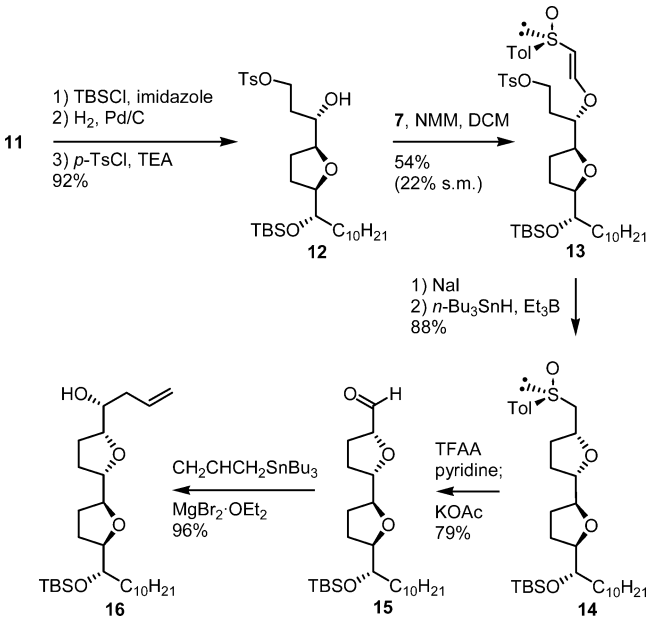
reaction[13] and hydrolysis. When aldehyde **10** was allowed to react with *n*-decylmagnesium bromide, a 2:1 mixture of products was obtained favoring the *erythro* derivative **11**[14] (Scheme 2).

TBS-protection of the secondary hydroxyl group in **11**, benzylidene acetal deprotection, and regioselective tosylation furnished tosylate **12**. Treatment of **12** with ethynyl *p*-tolyl (*S*)-sulfoxide (**7**) in the presence of *N*-methylmorpholine resulted in the formation of (*E*)-alkoxyvinyl (*S*)-sulfoxide **13** in 54% yield with 22% recovery of the starting material **12**. The yield of **13** did not improve under a variety of different conditions. Iodide substitution of **13** and low temperature radical cyclization proceeded smoothly to yield bis-oxolane product **14** efficiently. Aldehyde **15** was prepared from sulfoxide **14** via Pummerer rearrangement, and homoallylic alcohol **16** was obtained stereoselectively from **15** via reaction with allyltributylstannane in the presence of magnesium bromide etherate (Scheme 3).

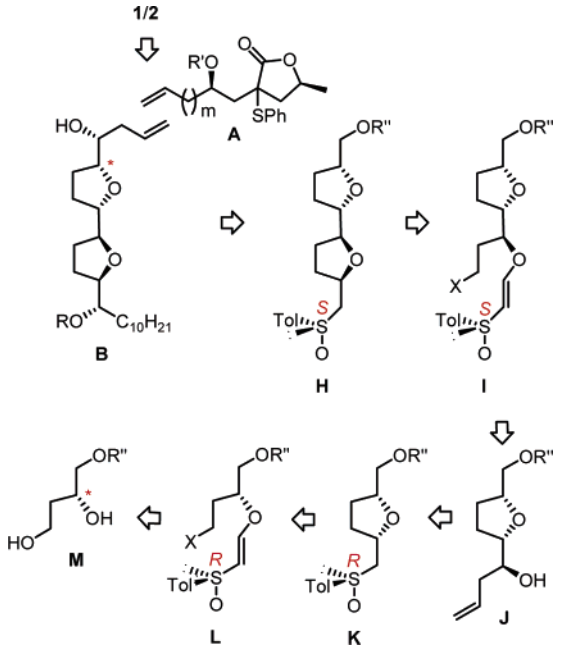
The original scheme provided homoallylic alcohol **16** in a stereoselective manner, but it was plagued by the low conversion of **12** to **13** and the low selectivity in the conversion of **10** to **11**. Realizing difficulty in overcoming the intrinsic steric hindrance problems, it was decided to pursue an alternative route to intermediate **16**. Oxolanyl sulfoxide **K** was to be prepared from (*E*)-*β*-alkoxyvinyl (*R*)-sulfoxide precursor **L** (matched

(8) (a) Yamanaka, H.; Yokoyama, M.; Sakamoto, T.; Shiraishi, T.; Sagi, M.; Mizugaki, M. *Heterocycles* **1983**, *20*, 1541−1544. (b) Harcken, C.; Brückner, R. *New J. Chem.* **2001**, *25*, 40−54.
(9) Torneiro, M.; Still, W. C. *Tetrahedron* **1997**, *53*, 8739−8750.
(10) Kosugi, H.; Kitaoka, M.; Tagami, K.; Takahashi, A.; Uda, H. *J. Org. Chem.* **1987**, *52*, 1078−1082.
(11) Use of ethynyl *p*-tolyl (*R*)-sulfoxide (**19**) in the present synthetic sequence yielded the corresponding oxolanyl product in 98% yield, but the stereoselectivity was lower (mismatched, d.r. = 16:1).
(12) Lee, E.; Han, H. O. *Tetrahedron Lett.* **2002**, *43*, 7295−7296.
(13) Sugihara, H.; Tanikaga, R.; Kaji, A. *Synthesis* **1978**, 881.
(14) The expected major product was the *threo* product via chelation model, but the *erythro* product **11** was the major product in this case.

Scheme 3. Synthesis of Bis-Oxolane Intermediate **16**



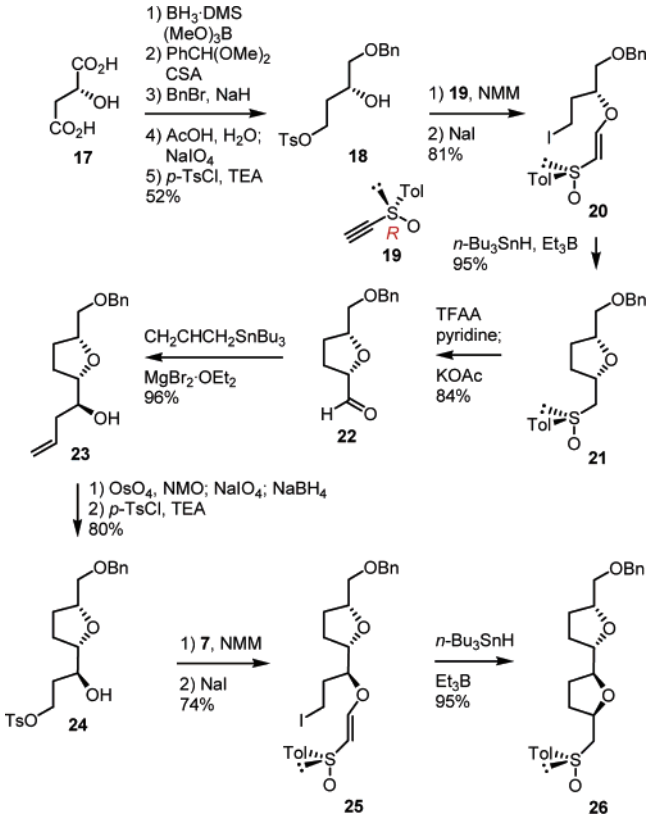
Scheme 4. Retrosynthetic Analysis 2



case) via stereoselective radical cyclization. Bis-oxolane derivative **H** was envisaged to arise via a second stereoselective radical cyclization of (*E*)-*β*-alkoxyvinyl (*S*)-sulfoxide **I** (matched case), which may be obtained from homoallylic alcohol **J** (Scheme 4).

Hydroxy tosylate **18** was prepared from D-malic acid (**17**) via a known five-step sequence. Reaction of **18** with ethynyl *p*-tolyl (*R*)-sulfoxide (**19**) in the presence of *N*-methylmorpholine produced the corresponding (*E*)-*β*-alkoxyvinyl (*R*)-sulfoxide, which was converted into iodide **20** via substitution reaction. Radical cyclization of **20** proceeded stereoselectively (d.r. = 99:1) to give *cis*-2,5-disubstituted oxolane product **21**. Aldehyde **22** which was obtained from **21** via Pummerer rearrangement reacted with allyltributylstannane in the presence of magnesium bromide etherate, and homoallylic alcohol **23** was obtained in high stereoselectivity (>99:1).[15]

Scheme 5. Synthesis of Bis-Oxolane Intermediate **26**

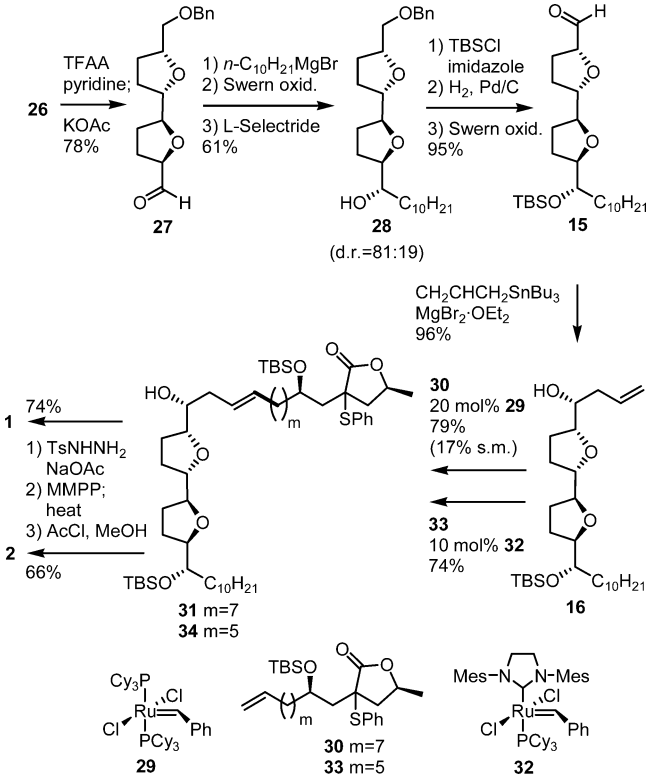


Oxidative cleavage of the double bond in **23** and reduction-tosylation provided hydroxy tosylate **24**, which was converted into (*E*)-*β*-alkoxyvinyl (*S*)-sulfoxide **25** via reaction with **7** and iodide substitution. Radical cyclization proceeded uneventfully to yield bis-oxolane **26** in high yield (Scheme 5).

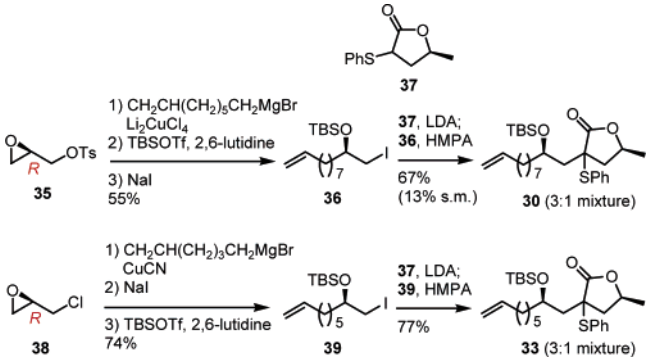
When aldehyde **27**, which was obtained from **26** via Pummerer rearrangement reaction, was allowed to react with *n*-decylmagnesium bromide, the major product was the *threo* derivative. The epimeric mixture favoring (81:19) the *erythro* derivative **28**[16] was obtained via Swern oxidation−L-Selectride reduction sequence. TBS-protection, benzyl deprotection, and Swern oxidation provided aldehyde **15** in good yield, from which homoallylic alcohol **16** was prepared following the established procedure. The crucial cross metathesis reaction of **16** was carried out in dichloromethane at 45 °C in the presence of 4 equiv of terminal olefin **30** and 10 mol % of the first-generation Grubbs catalyst **29**: 79% yield of the cross metathesis reaction product **31** was obtained after supplementary addition of 10 mol % of the catalyst. Rolliniastatin 1 (**1**) was prepared from **31** via diimide reduction of the double bond, oxidation−elimination of the phenylthio group, and TBS-deprotection. Use of an alternative terminal olefin **33** (4 equiv) in the cross metathesis reaction of **16** in the presence of the second-generation Grubbs catalyst **32** (10 mol %) led to the product **34** in 74% yield, which was converted to rollimembrin (**2**) via the established three-step sequence (Scheme 6). Use of 1 equiv of **33** led to 46% yield of **34** accompanied by 28% yield of the homodimer of **16**, and 57% of **34** and 19% of the homodimer were obtained when 2 equiv of **33** was used.

(15) Synthesis of *ent*-**23** was reported in ref 7.
(16) Use of the intermediates **27** and **28** was reported in ref 4.

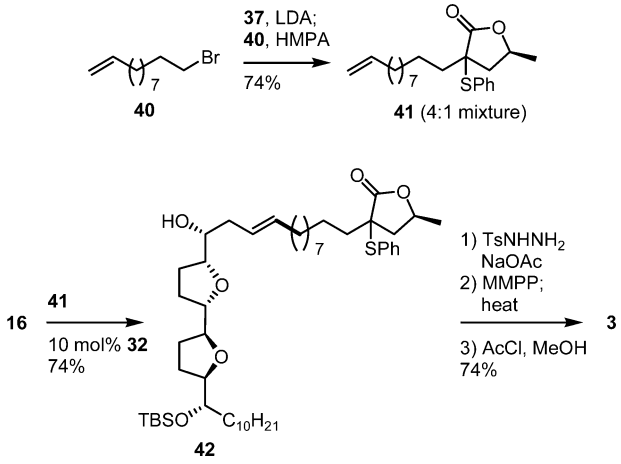
Scheme 6. Synthesis of Rolliniastatin 1 (**1**) and Rollimembrin (**2**)



Scheme 7. Synthesis of Butenolide Segments



Scheme 8. Synthesis of Membranacin (**3**)



Terminal olefin **30**[17] was prepared from phenylthiolactone **37**, and iodide **36** derived from (*R*)-glycidyl tosylate (**35**) (Scheme 7). A similar reaction sequence provided terminal olefin **33** from (*R*)-epichlorohydrin (**38**).[18]

For synthesis of membranacin (**3**), terminal olefin **41** was prepared from **37** and bromide **40** (Scheme 8). A cross olefin metathesis reaction of **16** and **41** provided intermediate **42**, which was converted into membranacin (**3**) via the three-step sequence.

In this synthesis, a radical cyclization of β-alkoxyvinyl sulfoxides−Pummerer rearrangement−allylation protocol was successfully applied to the synthesis of the *threo*/*cis*/*threo*/*cis*/*erythro* dihydroxy bis-oxolane moiety in **1**, **2**, and **3**. Expeditious synthesis was achieved via an allylation−olefin cross metathesis protocol for coupling two major fragments. The modular approach employed in the present synthesis is selective and efficient and can easily be adapted to analogue synthesis.

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Supporting Information Available: Experimental procedures (34 pages, print/PDF), ^{1}H and ^{13}C NMR spectra of the compounds (38 pages, print/PDF), and X-ray crystallographic structure of **9** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0526867

(17) For preparation of a lower homologue of **30**, see: Avedissian, H.; Sinha, S. C.; Yazbak, A.; Sinha, A.; Neogi, P.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **2000**, *65*, 6035−6051.

(18) For a reported use of **37** and **38** for similar purposes, see: Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 4876−4877.