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Total Synthesis of the Microtubule Stabilizing Antitumor Agent Laulimalide and Some Nonnatural Analogues: The Power of Sharpless' Asymmetric Epoxidation

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Three different routes are described for the synthesis of deoxylaulimalide (**3**), which is the immediate precursor of the marine sponge metabolite laulimalide (**1**). These routes mainly differ with respect to their ring closing step. Thus, route 1 uses a Still−Gennari olefination, route 2 a Yamaguchi lactonization, and route 3 an intramolecular allylsilane-aldehyde addition for establishing the macrocyclic structure. The unprotected deoxy derivative **3** was subjected to Sharpless' asymmetric epoxidation (SAE). With (*R*,*R*)-tartrate the 16,17-epoxide laulimalide (**1**) is formed selectively, whereas (*S*,*S*)-tartrate generates the 21,22-epoxide **142**. This demonstrates the high reagent control involved in the SAE process, which in this case is used to achieve high stereo- and regioselectivity. Laulimalide and some derivatives thereof have been tested with respect to antitumor activity and compared to standard compounds paclitaxel and epothilone B.

Introduction

Laulimalide (**1**),[1a] also known as fijianolide B,[1b] is a 20-membered macrolide that was isolated together with its tetrahydrofuran containing isomer isolaulimalide (**2**) (fijianolide A) from various marine sponges such as *Hyattella sp.*,[1a] *Cacospongia mycofijiensis*,[1b] *Fasciospongia rimosa*,[1c,d] and very recently a sponge in the genus *Dactylospongia*.[1e] Interestingly, both compounds were also isolated from a nudibranch, *Chromodoris lochi*, that was found grazing on the sponge.[1a,b] The structure of **1** was initially established by NMR analysis,[1a,b] and later corroborated through X-ray diffraction studies.[1c] Laulimalide is a potent inhibitor of cellular proliferation, with IC_{50} values against numerous drug sensitive cell lines in the low nanomolar range [KB cell line, 15 ng/mL;[1a] P388, A549, HT29, MEL28, 10−50 ng/mL;[1d] MDA-MB-435, 6 ng/mL;[2] SK-OV-3, 12 ng/mL;[2] MCF-7, 7 ng/mL[3]], whereas isolaulimalide is much less potent with IC_{50} values in the low micromolar range. The high cytotoxicity of **1** originates from its ability to promote and stabilize tubulin polymerization, leading to the formation of abnormal mitotic spindles, mitotic arrest, and apoptosis.[2] Thus, laulimalide has to be considered as a new member of the MSAA (microtubule stabilizing antitumor agents) family of compounds, which share the same mechanism of action as the frontline anticancer drugs Taxol (paclitaxel)[4] and Taxotere (docetaxel). Thus, the family of compounds with "taxol-like" activity[5] currently includes the following members: taxanes (isolated from yew trees), marine metabolites (sarcodictyins/eleutherobin, discodermolide, laulimalide, and peloruside A[6]), microbial metabolites (the epothilones,[7] which are already under clinical investigation, and the polycyclic compound FR182877, formerly known as WS9885B[8]), other natural products (taccalonolide,[9a] tryprostatin,[9b] and xanthochymol[9c]), and nonnatural compounds (for instance, an

(1) (a) Corley, D. G.; Herb, R.; Moore, R. E.; Scheuer, P. J.; Paul, V. J. *J. Org. Chem*. **1988**, *53*, 3644−3646. (b) Quinoà, E.; Kakou, Y.; Crews, P. *J. Org. Chem*. **1988**, *53*, 3642−3644. (c) Jefford, C. W.; Bernardinelli, G.; Tanaka, J.-i.; Higa, T. *Tetrahedron Lett*. **1996**, *37*, 159−162. (d) Tanaka, J.-i.; Higa, T.; Bernardinelli, G.; Jefford, C. W. *Chem. Lett*. **1996**, 255−256. (e) Cutignano, A.; Bruno, I.; Bifulco, G.; Casapullo, A.; Debitus, C.; Gomez-Paloma, L.; Riccio, R. *Eur. J. Org. Chem*. **2001**, 775−778.

(2) Mooberry, S. L.; Tien, G.; Hernandez, A. H.; Plubrukarn, A.; Davidson, B. S. *Cancer Res*. **1999**, *59*, 653−660.

(3) Pryor, D. E.; O'Brate, A.; Bilcer, G.; Diaz, J. F.; Wang, Yu.; Wang, Yo.; Kabaki, M.; Jung, M. K.; Andreu, J. M.; Ghosh, A. K.; Giannakakou, P.; Hamel, E. *Biochemistry* **2002**, *41*, 9109−9115.

(4) For reviews, see: (a) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 15−44. (b) Kingston, D. G. I. *Chem. Commun*. **2001**, 867−880.

(5) (a) Stachel, S. J.; Biswas, K.; Danishefsky, S. J. *Curr. Pharm. Des*. **2001**, *7*, 1277−1290. (b) He, L.; Orr, G. A.; Horwitz, S. B. *Drug Discovery Today* **2001**, *6*, 1153−1164. (c) Altmann, K.-H. *Curr. Opin. Chem. Biol*. **2001**, *5*, 424−431. (d) Jordan, M. A. *Curr. Med. Chem.: Anti-Cancer Agents* **2002**, *2*, 1−17. (e) Jimenez-Barbero, J.; Amat-Guerri, F.; Snyder, J. P. *Curr. Med. Chem.: Anti-Cancer Agents* **2002**, *2*, 91−122.

(6) *Sarcodictyins*: D'Ambrosio, M.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1987**, *70*, 2019−2027. D'Ambrosio, M.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1988**, *71*, 964−976. *Eleutherobin*: Lindel, T.; Jensen, P. R.; Fenical, W.; Long, B. H.; Casazza, A. M.; Carboni J.; Fairchild, C. R. *J. Am. Chem. Soc*. **1997**, *119*, 8744−8745. *Discodermolide*: Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem*. **1990**, *55*, 4912−4915. The original structure of discodermolide was revised in: *J. Org. Chem*. **1991**, *56*, 1346. *Peloruside A*: (a) West, L. M.; Northcote, P. T.; Battershill, C. N. *J. Org. Chem*. **2000**, *65*, 445−449. (b) Hood, K. A.; West, L. M.; Rouwe, B.; Northcote, P. T.; Berridge, M. V.; Wakefield, St. J.; Miller, J. H. *Cancer Res*. **2002**, *62*, 3356−3360.

(7) For reviews, see: (a) Nicolaou, K. C.; Roschangar, F.; Vourloumis, D. *Angew. Chem., Int. Ed*. **1998**, *37*, 2015−2045. (b) Mulzer, J. *Monatsh. Chem*. **2000**, *131*, 205−238. (c) Nicolaou, K. C.; Ritzen, A.; Namoto, K. *Chem. Commun*. **2001**, 1523−1535. (d) Wartmann, M.; Altmann, K.-H. *Curr. Med. Chem.: Anti-Cancer Agents* **2002**, *2*, 123−148.

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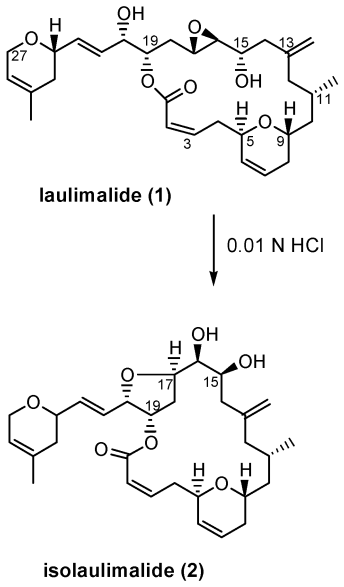


FIGURE 1. Laulimalide (**1**) and isolaulimalide (**2**).

analogue of estradiol,[10a] a combretastatin D analogue,[10b] and GS-164[10c]). However, while the epothilones, discodermolide, and eleutherobin inhibit the binding of [^{3}H]-paclitaxel to tubulin polymer in a competitive manner, and thus apparently bind to the same or an overlapping site at the protein, it was recently discovered[3] that laulimalide binds at a distinct site.

Our interest in laulimalide was kindled in February 1999 by the work of Mooberry and co-workers,[2] which underlined that **1** is as much as 100-fold more potent than paclitaxel against SKVLB-1 cells, a P-glycoprotein overexpressing ovarian cancer cell line, which exhibits multidrug resistance. Very recently, the high therapeutic potential of **1** was further underlined by Hamel,[3] who found that laulimalide also kills human ovarian carcinoma cells which, due to taxoid site mutations in the M 40 human β-tubulin gene, are resistant to paclitaxel (PTX10, PTX22), epothilone A (A8), and epothilone B (B1).

Apart from the significant clinical potential of **1** and its restricted natural supply, the attraction of laulimalide as a synthetic target originates from its unique and complex molecular architecture. Specifically, its 16,17-epoxide is susceptible to nucleophilic attack from the 20-hydroxy group to form the more stable and biologically less active tetrahydrofuran isomer **2** (Figure 1),[1a] and the 2,3-*cis*-enoate moiety readily undergoes *Z*/*E*-isomerization. When we started our synthetic efforts in late 1999, no more than three reports from the Ghosh[11a] and Nishiyama[11d,e] groups were available on the synthesis of major fragments of **1**. To date, in addition to an impressive number of 15 approaches to key fragments by several groups,[11] as many as 10 total syntheses of **1** have been completed.[12−16] The first synthesis was accomplished by Ghosh and Wang,[12a,c] who later refined their first approach by a stereoselective introduction of the 2,3-*cis*-enoate.[12b,c] These two reports were followed in close succession by three syntheses from our group[13] and one from Paterson,[14] which all avoid low-yielding protective group manipulations during the endgame by using a regio- and stereoselective epoxidation of the unprotected macrocycle as the last step. This strategy has also been adopted in the total synthesis by Wender and co-workers,[15] which features a diastereoselective Sakurai reaction for fragment coupling and a regioselective macrolactonization of a 2,3-alkynoic acid with an unprotected vicinal 19,20-diol. Lately, the series of total syntheses of **1** has been complemented by two closely related approaches from the Crimmins[16a] and the Williams[16b] groups which both focus on a diastereoselective allylic transfer of a C_1−C_{14} allylstannane[16a] (or silane[16b]) to a C_{15}−C_{27} α,β-epoxyaldehyde. A very recent synthesis by Nelson[16c] is characterized by extensive use of asymmetric acyl halide−aldehyde cyclocondensation methodology for the construction of main fragments.

Herein, we report the full details of our synthetic studies, which so far culminated in three total syntheses. All of them use the same endgame, namely the regio- and stereoselective epoxidation of 16,17-deoxylaulimalide (**3**). In view of the easy isomerization of **1** to **2**, we decided to avoid any protecting group manipulation at the C_{15}- and C_{20}-OH functions after the introduction of the C_{16}−C_{17} epoxide[17] and to rely on a chirally induced epoxidation[18]

(8) (a) Sato, B.; Muramatsu, H.; Miyauchi, M.; Hori, Y.; Takase, S.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 123−130. (b) Sato, B.; Nakajima, H.; Hori, Y.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 204−206. (c) Yoshimura, S.; Sato, B.; Kinoshita, T.; Takase, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 615−622. The structure of FR182877 was revised in: *J. Antibiot.* **2002**, *55*, C1.

(9) (a) Chen, Z.; Wang, B.; Chen, M. *Huaxue Xuebao* **1988**, *46*, 1201−1206. (b) Kondoh, M.; Usui, T.; Mayumi, T.; Osada, H. *J. Antibiot.* **1998**, *51*, 801−804. (c) Roux, D.; Hadi, H. A.; Thoret, S.; Guenard, D.; Thoison, O.; Paies, M.; Sevenet, T. *J. Nat. Prod.* **2000**, *63*, 1070−1076.

(10) (a) Wang, Z.; Yang, D.; Mohanakrishnan, A. K.; Fanwick, P. E.; Nampoothiri, P.; Hamel, E.; Cushman, M. *J. Med. Chem.* **2000**, *43*, 2419−2429. (b) Couladouros, E. A.; Li, T.; Moutsos, V. I.; Pitsinos, E. N.; Soufli, I. C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2927−2928. (c) Shintani, Y.; Tanaka, T.; Nozaki, Y. *Cancer Chemother. Pharmacol.* **1997**, *40*, 513−520.

(11) (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1997**, *38*, 2427−2430. (b) Ghosh, A. K.; Wang, Y. *Tetrahedron Lett.* **2000**, *41*, 2319−2322. (c) Ghosh, A. K.; Wang, Y. *Tetrahedron Lett.* **2000**, *41*, 4705−4708. (d) Shimizu, A.; Nishiyama, S. *Tetrahedron Lett.* **1997**, *38*, 6011−6014. (e) Shimizu, A.; Nishiyama, S. *Synlett* **1998**, 1209−1210. (f) Mulzer, J.; Hanbauer, M. *Tetrahedron Lett.* **2000**, *41*, 33−36. (g) Dorling, E. K.; Öhler, E.; Mulzer, J. *Tetrahedron Lett.* **2000**, *41*, 6323−6326. (h) Dorling, E. K.; Öhler, E.; Mantoulidis, M.; Mulzer, J. *Synlett* **2001**, 1105−1108. (i) Ahmed, A.; Öhler, E.; Mulzer, J. *Synthesis* **2001**, 2007−2010. (j) Nadolski, G. T.; Davidson B. S. *Tetrahedron Lett.* **2001**, *42*, 797−800. (k) Messenger, B. T.; Davidson B. S. *Tetrahedron Lett.* **2001**, *42*, 801−804. (l) Sivaramakrishnan, A.; Nadolski, G. T.; McAlexander, I. A.; Davidson B. S. *Tetrahedron Lett.* **2002**, *43*, 213−216. (m) Paterson, I.; De Savi, C.; Tudge, M. *Org. Lett.* **2001**, *3*, 213−216. (n) Lee, H. W.; Jeong, C.-S.; Yoon, S. H.; Lee, I.-Y. C. *Bull. Korean Chem. Soc.* **2001**, *22*, 791−792. (o) Lee, H. W.; Yoon, S. H.; Lee, I.-Y. C.; Chung, B. Y. *Bull. Korean Chem. Soc.* **2001**, *22*, 1179−1180.

(12) (a) Ghosh, A. K.; Wang, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11027−11028. (b) Ghosh, A. K.; Wang, Y. *Tetrahedron Lett.* **2001**, *42*, 3399−3401. (c) Ghosh, A. K.; Wang, Y.; Kim, J. T. *J. Org. Chem.* **2001**, *66*, 8973−8982.

(13) (a) Mulzer, J.; Öhler, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 3842−3846. (b) Enev, V. E.; Kählig, H.; Mulzer, J. *J. Am. Chem. Soc.* **2001**, *123*, 10764−10765. (c) Mulzer, J.; Hanbauer, M. *Tetrahedron Lett.* **2002**, *43*, 3381−3383.

(14) Paterson, I.; De Savi, C.; Tudge, M. *Org. Lett.* **2001**, *3*, 3149−3152.

(15) Wender, P. A.; Hegde, S. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 4956−4957.

(16) (a) Crimmins, M. T.; Stanton, M. G.; Allwein, S. P. *J. Am. Chem. Soc.* **2002**, *124*, 5958−5959. (b) Williams, D. R.; Mi, L.; Mullins, R. J.; Stites, R. E. *Tetrahedron Lett.* **2002**, *43*, 4841−4844. (c) Nelson, S. G.; Cheung, W. S.; Kassick, A. J.; Hilfiker, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 13654−13655.

(17) The recent work of Crimmins[16a] revealed that removal of two TBS protecting groups from the C_{15} and C_{20} hydroxyls is possible without rearrangement to isolaulimalide (**2**).

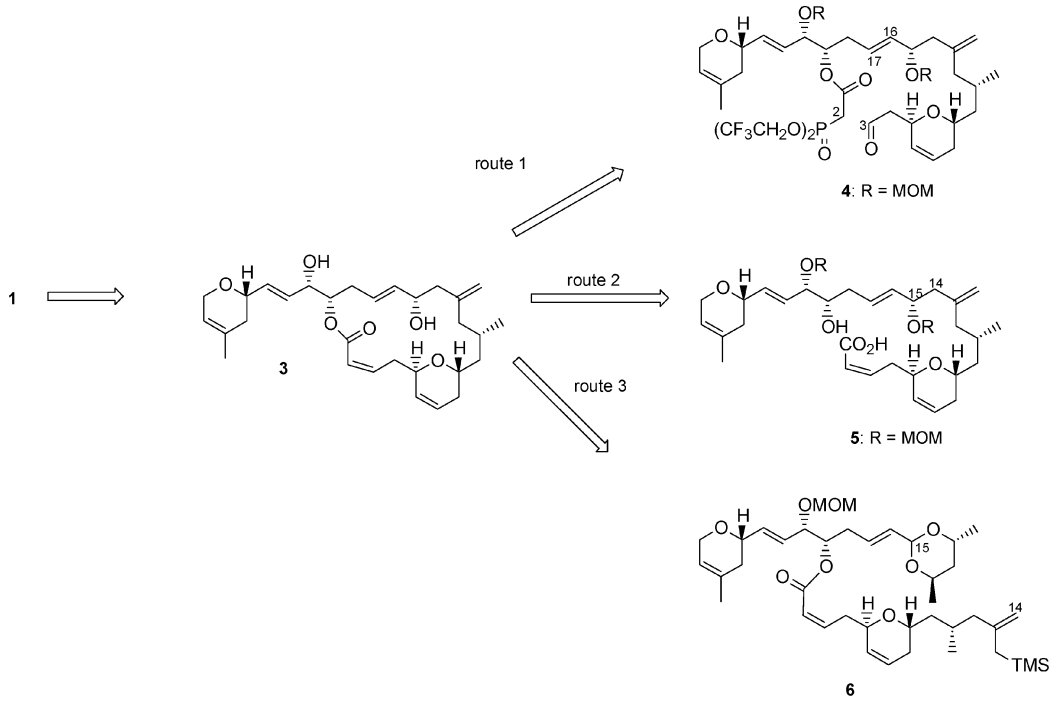


FIGURE 2. Retrosynthetic routes to deoxylaulimalide (**3**) and the corresponding ring closure reactions.

of the unprotected macrocycle (vide infra). In consequence, **3** was envisaged as the common intermediate of our three routes which, otherwise, mainly differ with respect to the macrocyclization step (Figure 2). The first route[13a] employs an intramolecular Still−Gennari olefination of phosphonate aldehyde **4**. Our second route[13c] involves a final Yamaguchi macrolactonization of *seco*-acid **5**, and in the third and so far only fully stereocontrolled route,[13b] the ring closure has been achieved by adding the C_{14}-allylsilane to the C_{15}-acetal in *seco*-compound **6**.

Results and Discussion

Route 1. Fragment Union by Julia−Kocienski Olefination, Macrocyclization by Still−Gennari Reaction. The underlying synthetic strategy is illustrated in Figure 3. Inspired by precedence from the syntheses of phorboxazole A,[19] we envisaged an intramolecular Still−Gennari olefination[20] of *seco*-precursor **4** for macrocyclization and introduction of the C_2-C_3 (*Z*)-enoate. Identical protective groups (i.e. MOM) at the C_{15} and C_{20} allylic alcohols of **4** would significantly simplify the protective group strategy.

An *E*-selective one-step Julia−Kocienski olefination[21,22] was envisioned to connect the two advanced synthetic intermediates **7** and **8**, which were to be assembled from the smaller fragments **9**, **11**, and **10**, **12**, respectively. It

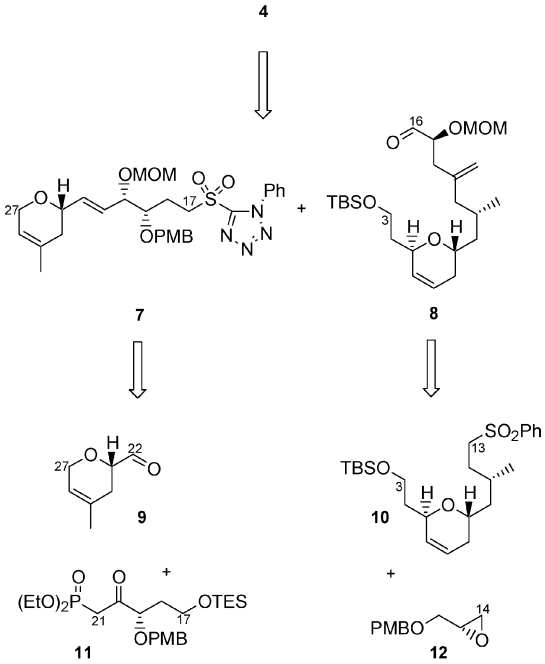


FIGURE 3. Retrosynthetic disconnection of key intermediate **4**.

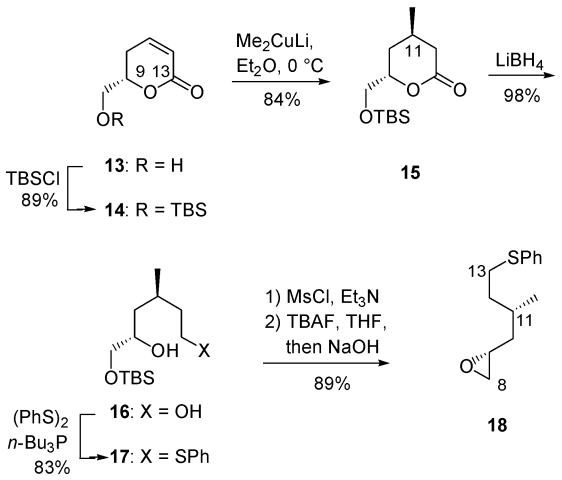
was decided to prepare the dihydropyrans **9** and **10** not only by the relative obvious ring-closing olefin metathesis (RCM),[23] but also by other competing methodology. The $C_{17}-C_{27}$ sulfone **7** should be assembled via Horner−Wadsworth−Emmons olefination from aldehyde **9** and ketophosphonate **11**, whereas C_3-C_{16} aldehyde **8** should be prepared by addition of the anion derived from sulfone **10** to glycidyl ether **12**, and subsequent introduction of the C_{13} methylene group. To keep costs low, intermediates **9**, **10**, and **11** should be derived from inexpensive

(18) (a) Rossiter, B. E. Chiral Catalysis. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1985; Vol. 5, pp 193−246. (b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993; p 103.

(19) (a) Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 5597−5598. (b) Williams, D. R.; Clark, M. B. *Tetrahedron Lett.* **1999**, *40*, 2291−2294. (c) Smith, A. B., III; Minbiole, K. B.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 4834−4836 and 10942−10953.

(20) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405−4408.

SCHEME 1. Synthesis of Epoxide 18



compounds of the chiral carbon pool, such as D-mannitol, D-glucose, and (*S*)-malic acid.

Synthesis of the C_3-C_{16} Fragment. For the construction of the C_5-C_9 dihydropyran moiety, epoxide **18** was envisaged as a suitable intermediate (Scheme 1). We started from the known α,β-unsaturated lactone **13**, which is readily prepared from commercially available triacetyl D-glucal in four steps.[24] Lactone **13** was silylated to give **14**, which underwent axial conjugate addition with lithium dimethyl cuprate to provide the desired 1,4-adduct **15** with laulimalide stereochemistry at C_{11} as a single diastereomer (by ^{1}H NMR) in 84% yield.[25] The expected trans-disubstitution in **15** was confirmed by a strong NOE between the signals of the C_{11} methyl group and H-9. To enable the introduction of the sulfonyl group and inversion at C_9, lactone **15** was reduced with lithium borohydride to provide the 1,5-diol **16** almost quantitatively. The primary alcohol in **16** was selectively transformed to the corresponding phenyl sulfide **17** in 83% yield by treatment with tributyl phosphine/diphenyl disulfide.[26] Epoxide **18** was obtained without isolation of intermediates in 89% overall yield via mesylation of the secondary hydroxy group, deprotection of the primary silyl ether with tetrabutylammonium fluoride, and ring closure under inversion with sodium hydroxide. Thus, the desired configurations at C_{11} and C_9 had been introduced without any additional chiral auxiliary.

Elaboration of epoxide **18** into the dihydropyran **21** (Scheme 2) was accomplished with Ghosez's one-pot lactonization procedure.[27] Boron trifluoride etherate mediated addition of of lithium methyl phenylsulfonyl orthopropionate[28] (**19**) to epoxide **18**, followed by acid-catalyzed lactonization with trifluoroacetic acid in dichloromethane and subsequent elimination of phenyl sulfinic acid with DBU, afforded the α,β-unsaturated lactone **20** in 88% overall yield. Lactone **20** was converted into anomerically pure ethyl glycoside **21**[29] in 93% overall yield by sequential oxidation of the C_{13} thioether with magnesium monoperoxy phthalate (MMPP) in ethanol to the corresponding sulfone, reduction of the lactone with diisobutyl aluminum hydride, and subsequent treatment of the resulting lactol with PPTS in ethanol.

A second synthesis of **21** was performed via a RCM strategy (Scheme 2), by analogy to our previous work.[11f] This included oxidation of the phenyl sulfide **18** to the corresponding sulfone **22** (MMPP, 96% yield), followed by copper(I) iodide catalyzed addition of vinylmagnesium bromide (4 equiv, THF, −40 °C), to provide the desired homoallylic alcohol **23** in 96% yield. Next, PPTS-catalyzed transacetalization of alcohol **23** with acrolein diethylacetal was carried out by a modification of Crimmins' procedure[30] in toluene under reduced pressure with azeotropic removal of ethanol[11f] to give mixed acetal **24** as an epimeric mixture in 86% yield. RCM of diene **24** in boiling dichloromethane with 5 mol % of Grubbs' ruthenium catalyst I[23a] provided, after treatment with PPTS in ethanol, ethyl glycoside **21** in 85% yield.

The stereoselective introduction of the C_3-C_4 side chain was attempted by treatment of acetal **21** with *tert*-butyldimethylsilyl vinyl ether[31] in dry dichloromethane at 0 °C, using montmorillonite K-10 clay[32] as a Lewis acid (Scheme 3). Under these conditions the desired trans-disubstituted C_3-aldehyde **25a** was obtained stereoselectively, but depending on the reaction time, substantial amounts of the corresponding C_3-diethyl acetal **25b** were also formed. After some experimentation, it was found that **25b** was easily reconverted to aldehyde **25a** by

(21) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26−28. For recent applications of the Julia−Kocienski protocol in natural product syntheses, see: (a) Smith, A. B., III; Wan, Z. *J. Org. Chem*. **2000**, *65*, 3738−3753 and references therein. (b) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772−10773. (c) Smith, A. B., III; Safonov, I. G.; Corbett, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 12426−12427. (d) Takano, D.; Nagamitsu, T.; Ui, H.; Shiomi, K.; Yamaguchi, Y.; Masuma, R.; Kuwajima, I.; Omura, S. *Org. Lett*. **2001**, *3*, 2289−2291. (e) Lee, E.; Song, H. Y.; Kang, J. W.; Kim, D.-S.; Jung, C.-K.; Joo, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 384−385. (f) Lautens, M.; Colucci, J. T.; Hiebert, S.; Smith, N. D.; Bouchain, G. *Org. Lett*. **2002**, *4*, 1879−1882.

(22) A standard but low-yielding Julia olefination to connect a $C_{27}-C_{17}$ phenyl sulfone with a $C_{12}-C_{16}$ aldehyde fragment has been used initially by Nishiyama and Shimizu,[11d] and was later also adopted by Ghosh and Wang[12a,c] to generate the $C_{16}-C_{17}$ double bond.

(23) For reviews, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413 − 4450. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (c) Fürstner, A. *Angew. Chem., Int. Ed*. **2000**, *39*, 3012−3043. (d) Trinka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29.

(24) (a) Corey, E. J.; Pyne, S. G.; Su, W.-g. *Tetrahedron Lett*. **1983**, *24*, 4883−4886. (b) Roth, B. D.; Roark, W. H. *Tetrahedron Lett*. **1988**, *29*, 1255−1258. See also: (c) Rollin, P.; Sinay, P. *Carbohydr. Res*. **1981**, *98*, 139−142. (d) Lichtenthaler, F. W.; Rönninger, S.; Jarglis, P. *Liebigs Ann. Chem*. **1989**, 1153−1161.

(25) For related protocols, see: (a) Takano, S.; Shimazaki, Y.; Iwabuchi, Y.; Ogasawara, K. *Tetrahedron Lett*. **1990**, *31*, 3619−3622. (b) Kim, D.; Lee, J.; Shim, P. J.; Lim, J. I.; Doi, T.; Kim, S. *J. Org. Chem*. **2002**, *67*, 772−781.

(26) Nakagawa, I.; Abi, K.; Hata, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1315−1318.

(27) Carretero, J. C.; Ghosez, L. *Tetrahedron Lett*. **1988**, *29*, 2059−2062. For recent applications of Ghosez's methodology, see: (a) Nicolaou, K. C.; Patron, A. P.; Ajito, K.; Richter, P. K.; Khatuya, H.; Bertinato, P.; Miller, R. A.; Tomaszewski, M. J. *Chem. Eur. J*. **1996**, *2*, 847−868. (b) Murakami, N.; Wang, W.; Aoki, M.; Tsutsui, Y.; Sugimoto, M.; Kobayashi, M. *Tetrahedron Lett*. **1998**, *39*, 2349−2352. (c) Surivet, J.-P.; Vatèle, J.-M. *Tetrahedron* **1999**, *55*, 13011−13028. (d) Williams, D. R.; Ihle, D. C.; Plummer, S. V. *Org. Lett*. **2001**, *3*, 1383−1386.

(28) De Lombaert, S.; Nemery, I.; Roekens, B.; Carretero, J. C.; Kimmel, T.; Ghosez, L. *Tetrahedron Lett*. **1986**, *27*, 5099−5102.

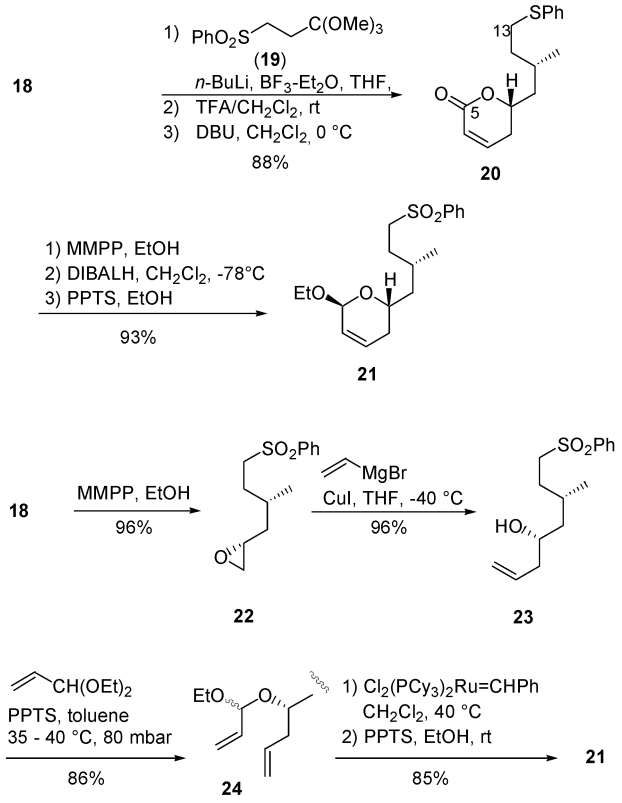
(29) The stereochemistry of **21** was assigned by NOESY experiments. See also ref 12c.

(30) Crimmins, M. T.; King, B. W. *J. Am. Chem. Soc.* **1998**, *120*, 9084−9085.

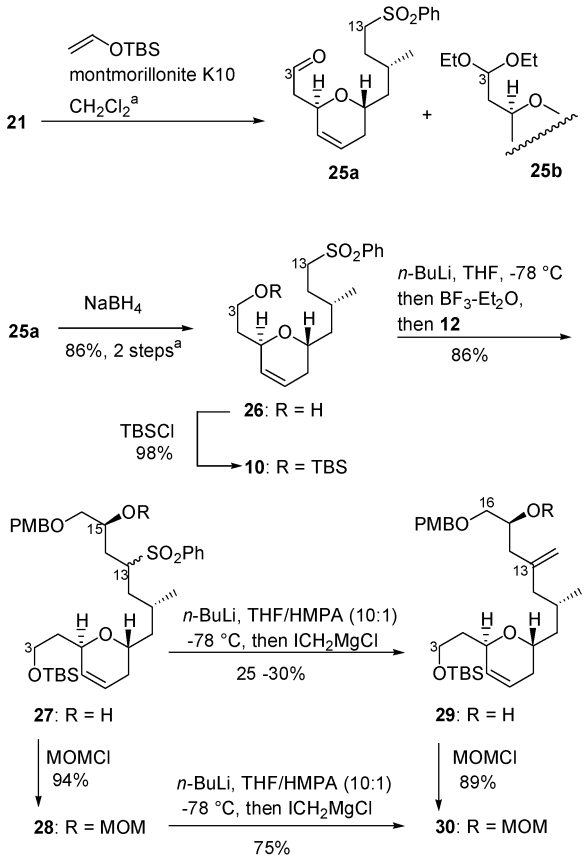
(31) Srisiri, W.; Padias, A. B.; Hall, H. K., Jr. *J. Org. Chem*. **1994**, *59*, 5424−5435.

(32) Toshima, K.; Miyamoto, N.; Matsuo, G.; Nakata, M.; Matsumura, S. *Chem. Commun*. **1996**, 1379−1380.

SCHEME 2. Two Syntheses of Ethyl Glycoside 21



SCHEME 3. Synthesis of C_3-C_{16} Fragment 30



[a] See text and Supporting Information.

subsequent treatment of the crude reaction mixture with K-10 clay in *wet* dichloromethane.[33] The crude aldehyde was reduced with sodium borohydride to deliver alcohol **26** in 86% overall yield from **21**.[34] After TBS protection of the hydroxyl function, sulfone **10** was deprotonated with *n*-butyllithium and treated with epoxide **12** at −78 °C in the presence of boron trifluoride etherate to afford a mixture of epimeric sulfones **27** (1:1, by ^{1}H NMR) in 86% yield. When sulfones **27** were subjected to the Julia methylenation procedure,[35,36] the yield of the desired C_{13}-methylene derivative **29**[37] was unvariably less than 30%. Therefore, the C_{15}-OH group in **27** was protected as the MOM-ether sulfones **28**, which underwent methylenation smoothly (deprotonation in THF/HMPA at −78 °C, then addition of 5 equiv of the carbenoid prepared from diiodomethane and isopropylmagnesium chloride), to furnish C_{13}-methylene compound **30** in 75% yield.

An alternative route to C_3-C_{13}-sulfone **10**[11f] also employing Grubbs RCM is shown in Scheme 4. Known alcohol **31**, which is readily prepared from commercially available methyl (*S*)-3-hydroxy-2-methylpropionate in 2 steps,[38] was tosylated and transformed to cyanide **32** (NaCN, DMSO, 80 °C) in 86% yield for the two steps. Reduction of **32** with DIBALH in THF provided aldehyde **33** (80% yield), which was allylated with (−)-allyl diisopinocampheylborane[39a] according to Brown's improved protocol[39b] to provide homoallylic alcohol **34** in 93% yield with high diastereoselectivity (de = 90%). Allylation of aldehyde **33** according to Duthaler's procedure[40] with (*R*,*R*)-TADDOLTiCpCl and allylmagnesium bromide in diethyl ether at −78 °C afforded alcohol **34** with better diastereoselection (de = 96%), but in a disappointing yield of 51%. Homoallylic alcohol **34** was then transformed to C_3-C_{12} dihydropyran **38** via transacetalization to **35** (84% yield), RCM to **36** (94% yield), stereoselective *C*-glycosidation at C_5 with vinyl-OTBS, followed by reduction of the resulting aldehyde with sodium borohydride to alcohol **37** (85% for the two steps), and silyl protection at C_3-O. Treatment of **38** with DDQ in wet dichloromethane cleaved the PMB group, and the resulting primary alcohol **39** was transformed to the corresponding iodide **40** in 91% yield, under standard conditions.[41,42] Treatment of **40** with the nucleophile derived from methyl phenyl sulfone and *n*-BuLi in THF/HMPA (20:1) led to the desired sulfone **10** in 85% yield.

(33) Gautier, E. C. L.; Graham, A. E.; McKillop, A.; Standen, S. P.; Taylor, R. J. K. *Tetrahedron Lett.* **1997**, *38*, 1881−1884.

(34) The stereochemistry at C_5 was determined by NOESY experiments and was further confirmed by a strong NOE between the protons at C_5 and C_9 in the NMR spectrum of the cis-isomer **25c**, which was isolated in traces (≤2%) by chromatography.

(35) De Lima, C.; Julia, M.; Verpeaux, J.-N. *Synlett* **1992**, 133−134.

(36) For recent applications of Julia's methodology, see: (a) Romo, D.; Meyer, S. D.; Johnson, D. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 7906−7907. (b) Smith, A. B., III; Doughty, V. A.; Lin, Q.; Zhuang, L.; McBriar, M. D.; Boldi, A. M.; Moser, W. H.; Murase, N.; Nakayama, K.; Sobukama, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 191−195. (c) Smith, A. B., III; Lin, Q.; Doughty, V. A.; Zhuang, L.; McBriar, M. D.; Kerns, Y. K.; Brook, C. S.; Murase, N.; Nakayama, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 196−199.

(37) Compound **29** is a key fragment in Ghosh's synthesis of **1**.[12a]

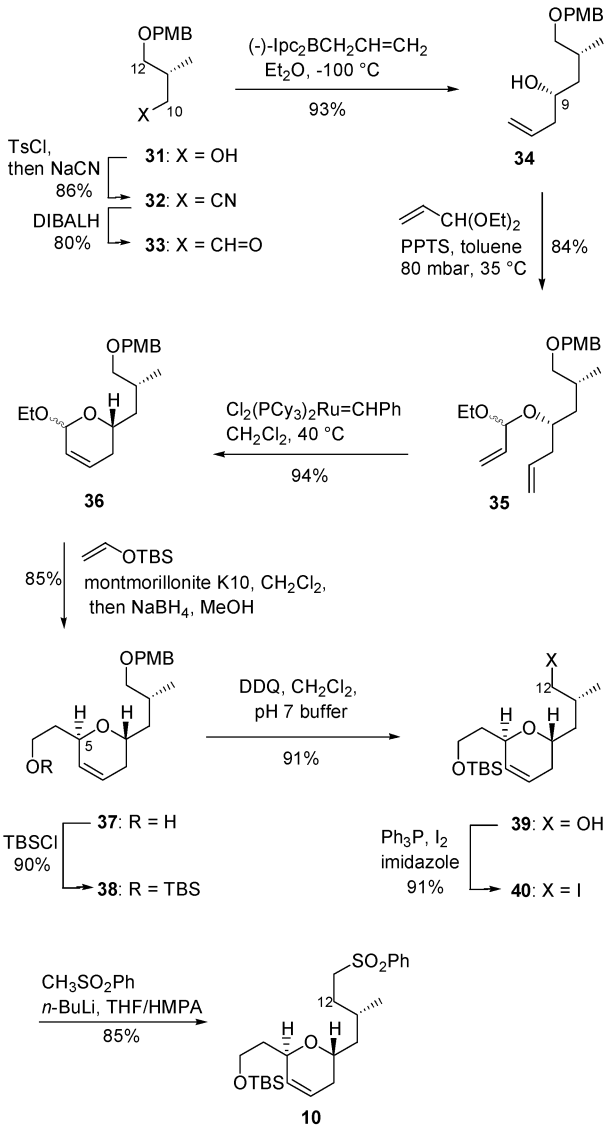
(38) Walkup, R. D.; Boatman, P. D., Jr.; Kane, R. R.; Cunningham, R. T. *Tetrahedron Lett.* **1991**, *32*, 3937−3940.

(39) (a) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570−1576. (b) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401−404.

(40) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. J. *J. Am. Chem. Soc.* **1992**, *114*, 2321−2336.

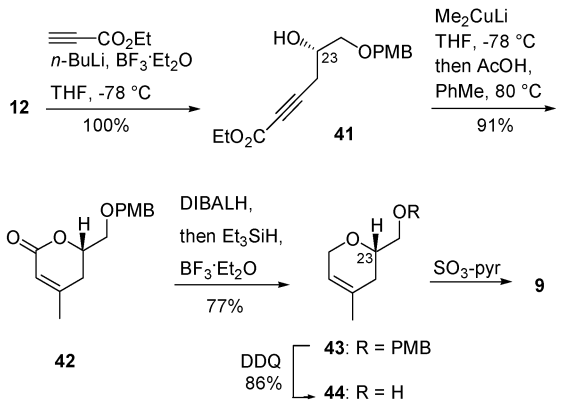
(41) Garegg, P. J.; Samuelsson, B. *Chem. Commun.* **1979**, 978−980.

SCHEME 4. Alternative Approach to C_3−C_{13} Sulfone 10

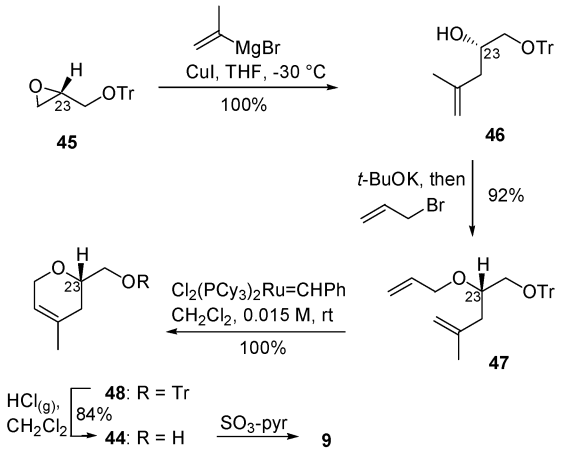


Synthesis of Sulfone 7. As shown in Figure 3, the C_{17}−C_{27} sulfone **7** was to be prepared by HWE-reaction of aldehyde **9** with C_{17}−C_{21} β-oxophosphonate **11**. Altogether three approaches to **9** were elaborated, two of which were based on RCM. In the first one (Scheme 5),[11g] we started from glycidyl ether **12**, which was regioselectively opened with the lithium salt of ethyl propiolate in the presence of BF_3·Et_2O to give alcohol **41** in near quantitative yield. Stereoselective addition of lithium dimethyl cuprate to the triple bond in **41** and in situ lactonization[25a] of the resulting (*Z*)-enoate with acetic acid in toluene at 80 °C furnished lactone **42** in 91% yield. Reduction of **42** to the lactol with diisobutyl aluminum-hydride and in situ ionic hydrogenation[43] with triethylsilane/BF_3·Et_2O at −78 °C gave the dihydropyran **43** in 77% yield. Removal of the PMB group with DDQ produced the highly water soluble alcohol **44**, which was converted into the volatile aldehyde **9** by Parikh−Doering oxidation.[44]

SCHEME 5. First Approach to Aldehyde 9



SCHEME 6. Second Approach to Aldehyde 9



In the second and more convenient approach to aldehyde **9**,[11g] the trisubstituted double bond was formed by RCM (Scheme 6). Thus, glycidyl trityl ether **45** was regioselectively opened with isopropenylmagnesium bromide (2 equiv) under copper(I) catalysis in THF at −30 °C to furnish the homoallylic alcohol **46** quantitatively, which was alkylated with allyl bromide to give diene **47** in 92% yield. When **47** (0.015 M in dichloromethane) was exposed to 2.5−3% of Grubbs' ruthenium catalyst I for only 1−2 h at room temperature,[45] the corresponding dihydropyran **48** was obtained in quantitative yield. This result was particularly remarkable, as literature precedence indicated that RCM of dienes bearing one *gem*-disubstituted double bond does not work with Grubbs' catalyst I.[46] Removal of the trityl group with hydrogen chloride in dichloromethane without aqueous workup provided alcohol **44** in 84% yield.[47]

In a third approach to aldehyde **9**[11i] (Scheme 7), two-

(42) Iodide **40** was also an intermediate in Ghosh's synthesis of **1**,[12a,c] who independently started from the benzyl protected analogue of alcohol **31** via a RCM route.

(43) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633−651.

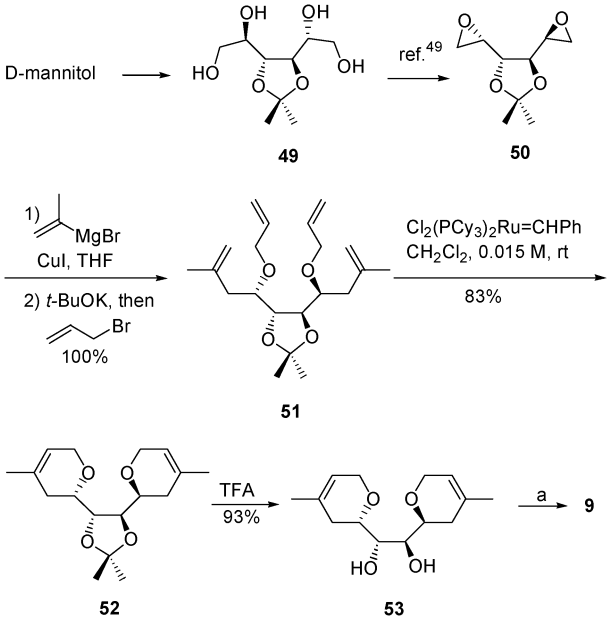
(44) Parikh, J. R.; von Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

(45) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310−7318.

(46) (a) Kinoshita, A.; Mori, M. *Synlett* **1994**, 1020−1022. (b) Callam, C. S.; Lowary, T. *Org. Lett.* **2000**, *2*, 167−169. (c) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 123−126. (d) Miller, J. F.; Termin, A.; Koch, K.; Piscpio, A. D. *J. Org. Chem.* **1998**, *63*, 3158−3159.

(47) A closely related approach to the C_{22}−C_{27} fragment of **1** was independently developed by Ghosh and Wang[11c] and was later on also used by other groups.[11k,l,n,o,14]

SCHEME 7. Third Approach to Aldehyde 9

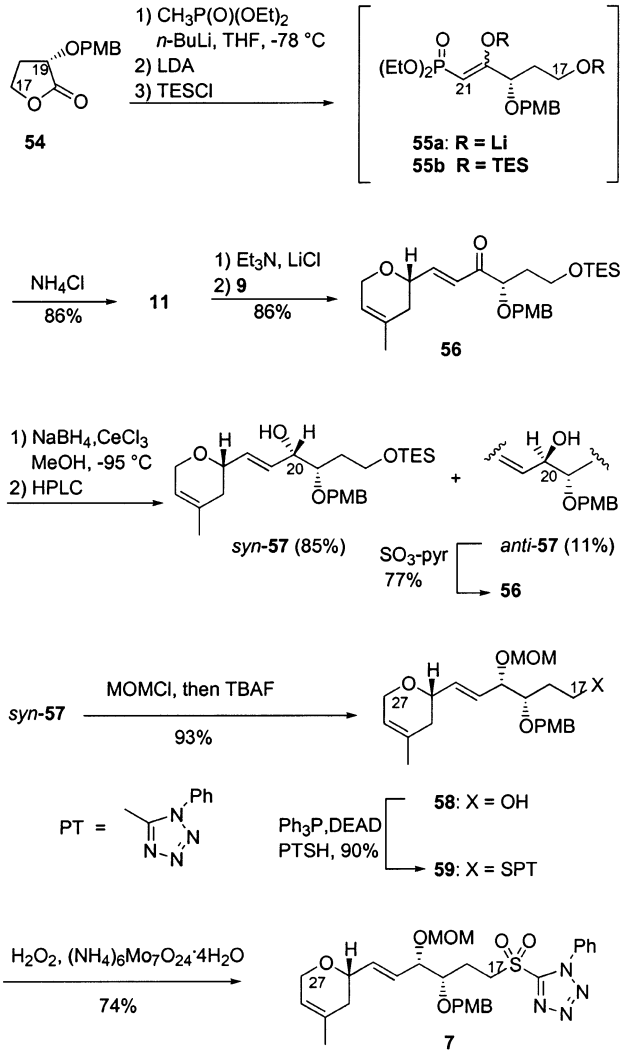


[a] See text and Supporting Information.

directional synthesis[48] was applied by starting from the known diepoxide **50**, which is available from the D-mannitol-acetonide **49** in three high-yielding steps.[49] Diepoxide **50** was transformed quantitatively in two steps into tetraene **51**, which was subjected to RCM under high dilution in CH_2Cl_2 at room temperature. No medium ring sized cycloolefins were formed across the central acetonide ring which, under these conditions, served as a barrier to crossover metathesis.[50] In this way the symmetric bis-dihydropyran **52** was obtained in 83% yield. To complete the synthesis of aldehyde **9**, the acetonide ring in **52** was cleaved with trifluoroacetic acid in dichloromethane at 0 °C (93% yield), and the resulting diol **53** was oxidized with sodium periodate/silica gel in CH_2Cl_2,[51] or with lead tetraacetate/sodium carbonate in CH_2Cl_2,[52] or with periodic acid in Et_2O. Simple filtration and careful evaporation of the low-boiling solvents gave aldehyde **9** in excellent purity and yield. This approach had the advantage of generating the highly volatile aldehyde in higher purity under neutral conditions, compared to preparation from alcohol **44**.

Completion of Key Fragment 7. As illustrated in Scheme 8, the synthesis of the chiral phosphonate **11**

SCHEME 8. Completion of Key Fragment 7



started from PMB-protected α-hydroxy butyrolactone **54**,[53] which is readily available from natural (*S*)-malic acid.[54] Lactone **54** was treated with an equimolar amount of the lithium salt of diethyl methanephosphonate. The resulting anionic adduct was further deprotonated with 1 equiv of LDA leading to dianion **55a**, which was silylated with 2 equiv of TESCl. The silylenol ether in bis-silyl ether **55b** was selectively hydrolyzed during workup with aqueous NH_4Cl solution, providing the triethylsilyl-protected *β*-oxophosphonate **11** without isolation of intermediates in 86% yield.[55] HWE olefination of phosphonate **11** with aldehyde **9** under Masamune–Roush conditions[56] with 2.5 equiv of triethylamine and lithium chloride in THF at 0 °C afforded enone **56** *E*-stereoselectively (*E*:*Z* > 40:1) in high yield. The Fel-

(48) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9. For a review, see: Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167−2213. For some recent examples of two-directional RCM, see: (a) Burke, S. D.; Quinn, K. J.; Chen, V. J. *J. Org. Chem.* **1998**, *63*, 8626−8627. (b) Lautens, M.; Hughes, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 129−162. (c) Baylon, C.; Heck, M.-P.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 3354−3360. (d) Heck, M.-P.; Baylon, C.; Noian, S. P.; Mioskowski, C. *Org. Lett.* **2001**, *3*, 1989−1991. (e) Clark, J. S.; Hamelin, O. *Angew. Chem., Int. Ed.* **2000**, *39*, 372−374.

(49) Le Merrer, Y.; Duréault, A.; Greck, C.; Micas-Languin, D.; Gravier, C.; Depezay, J.-C. *Heterocycles* **1987**, *25*, 541−548.

(50) For a review, see: Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073−2077. For the clean conversion of a bis-homoallylic alcohol derived from diepoxide **50** to the corresponding cyclooctene derivative by RCM, see: Gravier-Pelletier, C.; Andriuzzi, O.; Le Merrer, Y. *Tetrahedron Lett.* **2002**, *43*, 245−248.

(51) Zhong, Y. L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622−2624.

(52) Banwell, M. G.; Forman, G. S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2565−2566.

(53) Mulzer, J.; Mantoulidis, A.; Öhler, E. *J. Org. Chem.* **2000**, *65*, 7456−7467.

(54) Collum, D. B.; McDonald, J. H.; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2118−2120.

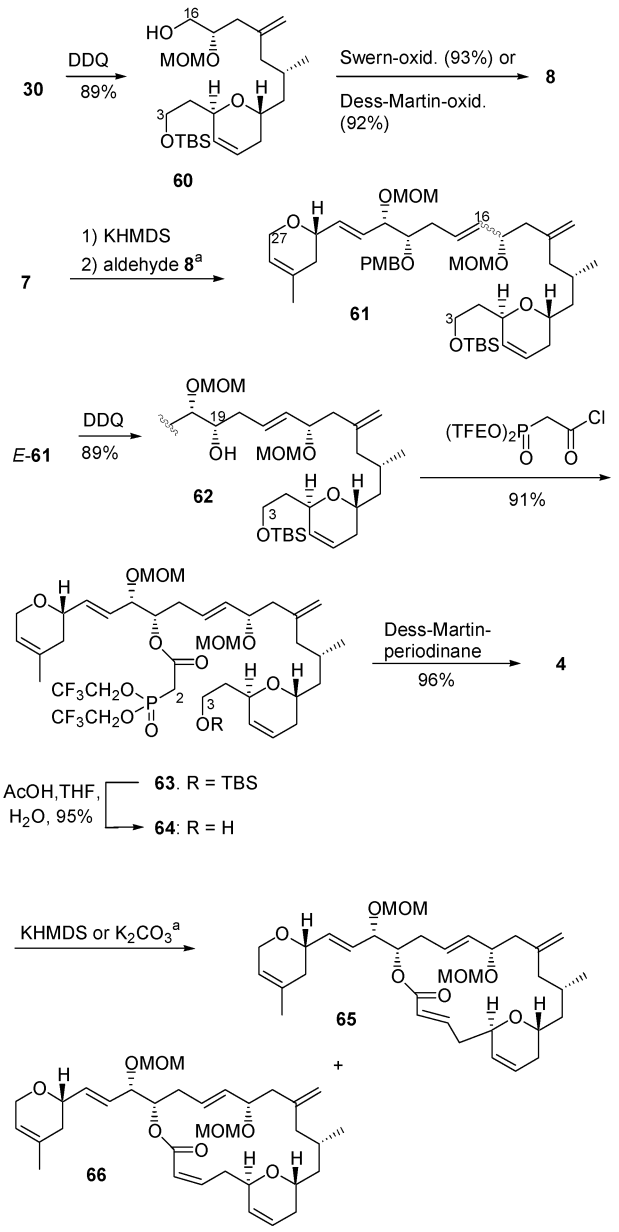
(55) For related protocols, see: (a) Ditrich, K.; Hoffmann, R. W. *Tetrahedron Lett.* **1985**, *26*, 6325−6328. (b) Hanessian S.; Roy, P. J.; Petrini, M.; Hodgesi, P. J.; Di Fabrio, R.; Carganico, G. *J. Org. Chem.* **1990**, *55*, 5766−5777.

(56) Blanchette, M. A.; Choy, W.; Davis J. T.; Essenfeld, A. P.; Masamune, S.; Roush W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183−2186.

kin−Anh selective reduction of the C_{20}-carbonyl group in **56** in the presence of the chelating vicinal PMB-ether was a challenging task. Preliminary experiments with L-Selectride were hampered by tedious workup, and standard Luche reduction[57] at −78 °C furnished an unsatisfactory 5.6:1 syn:anti ratio of epimers **57**. Finally, optimal conditions were found by performing the Luche reduction at −95 °C under slow addition of sodium borohydride to a vigorously stirred mixture of enone **56** and $CeCl_3 \cdot 7H_2O$ in methanol. This procedure resulted in an 8:1 mixture (monitored by ^{1}H NMR) in favor of the desired epimer *syn*-**57** in 99% combined yields. After separation by HPLC, the C_{20}-(*S*)-configuration of *syn*-**57** was confirmed by Mosher-ester analysis,[58] and the undesired epimer *anti*-**57** was recycled by oxidation with sulfur trioxide−pyridine complex.[44] Alcohol *syn*-**57** was converted to alcohol **58** in 93% yield by sequential MOM protection of the secondary hydroxyl group and deprotection of the primary triethylsilyl ether with tetrabutylammonium fluoride. Alcohol **58** was then treated with 1-phenyl-1*H*-tetrazol-5-thiol (PT-SH) under Mitsunobu conditions[59] to give sulfide **59** in 90% yield. Careful oxidation of thioether **59** with hydrogen peroxide in the presence of ammonium heptamolybdate tetrahydrate in ethanol[60] produced after 4.5 h a mixture of sulfone **7**, unreacted thioether **59**, and the intermediate sulfoxides, from which most of the crystalline sulfone **7** could be separated by filtration. The residue was resubmitted to oxidation to produce a second crop of sulfone in 74% combined yield.[61] Thus, the C_{17}−C_{27} fragment **7** was available from butyrolactone **54** in six steps and 42% overall yield, and from glycidyl ether **45**, respectively, in 10 steps and 38% total yield.

Fragment Assembly and Completion of the Synthesis. For the completion of the synthesis, fragments **7** and **8** were connected by using an *E*-selective one-step Julia−Kocienski olefination[21,22] (Scheme 9). Thus, the C_{16}-OPMB ether in **30** was removed with DDQ to give alcohol **60** in 89% yield. Swern[62] or Dess−Martin[63] oxidation of **60** provided crude aldehyde **8**, which was treated with the anion derived from sulfone **7** and KHMDS. When the olefination was performed in 1,2-dimethoxyethane (DME) at −60 °C, we obtained *E*/*Z*-mixtures of olefins **61** varying from 11.4:1 to 6.3:1 in 60−67% combined yields, depending on slight variations of the reaction conditions (deprotonation time for sulfone **7**, rate of rise in temperature after union of components). In THF as solvent, the yield rose to 71%, but the *E*/*Z* ratio dropped to 2.8:1. Isomer *E*-**61** was readily separated

SCHEME 9. Fragment Union and Macrocyclization



[a] For reaction conditions, yield, and ratio of isomers, see text and Supporting Information.

by chromatography, and the PMB ether was cleaved with DDQ to give alcohol **62** in 89% yield, which was acylated with bis(2,2,2-trifluoroethyl) chlorocarbonylmethyl-phosphonate[64] to afford phosphonate **63** in 91% yield. Treatment of **63** with aqueous acetic acid in THF at room temperature removed the silyl ether smoothly in 3.5 h to generate alcohol **64** in 95% yield.[65] Oxidation with Dess−Martin periodinane[63] provided cyclization precursor **4** in 96% yield, which was subjected to an intramolecular Horner−Emmons olefination using Still's optimized base system[20] (0.95 equiv of KHMDS, 18-crown-6,

(57) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226−2227.

(58) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096. (c) Rieser, M. J.; Hui, Y.-h.; Rupprecht, J. K.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z.; Hoye, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10203−10213, and references therein.

(59) Mitsunobu, O. *Synthesis* **1981**, 1−28.

(60) Schultz, H. S.; Freyermuth, H. B.; Buc, S. R. *J. Org. Chem.* **1963**, *28*, 1140−1142.

(61) Prolonged reaction times resulted in olefin epoxidation products. In a recent synthesis of the C_{15}−C_{27} fragment of **1**, Davidson's group[11l] also observed competing formation of a C_{25}−C_{26} epoxy derivative during oxidation of a PT-thioether derived from alcohol **44**. However, the epoxide could be reconverted to the desired alkene, by treatment with Ph_3P/I_2.

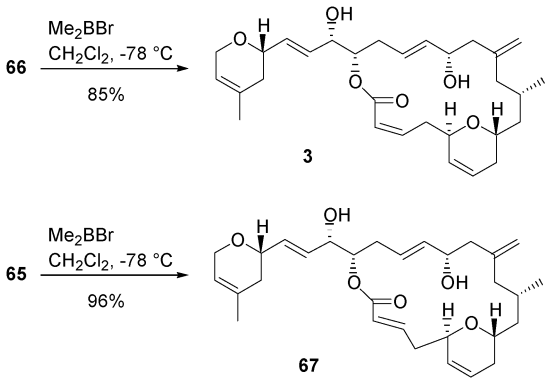
(62) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165−185.

(63) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

(64) The acylating agent was prepared from commercially available methyl ester by means of enzymatic hydrolysis with PLE (Fluka 46058) and subsequent reaction of the acid with oxalyl chloride.

(65) Attempted desilylation of **63** with TBAF resulted in decomposition of the phosphonate moiety.

SCHEME 10. Synthesis of the Deoxylaulimalides 3 and 67



THF, 50 min, −78 °C). This procedure led to a disappointing 1.8:1 *E*/*Z*-mixture of macrolactones **65** and **66** in 80% yield. Alternatively, treatment of phosphonate-aldehyde **4** with K_2CO_3 (6 equiv)/18-crown-6 (12 equiv) for 1 h in toluene *at room temperature*[66] provided the olefination products **65** and **66** quantitatively, but did not improve the isomeric ratio ($E:Z = 2.1:1$).[67] Separation of **65** and **66** by chromatography on silica gel, followed by removal of both MOM groups with dimethylboron bromide (3 equiv) in dichloromethane at −78 °C,[68] generated the deoxylaulimalides **67** and **3** in 96 and 85% yield, respectively (Scheme 10).

Second-Generation Syntheses (Routes 2 and 3): Fragment Union by Allyl Transfer, Macrocyclization by Yamaguchi Lactonization (Route 2). To obtain the *Z*-enoate moiety stereoselectively, an alternative strategy was developed by envisaging an asymmetric allyl transfer for the connection of appropriately functionalized $C_{15}-C_{27}$ and C_3-C_{14} fragments[11g,h,13c] (Figure 4). The simplest version of the $C_{15}-C_{27}$ part would have been aldehyde **74**, where the allylsilane or allylstannane moiety would add in the presence of a chiral Lewis acid[69,70] to achieve notable stereocontrol at the stereogenic center C_{15}. This option, however, did not appeal to us, considering the known toxicity of organostannanes and the uncertain stereodirecting efficiency of the chiral catalyst. Rather, derivatives **69**[11g] and **73**[13c] were taken into consideration, both of which could provide the desired stereochemistry at C_{15}, either in the form of Felkin−Anh type 1,2-induction (**69**)[71] or via a diastereotopos-selective S_N2-type opening of the chiral acetal

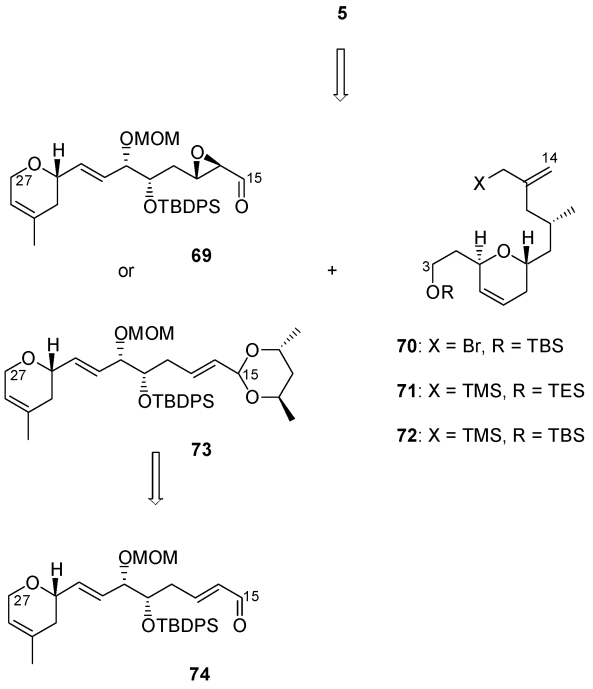


FIGURE 4. Second retrosynthetic analysis.

in **73**.[72−75] For the C_3-C_{14} allylic part two variations were obvious, namely bromide **70**, which would call for a Nozaki−Hiyama-type addition[76] to epoxy aldehyde **69**, or the silanes **71**/**72**, which could be added to acetal **73** under Lewis acid catalysis.[72−75]

Synthesis of $C_{15}-C_{27}$ Fragments. First, we aimed for the synthesis of epoxy aldehyde **69** (Scheme 11).[11g] Thus, our previous intermediate **41** was protected as the TBDPS ether **75** and the ester group in **75** was reduced (DIBALH, CH_2Cl_2, −78 °C) to provide the primary alcohol **76** (91% yield), which was then converted to the THP ether **77**. Next, the PMB ether in **77** was cleaved with DDQ to give alcohol **78**. Oxidation of **78** with pyridine−SO_3 complex,[44] followed by Pinnick oxidation to the acid[77] and esterification with diazomethane gave methyl ester

(66) Improved *Z*-selectivity at higher temperatures was observed during phorboxazole A synthesis.[19c]

(67) For similar results obtained with differently protected analogues of aldehyde phosphonate **4**, see refs 12a,c.

(68) Guindon, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem*. **1984**, *49*, 3912−3920.

(69) (a) Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc*. **1993**, *115*, 11490−11495. (b) Marshall, J. A.; Tang, Y. *Synlett* **1992**, 653−654. (c) Keck, G.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc*. **1993**, *115*, 8467−8468. (d) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc*. **1993**, *115*, 7001−7002. (e) Yanagisawa, A.; Nakashima, H.; Ishaba, A.; Yamamoto, H. *J. Am. Chem. Soc*. **1996**, *118*, 4723−4724 and references therein.

(70) A TBS-protected analogue of aldehyde **74** has been a key fragment in Wender's recent total synthesis of laulimalide,[15] and was connected stereoselectively with a 5-vinyl-substituted analogue of allyl silanes **71** and **72** by means of Yamamoto's chiral acyloxyborane.[69a] In the cyclization step, Wender and co-workers referred to the work of Ghosh[12b,c] by lactonization of a hydroxy alkynoic acid.

(71) Similarly to our retrosynthetic design,[11g] Williams[16b] utilized an analogue of epoxyaldehyde **69**, which was treated with an allylsilane to provide the (15*S*)-coupling product selectively in 53% yield. The groups of Davidson[11l] and Crimmins[16a] synthesized $C_{15}-C_{27}$ epoxyaldehyde fragments analogous to **69** but with (19*R*)-stereochemistry, as the coupling partners. To date, the critical allylation reaction was performed only by Crimmins and gave a rather low 3:1 stereoselectivity.

(72) (a) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *J. Am. Chem. Soc*. **1983**, *105*, 2088−2090. (b) Choi, V. M. F.; Elliott, J. D.; Johnson, W. S. *Tetrahedron Lett*. **1984**, *25*, 591−594. (c) Johnson, W. S.; Crackett, P. H.; Elliott, J. D.; Jagodzinski, J. J.; Lindell, S. D.; Natajaran, S. *Tetrahedron Lett*. **1984**, *25*, 3951−3954.

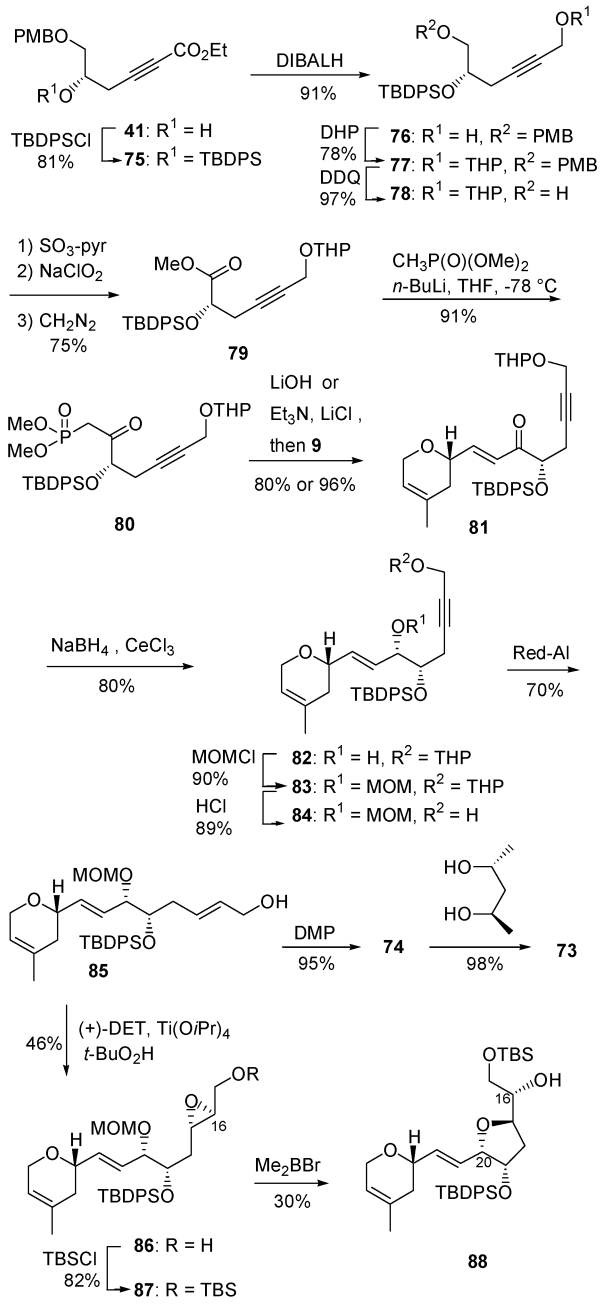
(73) For a review on chiral acetals derived from optically active alcohols, see: Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477−511.

(74) For extensive studies on the mechanism and origin of stereoselective opening of chiral dioxane acetals, and for leading references, see: (a) Denmark, S. E.; Willson, T. M.; Almstead, N. G. *J. Am. Chem. Soc*. **1989**, *111*, 9258−9260. (b) Denmark, S. E.; Almstead, N. G. *J. Org. Chem*. **1991**, *56*, 6485−6487. (c) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc*. **1991**, *113*, 8089−8110.

(75) For recent examples, see: (a) Yamamoto, Y.; Abe, H.; Nishii, S.; Yamada, J.-i. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3253−3257. (b) Chen, S.-H.; Sun, X.; Boyer, R.; Paschal, J.; Zeckner, D.; Current, W.; Zweifel, M.; Rodriguez, M. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 2107−2110.

(76) For reviews, see: (a) Cintas, P. *Synthesis* **1992**, 248−257. (b) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1−36.

SCHEME 11. Synthesis of $C_{15}-C_{27}$ Fragments 86 and 73



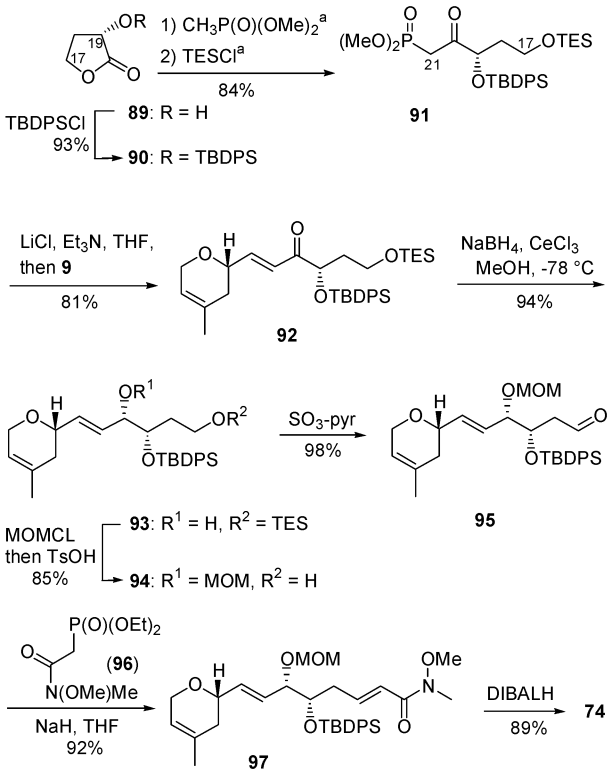
79 in 75% overall yield. Reaction of ester **79** with the lithium salt of dimethyl methanephosphonate afforded the *β*-oxophosphonate **80** in 91% yield. HWE-olefination of **80** with aldehyde **9** was first performed with lithium hydroxide, prepared in situ from *n*-butyllithium and water, and led selectively to (*E*)-olefin **81** in 80% yield.[11g] The reaction between phosphonate **80** with aldehyde **9** in THF in the presence of 2 equiv of lithium chloride and triethylamine[56] afforded enone **81** in 96% yield.[11i] The high yield in this case presumably results mainly from the fact that **9** had been prepared by glycol cleavage of **53**[11i] and not by Parikh Doering oxidation of **44**. Reduction of the C_{20} carbonyl group with L-Selectride yielded *syn*-alcohol **82** as a single diastereomer. However, extensive silyl migration from $C_{19}-O$ to $C_{20}-O$ was observed. This problem was overcome by applying Luche conditions[57] under which silyl migration was reduced to less than 5%. The cerium(III) counterion significantly reduced the nucleophilicity of the alkoxide, and alcohol **82** was isolated in 80% yield. MOM-protection of the newly formed hydroxy group led to **83** in 90% yield. Selective removal of the THP group in **83** with 2.5% aqueous HCl in methanol provided propargylic alcohol **84** in 89% yield. Reduction of the triple bond in **84** with Red-Al in diethyl ether furnished stereoselectively the (*E*)-allylic alcohol **85** in 70% yield. Finally, Sharpless epoxidation[18] with (+)-diethyl tartrate (DET) gave epoxy alcohol **86** in 46% yield and a diastereomeric ratio of 94:6 (determined by ^{1}H NMR). At that point we thought it advisable to test conditions for removing the MOM group at $C_{20}-O$ in the presence of the $C_{16}-C_{17}$ epoxide, using the TBS-protected derivative **87** as a model compound. However, to our dismay, even under the mildest conditions available (Me_2-BBr, CH_2Cl_2, Et*N*iPr_2, −78 °C) formation of the tetrahydrofuran **88** was observed, so that this approach was abandoned. Instead, allylic alcohol **85** was oxidized to aldehyde **74** with the Dess−Martin periodinane[63] and transformed to acetal **73** in 98% yield by reaction with commercially available (*R*,*R*)-(+)-pentane-2,4-diol in the presence of montmorillonite K-10 clay[32] in toluene under azeotropic removal of water.

A more efficient approach to $C_{15}-C_{27}$ aldehyde **74**[13c] is illustrated in Scheme 12. Commercially available (*S*)-α-hydroxybutyrolactone **89**[54] was protected as the TBDPS ether **90** (93% yield), which was transformed to *β*-oxophosphonate **91** by the one-pot procedure described in detail for analogue **11** in Scheme 8. HWE-olefination of **91** with aldehyde **9** (prepared by oxidation of alcohol **44**) under Masamune−Roush conditions[56] led stereoselectively to (*E*)-enone **92** in 81% yield. In contrast to the PMB-protected analogue **56**, 1,2-reduction of **92** under Luche conditions[57] delivered the desired *syn*-alcohol **93** with a diastereoselection of 20:1 (by ^{1}H NMR) in 94% yield. No problems with silyl migration were encountered when the reaction was performed in methanol at −78 °C and quenched after 10 min with a solution of ammonium chloride in methanol. Next, the secondary OH-function in **93** was protected as the MOM-ether by using a large excess of MOMCl and Hünig's base in the presence of tetrabutylammonium iodide in DMF. Without purification, the sensitive primary triethylsilyl-ether was cleaved with a catalytic amount of TsOH in methanol at room temperature to provide alcohol **94** in 85% yield after two steps. Parikh−Doering oxidation[44] of **94** yielded aldehyde **95** in 98% yield. Chain elongation to (*E*)-enal **74** was achieved by a stereoselective HWE-olefination of **95** with commercial available phosphonate **96** (NaH, THF, 92% yield) to give Weinreb amide **97**, which on reduction with DIBALH in THF at −78 °C furnished aldehyde **74** in 89% yield. Compared with other syntheses[11k,l,14−16] this approach to a $C_{15}-C_{27}$ aldehyde is by far the most effective with respect to the number of steps (8 steps from butyrolactone **89**, 13 steps from trityl glycidol **45**) and overall yield (41% from **89**, 32% from **45**).

Synthesis of the Allylic C_3-C_{14} Fragments 70−72. Although the prospect of performing the envisaged Hiyama−Nozaki coupling of allyl bromide **70** to epoxy-

(77) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091−2096.

SCHEME 12. Improved Approach to the $C_{15}-C_{27}$ Fragment; Synthesis of Aldehyde 74



[a] For reaction conditions, see text.

aldehyde **69** appeared rather bleak for the reasons outlined above, the synthesis of **70** was completed nonetheless. Our approach (Scheme 13a,b)[11h] was based on the similarity of the C_9-C_{14} section of laulimalide with naturally occurring (−)-citronellal **98**.[78]

Among several options, conversion of aldehyde **98** into epoxide **99** appeared attractive for introduction of the laulimalide stereochemistry at C_9 and subsequent elaboration of the dihydropyran moiety. The epoxide, in turn, should be generated in diastereomerically pure form by Jacobsen's hydrolytic kinetic resolution (HKR).[79] In this event, aldehyde **98** was converted to an 1:1 mixture of epoxide diastereomers **99** and 9-*epi*-**99** via Corey's sulfonium ylide addition.[80] Jacobsen-HKR with catalyst **100** in *tert*-butyl methyl ether (TBME) for 36 h led to the formation of diol **101** along with the desired epoxide **99**, both diastereomerically pure according to standard criteria (HPLC, ^{1}H and ^{13}C NMR spectra). Diol **101** was effectively transformed to epoxide **99** by a dehydrative cyclization under inversion of configuration at C_9, via regioselective protection of the primary hydroxy group (TBDPSCl, imidazole, DMF, 94% yield), followed by mesylation of the secondary alcohol, silyl deprotection with TBAF, and ring closure with sodium hydroxide (89% yield for the two steps). In this way, aldehyde **98** was converted into epoxide **99** with an overall yield of 76%.

For the conversion of **99** into lactone **103**, we first used Ghosez's lactonization method,[27] following the protocol that had been previously applied to epoxide **18** (cf. Scheme 2). However, due to concomitant attack on the trisubstituted double bond, the acid-promoted lactonization step could not be performed with TFA. When we used TsOH instead (toluene, rt), lactone **103** was obtained in yields up to 85%. Alternatively, the trusted method[81] previously used for the synthesis of the "upper" dihydropyran fragment (cf. Scheme 5) was also applied with success. Regioselective ring opening of epoxide **99** with lithium ethyl propiolate (THF, −95 °C) mediated by $BF_3 \cdot Et_2O$ led to alkynoate **102** in 91% yield. Lindlar hydrogenation in ethanol in the presence of quinoline afforded the (*Z*)-enoate, which was cyclized in situ to form lactone **103** in 96% yield. The electron-rich double bond in **103** was selectively epoxidized with *m*-chloroperbenzoic acid, the resulting epoxide was opened with perchloric acid in THF/H_2O, and the diol thus obtained was cleaved with $NaIO_4$ to provide aldehyde **104** in 77% overall yield. To introduce the C_{13} methylene group, **104** was subjected to Eschenmoser methylenation,[82] which led to aldehyde **105** in 66% yield. Reduction of **105** with DIBALH converted the enal into the allylic alcohol and the lactone into the corresponding lactol, which was transformed without purification into ethyl glycoside **106** with ethanol in the presence of TsOH (78% overall yield). After acetylation, compound **107** was ready for the introduction of the C_2-C_3 appendage. Commercially available vinyl-OTMS was added in the presence of lithium perchlorate[83] to provide the corresponding C_3 aldehyde as a single epimer (by ^{1}H NMR), which was reduced to alcohol **108** with $NaBH_4$ (85% yield over the two steps). TBS-protection delivered intermediate **109** (73% yield), which was selectively deprotected at the C_{14}-OAc position with potassium carbonate in methanol (85% yield) to give alcohol **110**. Standard bromination (CBr_4, PPh_3, MeCN) led to bromide **70** in 56% yield.

The synthesis of allylsilane **71**[13b] started from commercially available ethyl hydrogen (*R*)-3-methylglutarate **111** (Scheme 14). The carboxyl group in **111** was reduced regioselectively with $BH_3 \cdot Me_2S$ complex in THF, and the resulting alcohol was oxidized with the Dess−Martin periodinane[63] to give aldehyde **112**[84] in 97% yield after 2 steps. Brown's asymmetric allylboration[39] under the conditions described in Scheme 4 for the conversion of **33** to **34** furnished homoallylic alcohol **113** diastereoselectively (de = 91%, by ^{1}H NMR of the crude product) in 87% yield. Under the conditions necessary for transacetalization with acrolein diethylacetal, ester **113** underwent lactonization. Therefore, **113** was transformed to the more stable dimethylamide **114**, which was converted by transacetalization and subsequent RCM of the resulting dienes **115** into an anomeric mixture (1:1, by ^{1}H

(78) The synthetic potential of (−)-citronellal (**98**) was also used by Davidson[11j] and Crimmins[16a] to prepare C_1-C_{14} allyl stannane fragments of **1**.

(79) (a) Jacobsen, E. N.; Tokunaga, M.; Larrow, J. F.; Kakiuchi, F. *Science* **1997**, *277*, 936−938. (b) Jacobsen, E. N.; Furrow, M. E.; Schaus, S. E. *J. Org. Chem*. **1998**, *63*, 6776−6777. (c) Jacobsen, E. N.; Hinterding, K. *J. Org. Chem*. **1998**, *63*, 2164−2165.

(80) Borredon, E.; Delmas, M.; Gaset, A. *Tetrahedron Lett*. **1982**, *23*, 5283−5286.

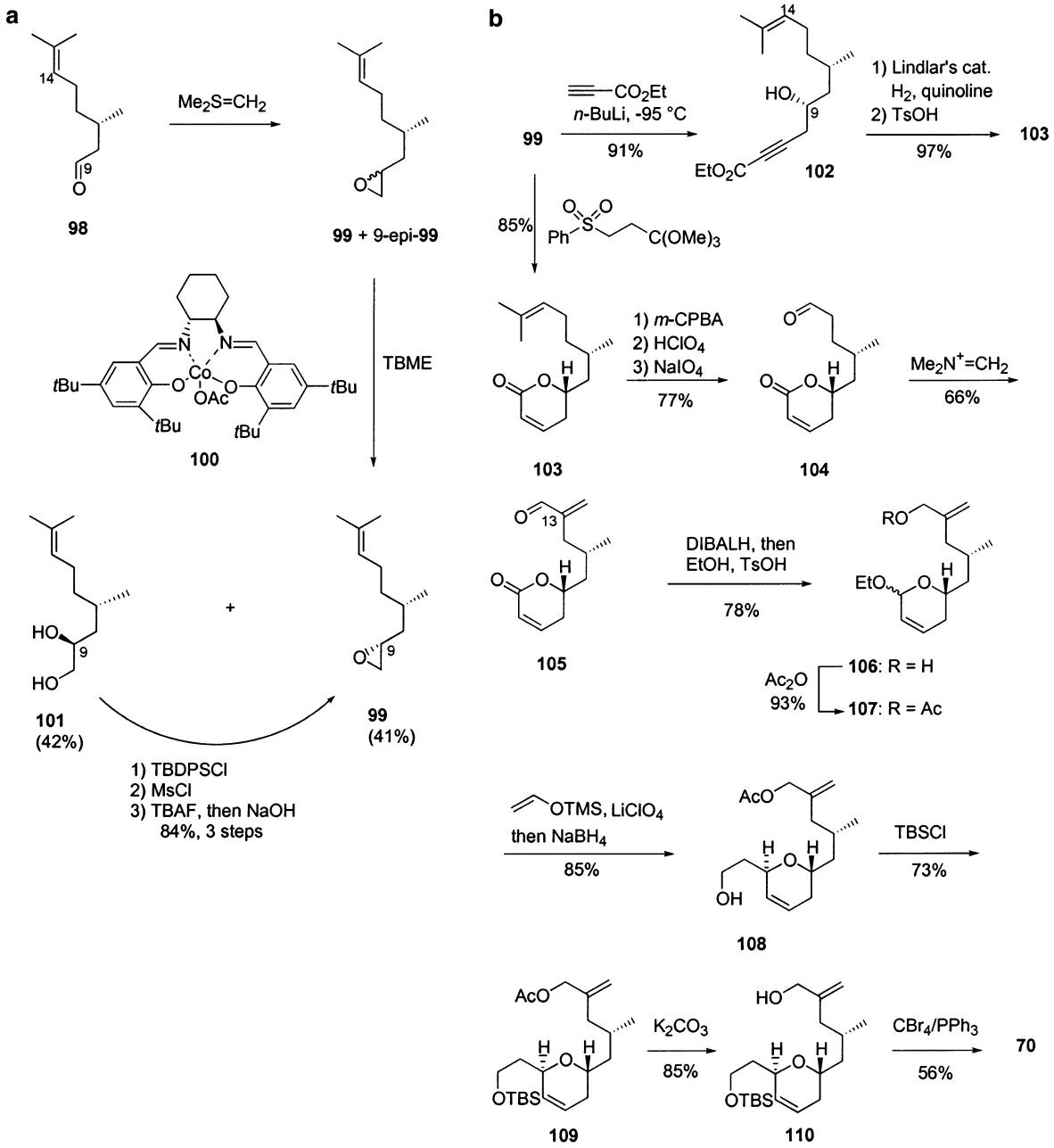
(81) For related protocols, see: Oizumi, M.; Takahashi, M.; Ogasawara, K. *Synlett* **1997**, 1111−1113. Also see ref 25a.

(82) For a related protocol, see: Paquette, L.; Dyck, B. P. *J. Am. Chem. Soc*. **1998**, *120*, 5953−5960.

(83) Grieco, P. A.; Speake, J. D. *Tetrahedron Lett*. **1998**, *39*, 1275−1278.

(84) The methyl ester analogue of aldehyde **112**, available from (*R*)-citronellic acid, has been used in Wender's recent total synthesis of **1**[15] to prepare a close analogue of allyl silanes **71** and **72**.

SCHEME 13. (a) Jacobsen HKR of Epoxide 99 and (b) Synthesis of Allyl Bromide 70



NMR) of the ethyl glycosides **116**. Introduction of the side chain at C_5 was achieved as before by treatment with vinyl-OTBS, using a solution of lithium perchlorate in ethyl acetate as the Lewis acid.[83] Aldehyde **117**, obtained as a single epimer (according to ^{1}H NMR of the crude product**)** in 88% yield, was reduced with sodium borohydride and the resulting alcohol protected as triethylsilyl ether **118** (96% yield for the 2 steps). Treatment of amide **118** with methyllithium in Et_2O at −78 °C provided methyl ketone **119** in excellent yield.

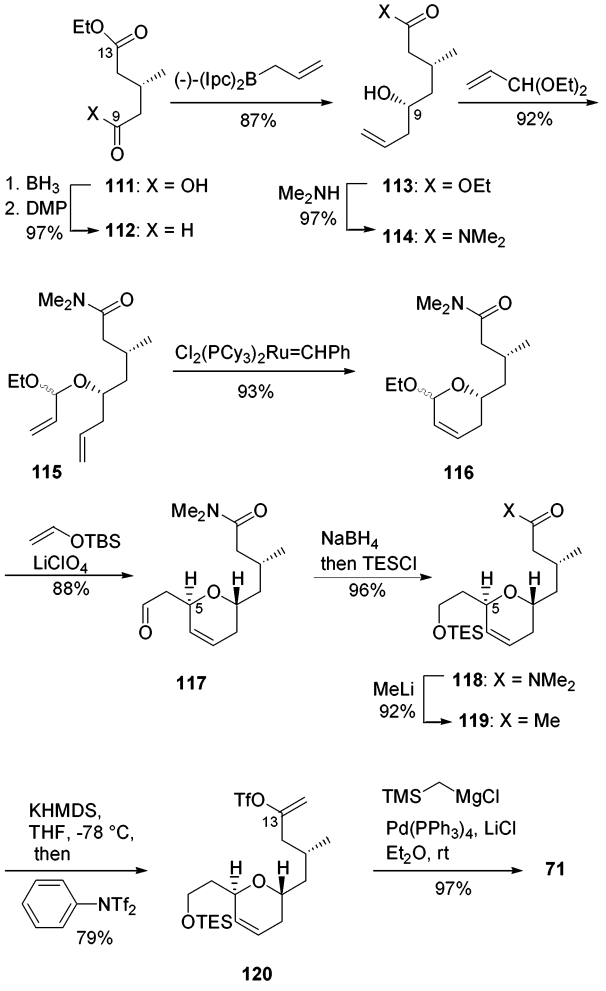
For the introduction of the allylsilane moiety, methyl ketone **119** was converted to the kinetic enolate (KHMDS, 1.5 equiv) and treated with $PhNTf_2$ (1.6 equiv)[85] to afford enol triflate **120** regioselectively in 79% yield. Next, following Kuwajima's protocol,[86] compound **120** was subjected to the reaction with trimethylsilylmethylmagnesium chloride (6 equiv) in the presence of $Pd(PPh_3)_4$ (30 mol %) to give, after 1 h, an inseparable mixture of compound **71** and its $\Delta^{12,13}$ isomers. Quite obviously, the large amount of the catalyst as well as the long reaction time led to isomerization. The similarity of the described protocol to the Stille coupling[87] prompted us to perform the reaction in the presence of lithium chloride. We were pleased to observe that in the presence of 5 equiv of LiCl and only 5 mol % of $Pd(PPh_3)_4$, triflate **120** reacted with

(85) Scott, W.; McMurry, E. *Acc. Chem. Res.* **1988**, *21*, 47−59.

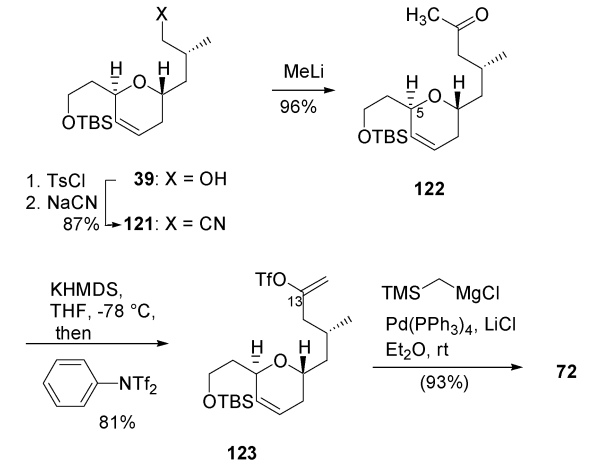
(86) (a) Morihira, K.; Hara, R.; Kawahara, S.; Nishimori, T.; Nakamura, N.; Kusama, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1998**, *120*, 12980−12981. (b) Kusama, H.; Hara, R.; Kawahara, S.; Nishimori, T.; Kashima, H.; Nakamura, N.; Morihira, K.; Kuwajima, I. *J. Am. Chem. Soc.* **2000**, *122*, 3811−3820.

(87) Stille, J. K.; Scott, J. W. *J. Am. Chem. Soc.* **1986**, *108*, 3033−3040.

SCHEME 14. Synthesis of Allylsilane 71



SCHEME 15. Synthesis of Allylsilane 72



$TMSCH_2MgCl$ (2 equiv) to furnish, after only 10 min, pure allylsilane **71** in 97% yield.

For the synthesis of allylsilane **72**[13c] (Figure 4 and Scheme 15), intermediate **39** was transformed to the cyanide **121** in 87% yield by treatment of the tosylate with sodium cyanide in DMSO at 80 °C. Treatment of nitrile **121** with methyllithium in diethyl ether at 0 °C provided methyl ketone **122** (96% yield), which was transformed into allylsilane **72** via enoltriflate **123** as described before.

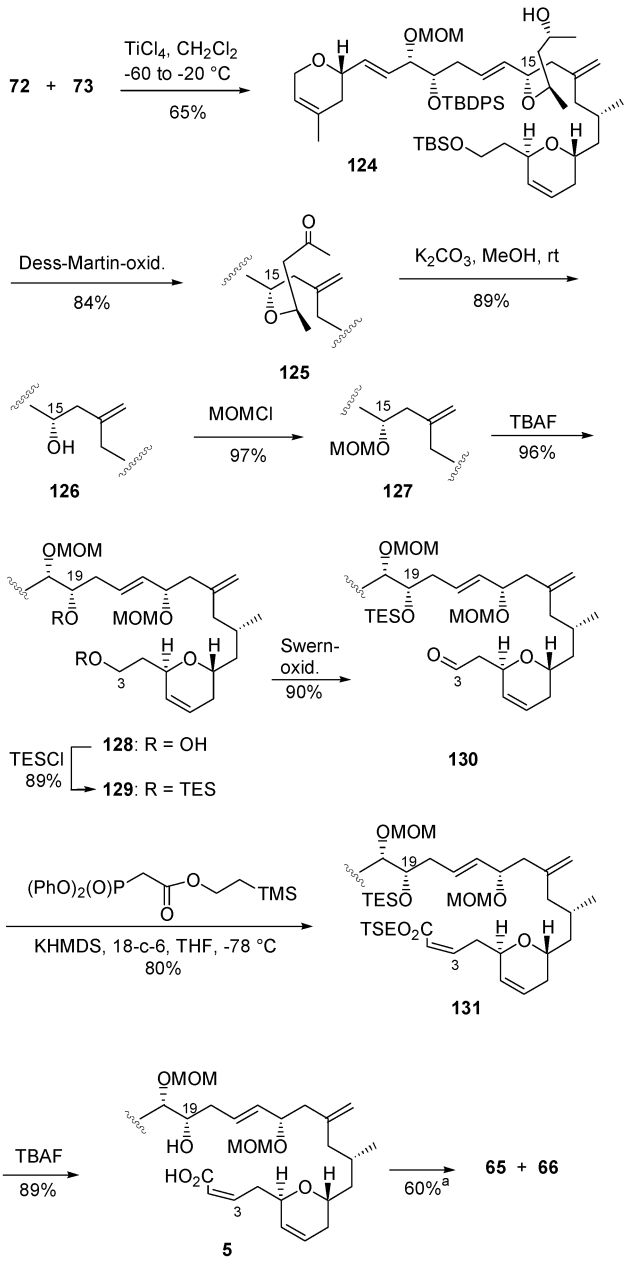
Completion of Route 2. Yamaguchi Macrolactonization. Extensive experimentation was necessary to obtain satisfactory results in the crucial allylation of acetal **73** with allylsilanes **71** or **72**. Traces of water and/or HCl arising from handling the moisture-sensitive Lewis acids ($SnCl_4$/DMF, $EtAlCl_2$, $TiCl_4$) led to concomitant loss of the protective groups (C_3-OTES, C_3-OTBS, C_{20}-OMOM). Moreover, the chiral auxiliary was partially lost, so that the coupling proceeded with low stereocontrol. Reproducible results were achieved by treating a solution of $TiCl_4$ (from a freshly opened bottle) in CH_2Cl_2 with a few drops of Et_3N, and adding an aliquot (1.2 equiv) of the resulting mixture via syringe filter to a precooled (−60 °C) solution of acetal **73** (1 equiv) and the more stable allylsilane **72** (1.2 equiv). This procedure reproducibly furnished the fully protected coupling product **124** (de = 92%, monitored by ^1H NMR) in 65% yield. After Dess−Martin oxidation of alcohol **124** to methyl ketone **125**, base-induced retro-hetero-Michael reaction with potassium carbonate in methanol at room temperature[88] provided alcohol **126** in 89% yield. Alcohol **126** was protected as the MOM ether **127** in high yield with 20 equiv of MOMCl in DMF in the presence of tetrabutylammonium iodide. Next, both silyl groups in **127** were removed with TBAF and replaced by triethylsilyl ethers to give intermediate **129** (85% yield for the 2 steps). Selective Swern oxidation of the primary TES ether[89] in **129** afforded aldehyde **130** in excellent yield.

To complete the carbon skeleton, aldehyde **130** was subjected to an Ando−Horner−Emmons olefination[90] with 2-trimethylsilylethyl (TSE) (diphenoxyphosphoryl)-acetate.[91] Deprotonation of the phosphonate with KHMDS and reaction with aldehyde **130** in the presence of 18-crown-6 in THF at −78 °C led to the desired (*Z*)-enoate **131** in 80% yield. Treatment of the fully protected intermediate **131** with TBAF in THF removed both the C_{19}-OTBDPS ether and the TSE ester, and provided *seco*-acid **5** in 89% yield. However, Yamaguchi macrocyclization[92] was accompanied by *Z*/*E*-isomerization of the 2,3-enoate, and we isolated the MOM-protected macrolides **65** and **66** as an *E*/*Z*-mixture (*E*/*Z* = 2.7:1) in 60% combined yields.

Base-induced $C_{2,3}$-*Z*/*E* isomerization during Yamaguchi-type macrolactonization has been previously observed by Roush during a synthesis of verrucarin B,[93] and was assumed to occur through a reversible Michael addition of nucleophilic reagents to the active ester intermediate. The same *Z*/*E* isomerization was also painfully experienced by Ghosh, who submitted a close analogue of *seco*-acid **5** to cyclization,[12c] and by Paterson during a syn-

(88) Sugimura, T.; Yoshikawa, M.; Futagawa, T.; Tai, A. *Tetrahedron* **1990**, *46*, 5955−5966.
(89) Rodriguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J. J. *Tetrahedron Lett.* **1999**, *40*, 5161−5164 and references therein.
(90) Ando, K. *J. Org. Chem.* **1999**, *64*, 8406−8408 and references therein.
(91) The olefination reagent was prepared in two steps by acylation of 2-TMS-ethanol with bromoacetyl bromide and treatment of the resulting bromoacetate with diphenyl phosphite in the presence of triethylamine.[90]
(92) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.
(93) Roush, W. R.; Blizzard, T. A. *J. Org. Chem.* **1984**, *49*, 4332−4339 and references therein.

SCHEME 16. Diastereoselective Coupling of Fragments 72 and 73 and Yamaguchi Macrolactonization of *Seco* Acid 5



[a] See text and Supporting Information.

thesis of the C_1-C_{20} core of **1**.[11m] Ghosh overcame the problem by applying the Yamaguchi protocol to a 2,3-alkynoic acid,[12b] and Paterson used a Mitsunobu macrolactonization of a (2*Z*,19*R*)-*seco* acid.[11m,14]

Route 3. Fragment Assembly by Still−Gennari Olefination, Macrocyclization via Allyl Transfer. To avoid the base-induced isomerization of the 2,3-(*Z*)-enoate, we decided to reverse the order of the final steps. As shown in Figure 5, our synthetic design focused now on compound **6** as the macrocyclization precursor,[13b] which should be assembled from phosphonate **132** and aldehyde **133** by an intermolecular Still−Gennari olefination.[20]

Key fragments **132** and **133** were readily obtained from previous intermediates (Scheme 17). Thus, triethylsilyl

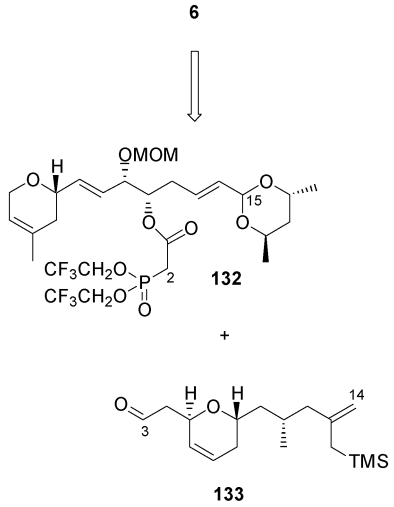


FIGURE 5. Third retrosynthetic analysis.

ether **71** was cleaved with K_2CO_3 in methanol at 0 °C to give alcohol **134** in 96% yield, which was subjected to Dess−Martin oxidation[63] to give aldehyde **133** in 87% yield. For the synthesis of key fragment **132**, the TBDPS ether in acetal **73** was removed with TBAF and the resulting alcohol **135** acylated with bis(2,2,2-trifluoroethyl) chlorocarbonylmethyl-phosphonate[64] to form phosphonate **132** in 96% yield.

Fragment Connection and Completion of the Synthesis. To connect fragments **132** and **133** (Scheme 18), phosphonate **132** was deprotonated with KHMDS in THF at −78 °C, in the presence of 18-crown-6 (5 equiv),[20] carefully avoiding an excess of base. Then, freshly prepared aldehyde **133** was added slowly at the same temperature. Under these conditions, (*Z*)-enoate **6** was obtained isomerically pure (monitored by ^{1}H NMR) in 85% yield. A 4:1 (*E*/*Z*)-mixture was obtained if more than 1 equiv of KHMDS was used, and the reaction time was extended over 1 h at −78 °C.

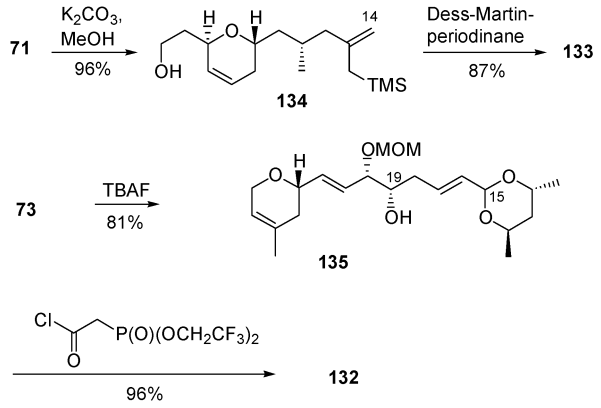
The cyclization was performed by adding *seco*-compound **6** slowly at −50 °C to a 4×10^{-4} M solution of ethylaluminum dichloride[94] in dichloromethane, providing macrocycle **137** as a single isomer in 82% yield. On monitoring the reaction by TLC, a transient intermediate was observed that was isolated and identified as the desilylated *seco*-compound **136**. We thus reasoned that the conversion of **6** to **137** had proceeded via two parallel pathways. One would be the direct cyclization of allylsilane **6**. The second way would have involved first a moisture-induced protodesilylation of **6** to **136**, which then underwent cyclization via an ene reaction.[95] Indeed, when we subjected compound **136** directly to the cyclization conditions described above, macrocycle **137** was obtained in 56% yield, along with 30% of the starting material. When repeated under rigorously anhydrous conditions, the cyclization of **6** proceeded without the appearance of **136** in 86% yield.

The removal of the protective groups from macrocycle **137** required some care. To initiate the envisaged retro-

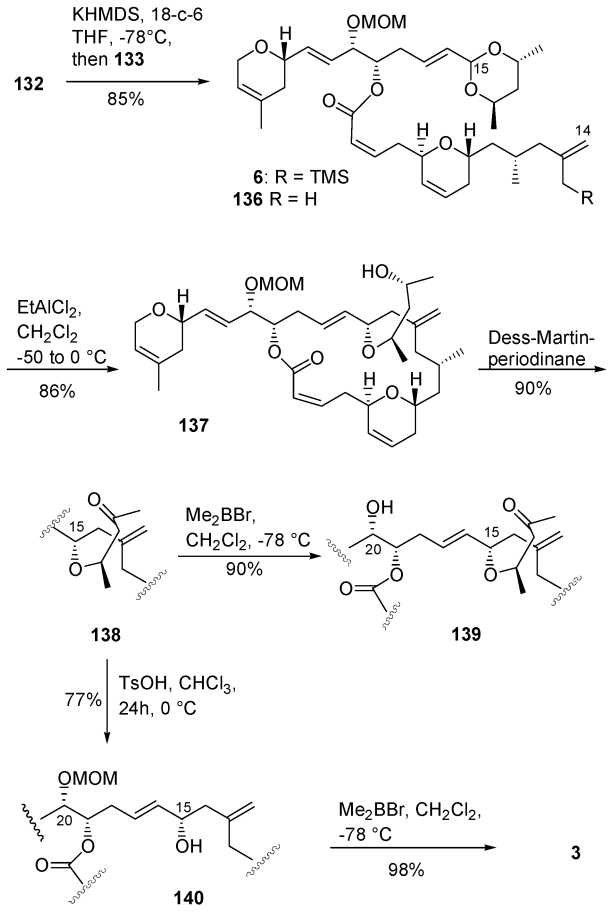
(94) Snider, B. B.; Rodini, D. J.; Karras, M.; Kirk, T. C.; Deutsch, E. A.; Cordova, R.; Price, R. T. *Tetrahedron* **1981**, *37*, 3927−3934.

(95) For allyl transfer to chiral dioxane acetals via ene reaction, see: Cambie, R. C.; Higgs, K. C.; Rustenhoven, J. J.; Rutledge, P. S. *Aust. J. Chem*. **1996**, *49*, 677−688.

SCHEME 17. Synthesis of Coupling Partners 132 and 133



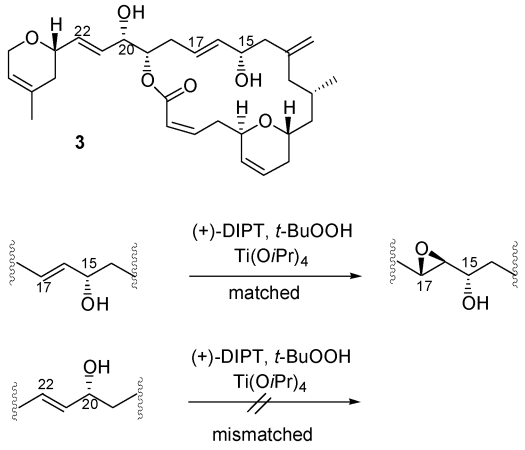
SCHEME 18. Fragment Connection and Completion of the Synthesis



Michael reaction under acidic conditions, intermediate **137** was oxidized with Dess−Martin periodinane to methyl ketone **138** in 90% yield. Treatment of methyl ketone **138** with Me_2BBr[68] in dichloromethane at −78 °C removed the MOM ether at C_{20}-O selectively, leading to compound **139**. Treatment of intermediate **139** with TsOH in chloroform, however, led to 2,3-*Z*-*E* isomerization.

Finally, we were successful by reversing the order of deprotection steps. Thus, treatment of methyl ketone **138** with TsOH (4 equiv) in chloroform at 0 °C for 24 h, smoothly furnished alcohol **140** in 77% yield. The remaining MOM ether in intermediate **140** was then cleaved as before by treatment with dimethylboron bromide (5 equiv) in dichloromethane at −78 °C to provide deoxylaulimalide **3** in high yield. This compound was identical in all respects with the compound obtained in our first approach and thus confirmed that the correct stereochemistry at C_{15} had be generated in the cyclization step. Additionally, the conversion of the fully protected macrocycle **138** to the monoprotected derivatives **139** and **140** by treatment with Me_2BBr and TsOH, respectively, demonstrates the orthogonality of MOM ether and the 4-oxopent-2-yl group, even under acidic conditions.

SCHEME 19. SAE Considerations for Deoxylaulimalide 3



Epoxidation of 3 and 67. As mentioned in the Introduction, there is a strong tendency of **1** to undergo isomerization to isolaulimalide (**2**) even under mildly acidic conditions. Therefore, it was thought unwise to try epoxidations of the 16,17-double bond in the presence of the MOM-protective group at C_{20}-O. Instead we decided to apply a SAE reaction to "naked" deoxylaulimalide **3** in the hope that the reagent control of this procedure would suffice to bring about the desired regioselectivity of the matched C_{15}−C_{17}-allylic alcohol moiety over the mismatched C_{20}−C_{22} section (Scheme 19).

Indeed, exposure of **3** to Sharpless epoxidation[18] with natural (+)-(*R*,*R*)-diisopropyl tartrate (DIPT) at −20 °C for 2 h (Scheme 20, eq 1) did provide a 2:1 mixture of **1** and unreacted compound **3**, from which **1** was separated by HPLC in 86% yield, based on recovered starting material (BORSM). Still, this selectivity might have been the result of a substrate-mediated epoxidation due to the exposed position of the $C_{16,17}$-olefin on the outside of the macrocyclic ring. Therefore, the epoxidation of **3** was repeated without the DIPT additive (Scheme 20, eq 2). Again, **1** was formed selectively; however, the reaction proceeded much more slowly and took about 18 h. This underscores the intrinsic preference for the 16,17-epoxidation and the catalytic effect of the tartrate, and leads to the conclusion that eq 1 represents the case in which substrate and reagent control are matched to each other. To test the power of the SAE process, epoxidation of **3** with (−)-(*S*,*S*)-tartrate was also performed, which indeed gave epoxide **142** (eq 3).

Figure 6 shows how these selectivities are reflected in the ^1H NMR spectra of compounds **1**, **3**, and **142**. The spectrum of **3** exhibits both a *pseudo*-AB pattern centered

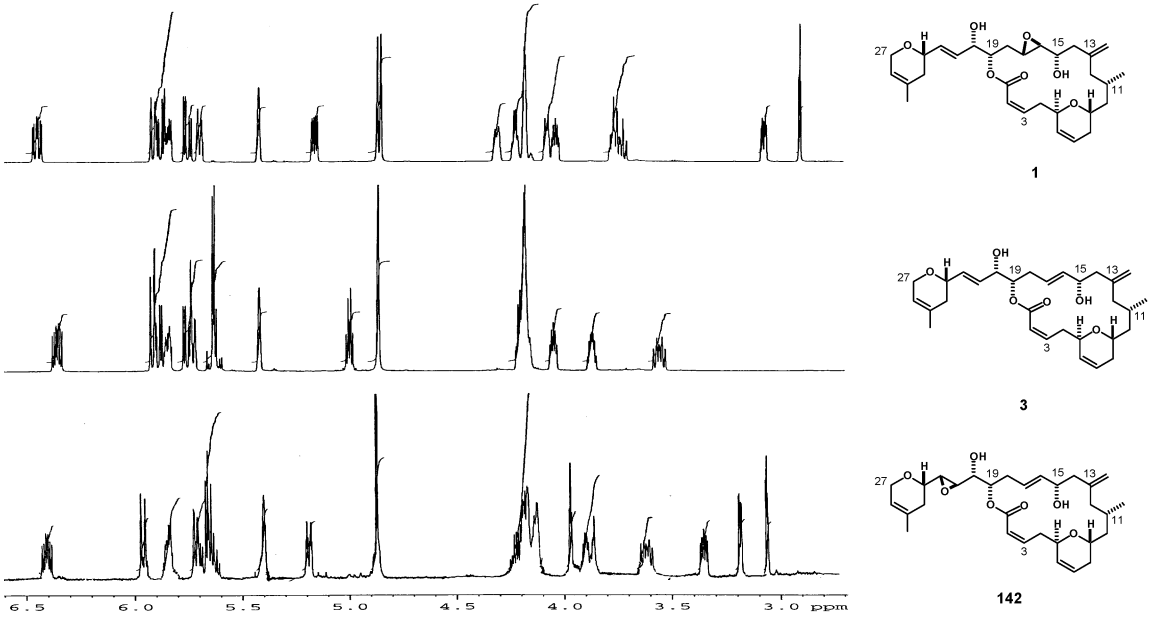
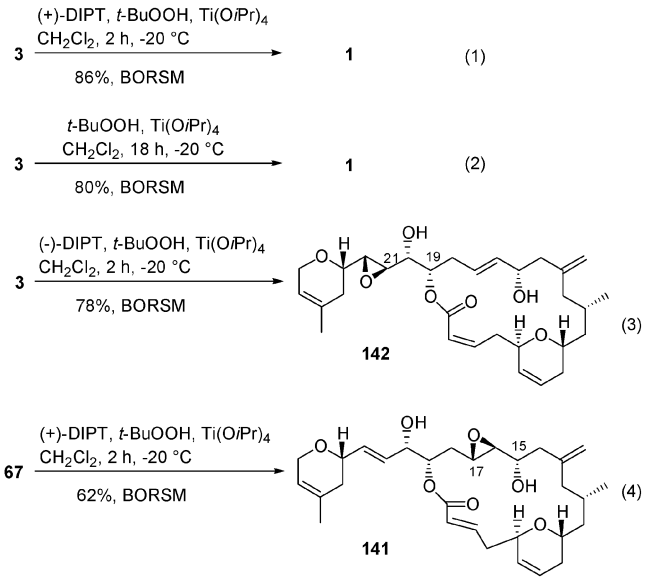


FIGURE 6. ^{1}H NMR spectra (600 MHz) of **1**, **3**, and **142**.

SCHEME 20. Regio- and Stereocontrolled Epoxidation of 3 and 67



at 5.63 ppm for the 16,17-vinylic part and the signals of the 21,22-moiety (H-22, ddd at 5.87 ppm; H-21, ddd at 5.73 ppm; $J_{21,22}$ = 15.6 Hz). In the spectrum of **1**, the signals of the 21,22-unit are still present (H-22, ddd at 5.87 ppm; H-21, ddd at 5.75 ppm), whereas the signals for H-17 (ddd at 3.06 ppm) and H-16 (br t with $J_{16,17}$ = 2.5 Hz) now appear in the epoxide range. In contrast, the spectrum of epoxide **142** still shows the AB pattern of the 16,17-unit, whereas the signals of H-21 (dd with J = 2.4 and 3.1 Hz at 3.06 ppm) and H-22 (dd with J = 2.4 and 5.7 Hz at 3.18 ppm) now are shifted to the epoxide range. As an additional experiment (eq 4), compound **67** was subjected to the "matched" SAE conditions. Not surprisingly, the 16,17-epoxide **141** was obtained as the main product, however, along with another unidentified epoxide.

TABLE 1. Antiproliferative Effects of Laulimalides[a]

	IC_{50} [nM]			
compd	MCF-7	NCI/ADR	MaTu	MaTu/ADR
3	89	ni	43	170
67	ni	ni	ni	ni
1	3.8	36	3.8	6.0
141	54	ni	38	250
epothilone B	0.59	3.5	0.46	1.2
paclitaxel	3.2	>1000	3.3	600

[a] ni: no inhibition measured up to 100 nM. MCF-7: human breast tumor cell line. NCI/ADR: human multi-drug-resistant breast tumor cell line. MaTu: human breast tumor cell line. MaTu/ADR: human multi-drug-resistant breast tumor cell line.

Biological Activities. Compounds **1**, **3**, **67**, and **141** were tested for their effects on the proliferation of four tumor cell lines (Table 1), along with the standard MSAAs paclitaxel and epothilone B.[96,97] It turned out that **1** is about as active as paclitaxel, but significantly less active than epothilone B. The laulimalide derivatives **3** and **141** show much lower activity, and **67** has no activity at all. Against multidrug resistant tumor cell lines, **1**, by contrast to paclitaxel, still reveals considerable activity, albeit less than epothilone B.

Conclusion

In conclusion, we have described three different routes to deoxylaulimalide **3**. Route 1 is not stereocontrolled with respect to the 2,3-enoate moiety; however, the overall yield and the reliability and simplicity of the reactions involved still render this route a viable one. Route 3 is entirely regio- and stereocontrolled, but it requires considerable experimental skill as some tricky reactions are involved. The same is true of route 2, which

(96) Stein, U.; Walther, W.; Lemm, M.; Naundorf, H.; Fichtner, I. *Int. J. Cancer* **1997**, *72*, 885−891.
(97) Kueng, W.; Silber, E.; Eppenberger, U. *Anal. Biochem*. **1989**, *182*, 6−19.

additionally has the disadvantage of lacking 2,3-(*Z*)-selectivity. Nevertheless, we have presented a broad spectrum of options for the preparation of **3** and various major fragments thereof, which should also be applicable to the synthesis of interesting analogues. For the ultimate conversion of **3** into the desired natural product (−)-laulimalide (**1**), we have shown that SAE reaction may be used for achieving regioselectivity in a molecule containing two allylic alcohol moieties with opposite topicity. Thus, **3** could be alternatively converted into laulimalide (**1**) and its regioisomer **142** simply by switching the chiral additive from (+)- to (−)-tartrate. The biological tests have shown that among our laulimalide derivatives **1**, **3**, **67**, and **141** the natural compound **1** is by far the most active one, and that, compared to paclitaxel and epothilone B, **1** is superior to paclitaxel, but inferior to epothilone B.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds, ^{1}H and ^{13}C NMR spectra of compounds **1**, **3**, **5**, **6**, **7**, **8**, **10**, **18**, **30**, *syn*-**57**, **62**, **64**−**67**, **72**, **73**, **124**, **137**, **138**, **140**, and **141**, and figures showing the effects of **1**, **3**, **67**, and **141** on tumor cell proliferation. This material is available free of charge via the Internet at http://pubs.acs.org.

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