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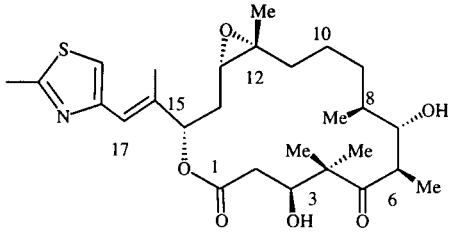
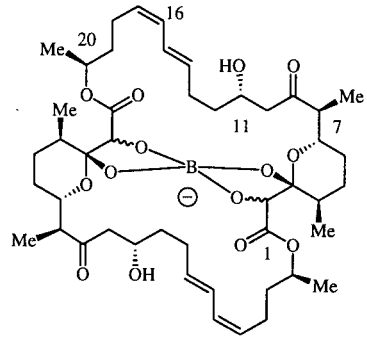
This lecture will describe the total synthesis of two polyketide macrolides, epothilone B (**1**) and tartrolon B (**2**), respectively. Both macrolides are secondary metabolites of the soil myxobacterium *sorangium cellulosum* and show interesting physiological properties: **1** acts as an antitumor agent, and **2** is an antibiotic with a broad spectrum against Gram positive bacteria.



1
Epothilone B

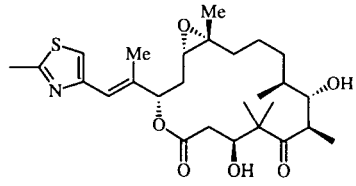


2
Tartrolon B

Formula 1.

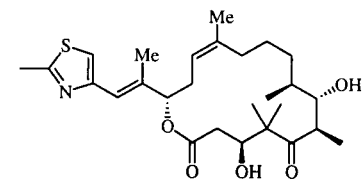
Quite sensationally, it was found three years ago that **1** is superior to the well-established paclitaxel (taxol®) with respect to the stabilization of microtubules in eucaryontic cells. This is a novel concept for killing tumor cells, as the mitotic cycle of these cells is based on a permanent de- and reaggregation of microtubules. Presently **1** is considered worldwide as a potential paclitaxel successor because it lacks multidrug resistance and shows much better bioavailability than paclitaxel does. Moreover, **1** can be obtained in large quantities by the fermentation of soil myxobacteria (*sorangium cellulosum*) [1]. However, quite recently it has been shown that the toxicity of **1** is too high for a clinical application in cancer treatment. This makes the development of more suitable synthetic derivatives inevitable. On the other hand, structural modification of natural **1** is rather limited so that efficient total syntheses in this class of compounds are urgently required. There are, in fact, altogether nine total syntheses of **1** all of which focus on the epoxidation of the corresponding olefin, namely epothilone D (**3**), a much less active metabolite, as the ultimate step [2].

We were intrigued by the idea that the 12,13-epoxide might be an essential part of the pharmacophor in the sense that the microtubule receptor could irreversibly add to **1** by opening the epoxide with a sulfur or nitrogen nucleophile. This would imply that the epoxide in **1** is highly sensitive towards a wide selection of reagents. To



1
Epothilone B

100



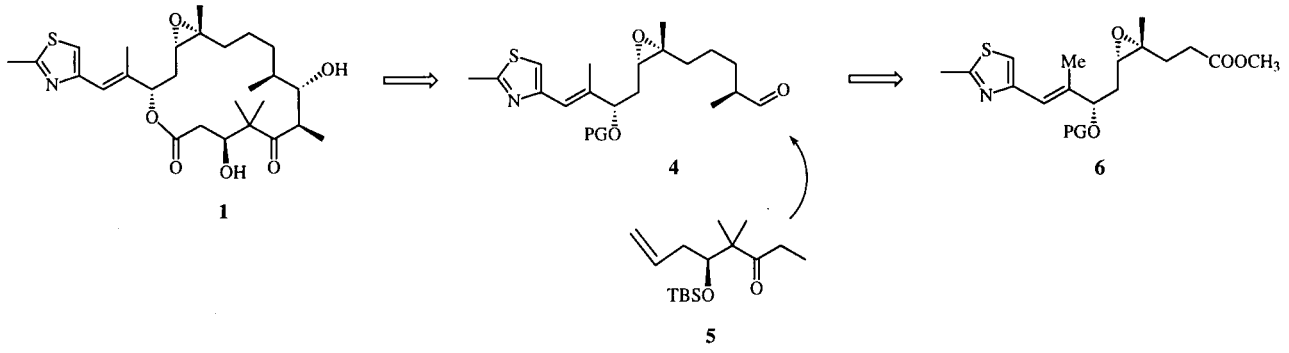
3
Epothilone D

1

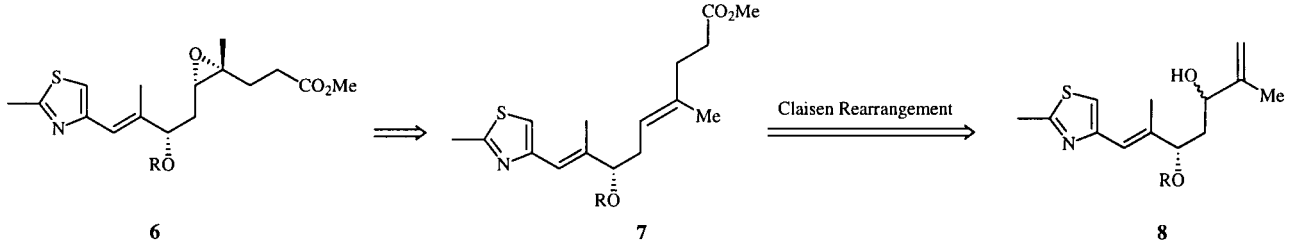
Activity towards tumor cells

Formula 2.

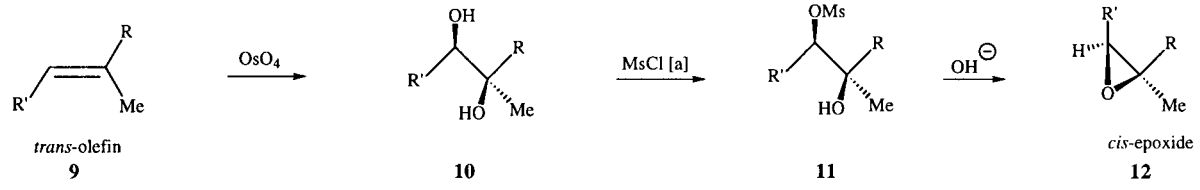
test this idea we initiated a total synthesis of **1** in which the epoxide should be installed at a very early stage and should then be carried through the entire sequence. So the crucial key aldol addition connecting C-6 and 7 should be performed with an epoxy aldehyde **4** and the known ketone **5** [2]. Aldehyde **4**, in turn, should be derived from ester **6** which can retrosynthetically be traced back to olefin **7** *via* dihydroxylation. Claisen rearrangement leads from **7** to allylic alcohol **8**. The conversion of a *trans*-olefin **9** to a *cis*-epoxide **12** *via* a *cis*-diol **10** is performed by an inversion of configuration from mesylate **11** to epoxide **12**.



Formula 3.



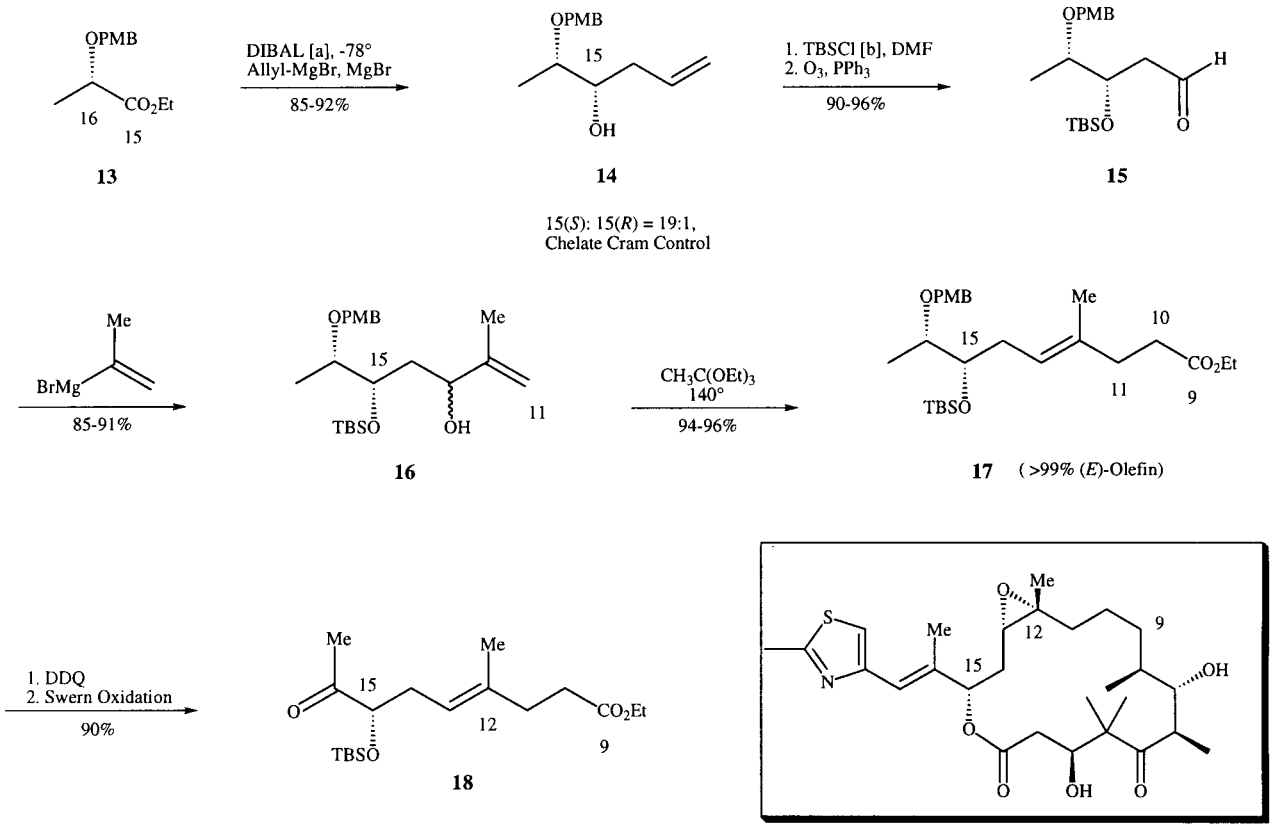
How to make a *cis*-epoxide from a *trans*-olefin:



Formula 4. [a] MsCl: Methanesulfonyl Chloride.

Specifically, our synthesis started from readily available (*S*)-lactic ester **13** which, in a one-pot operation, was reduced to the aldehyde and treated with allylmagnesium bromide. A chelate Cram selective allylation was observed forming alcohol **14**, which was converted into aldehyde **15** and subsequently into the allylic alcohol **16**. Claisen-Johnson rearrangement furnished the *E*-olefin **17** which was transformed into the methyl ketone **18**.

Synthesis of (*E*)-Olefin **18**

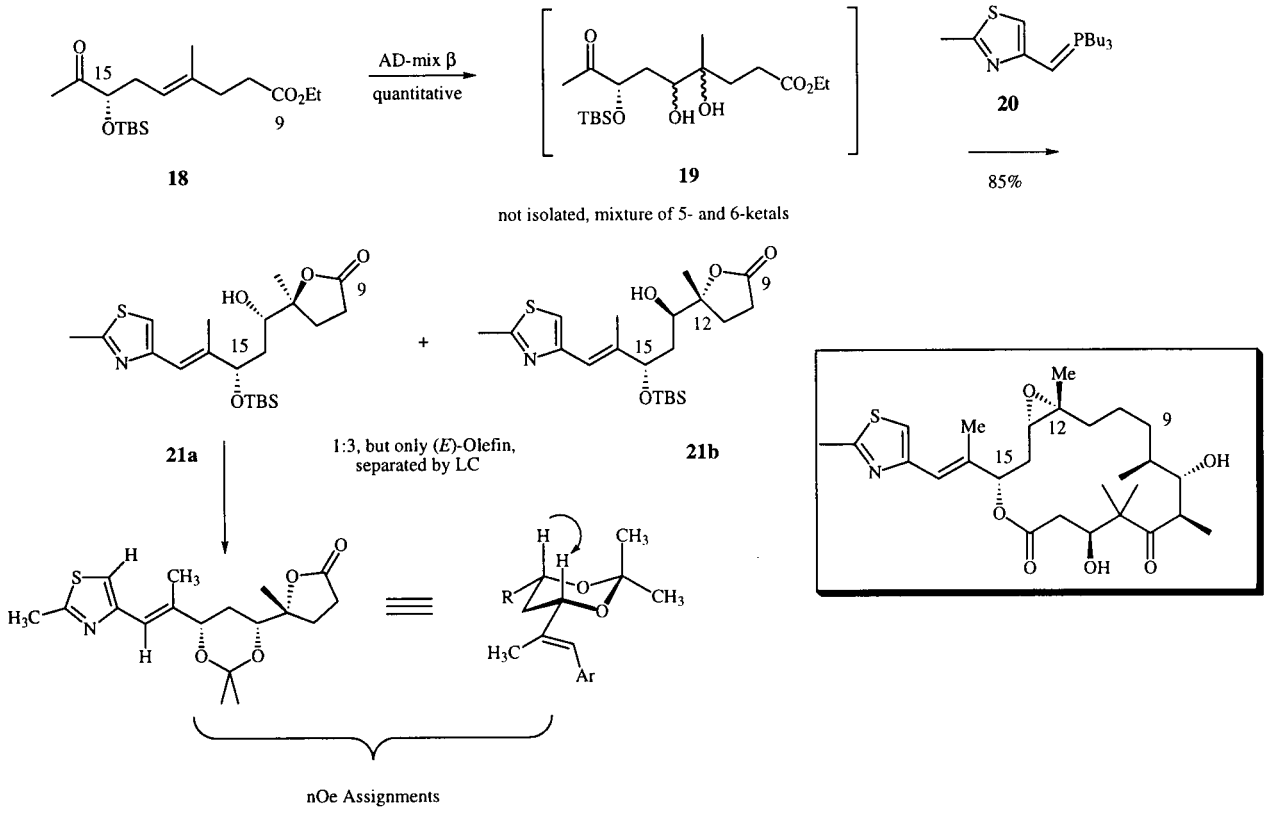


Formula 5. [a] DIBAL: Diisobutylaluminum Hydride; [b] TBSCl: *t*-Butyldimethylsilyl Chloride.

For the introduction of the 12,13-epoxide olefin **18** was submitted to an asymmetric dihydroxylation (AD) [3] to afford diol **19** as a mixture of ketals which was immediately transformed into a 1:3-mixture of olefinated hydroxylactones **21a/b**, easily separable by chromatography. The minor diastereomer was used for the assignment of the relative configurations at C-12, 13 and 15 *via* nOe spectroscopy. To convert the undesired diastereomer **21a** into the desired one (**21b**) a double inversion sequence *via* **22** and **23** was initiated to avoid any loss of misdirected stereoisomers in the synthesis.

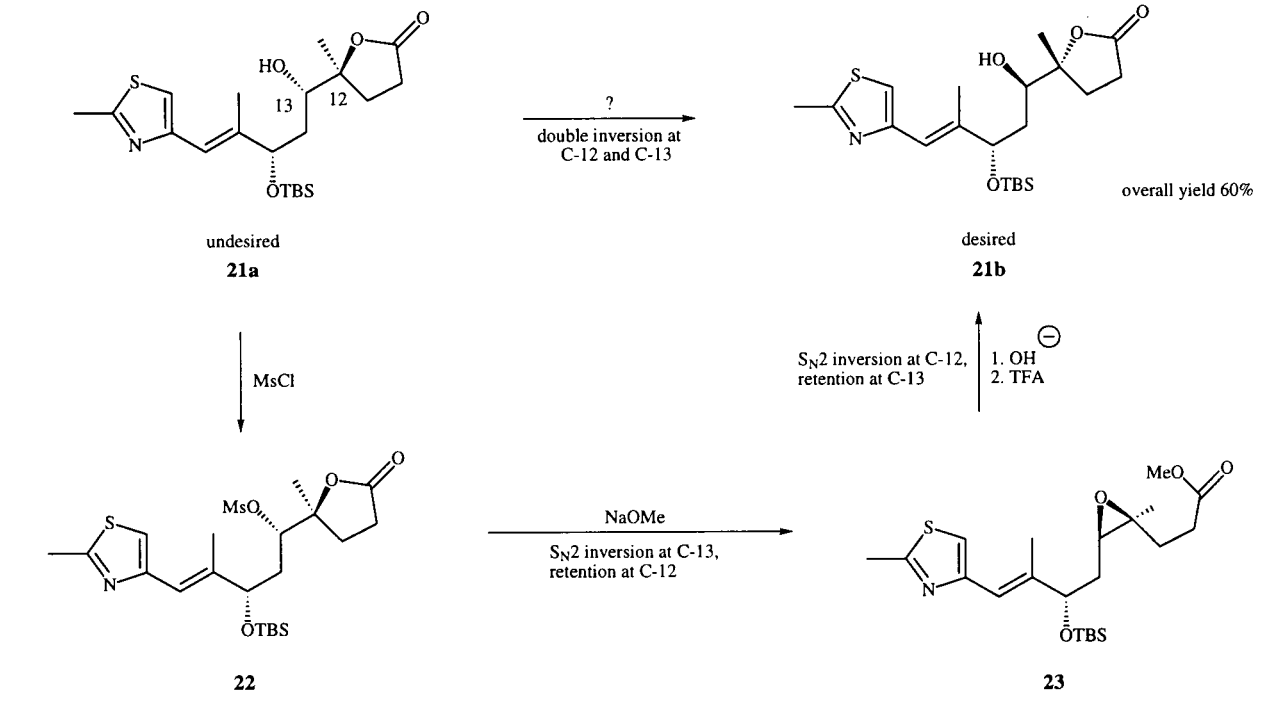
Epoxide **24** was smoothly generated from **21b**. Next, carbons C-8 and 7 were attached *via* a Horner-Oppolzer reaction [4] to generate the α,β-unsaturated sultam **25**. 1,4-Hydride addition with L-selectride led to the enolate which was alkylated at C-8 *in situ* with methyl iodide. Reductive removal of the sultam auxiliary with DIBAL generated the aldehyde **26**. Aldol addition of **26** to the known enolate **27** led to adduct **28** with high diastereoselectivity. The beneficial influence of the epoxide becomes clear on comparing the analogous aldol addition of the olefinic aldehyde **26a** to **27**, which generates **28a** only with 85:15 *ds*.

Asymmetric Dihydroxylation and Wittig-Reaction



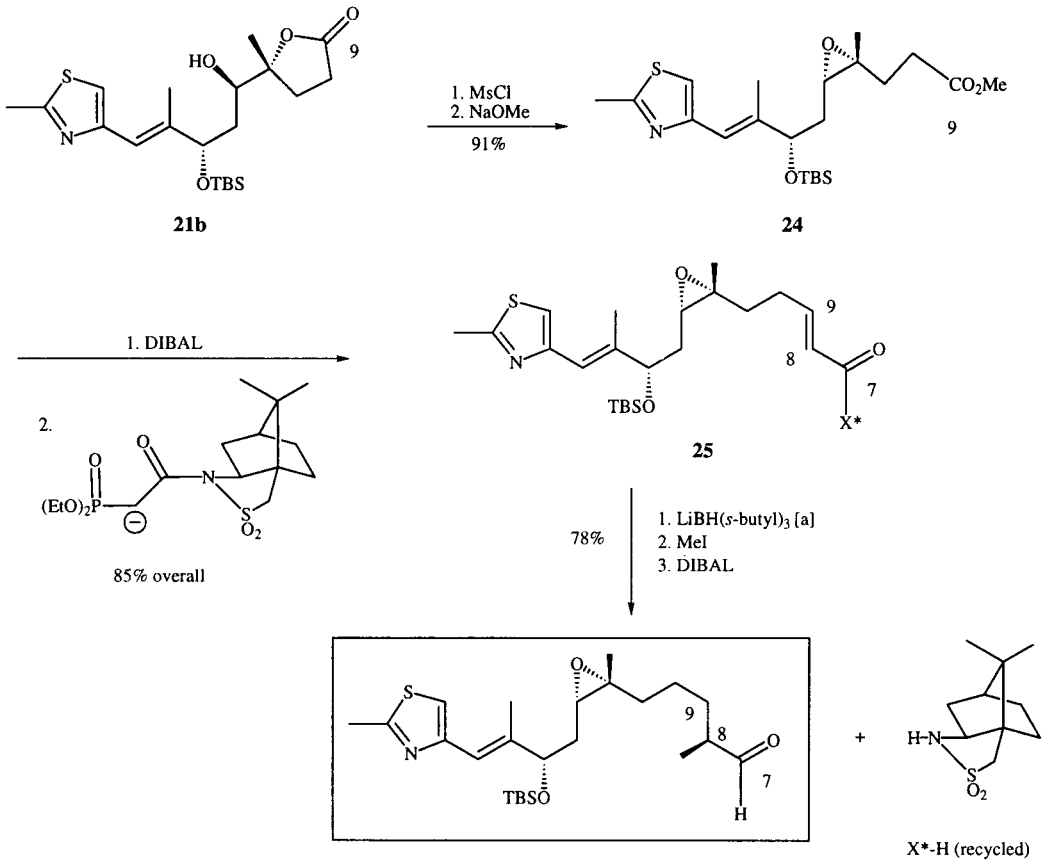
Formula 6.

How to Focus Material



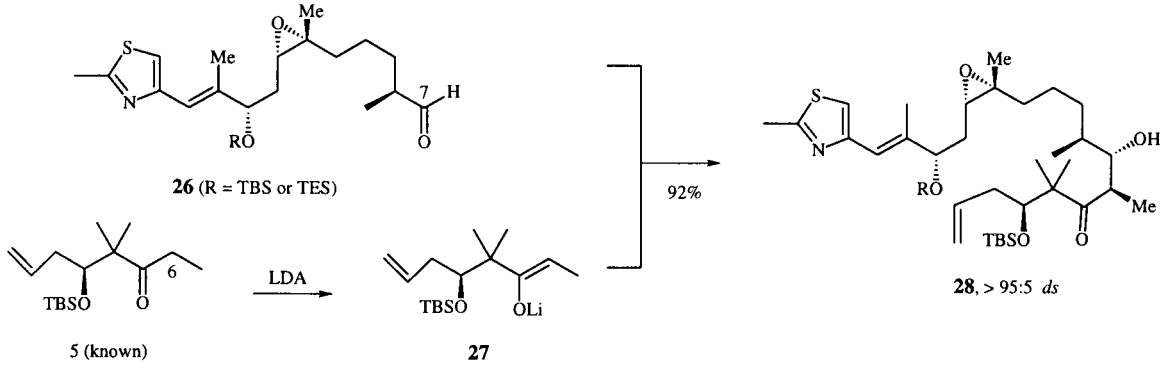
Formula 7.

Chain Elongation *via* Horner-Oppolzer Reaction

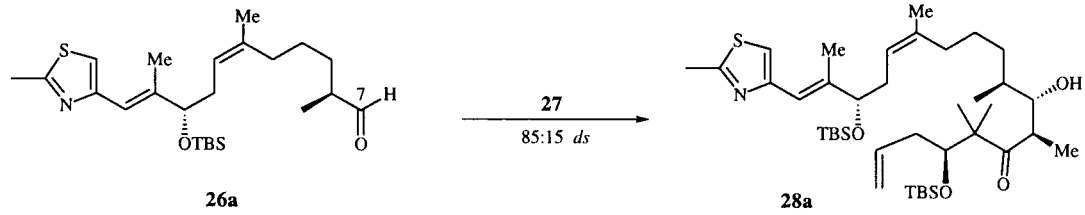


26 (15 steps from lactic ester in 36% overall yield)

Formula 8. [a] LiBH(*s*-butyl)$_3$: Lithium Tri-*sec*-butylborohydride (L-selectride).

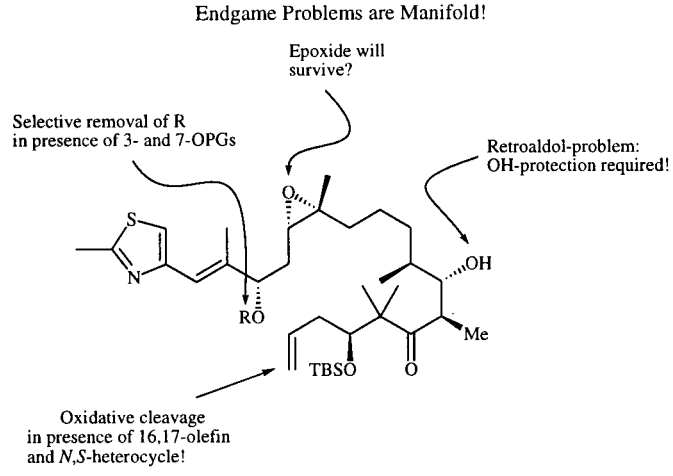


Influence of the 12,13-epoxide on the aldol addition

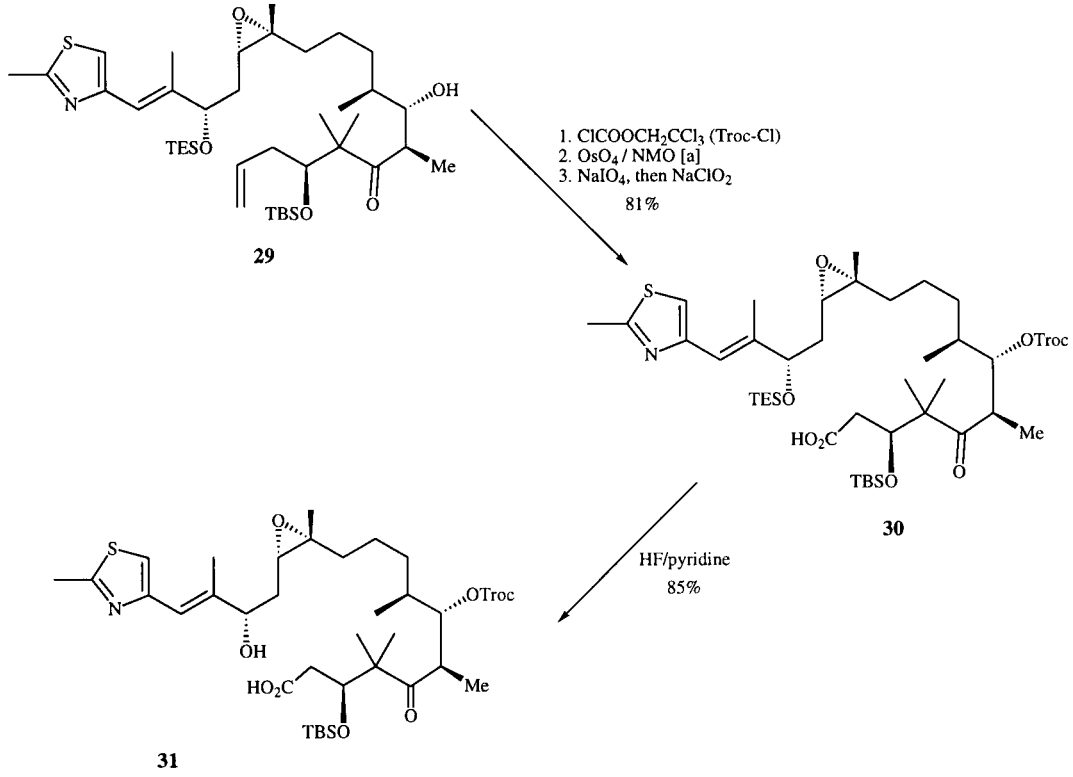


Formula 9.

To master the various endgame problems the proper choice of the protecting group of 7-OH was of the essence. A *tert*-butyl dimethysilyl group could only be introduced with the corresponding silyl triflate which, however, destroyed the epoxide. A better choice was the trichloroethyloxycarbonyl (Troc) group which was introduced cleanly and proved to be stable under the following operations (oxidation of the terminal olefin to carboxylic acid **30** and deprotection of the 15-OTBS to generate seco acid **31**). Yamaguchi lactonization [5] produced a high yield of lactone **32** which was deprotected successively at the 7- and 3-O positions to deliver epothilone B (**1**) in altogether 18 linear steps from lactic ester **13** in an overall yield of 7% [6].

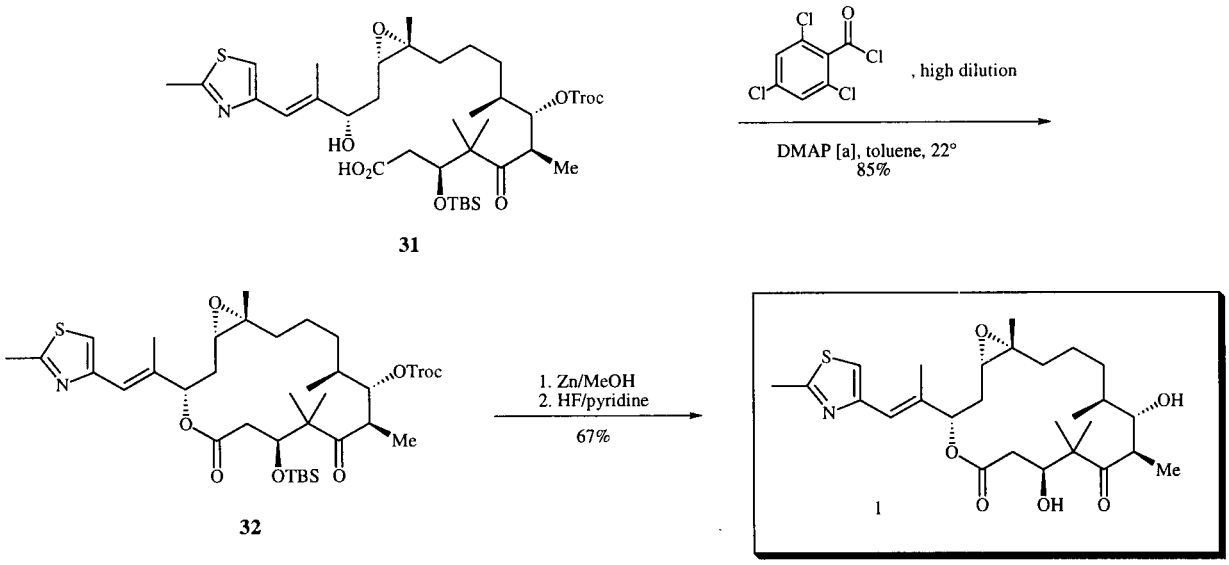


Formula 10.



Formula 11. [a] NMO: 4-methylmorpholine *N*-Oxide.

Final Steps



Formula 12. [a] DMAP: 4-Dimethylaminopyridine.

Results of our Epothilone B Synthesis

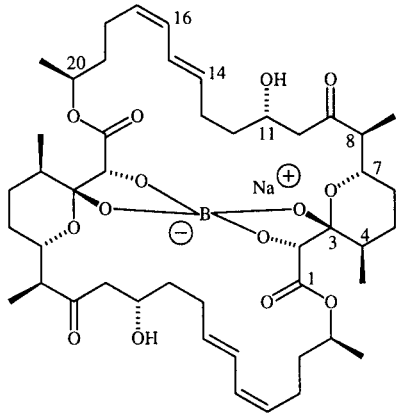
1. Shortest synthesis of all (18 linear, 23 overall steps)
2. High yielding (each step > 85%)
3. Epoxide is much more stable than expected
4. Epoxide route is >90% *ee* in every stereogenic unit

Formula 13.

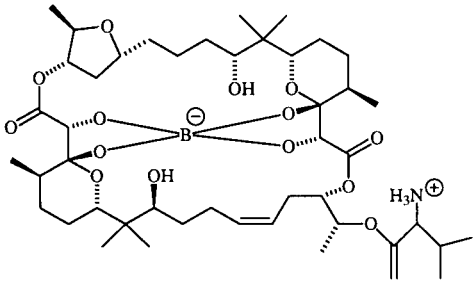
Tartrolon B (**2**) [7] is structurally related to boromycin and aplasmomycin both of which have been synthesized in the early eighties. All three boron containing macrodiolides act as potent potassium carriers and kill bacteria cells by increasing the potassium efflux from them. Unfortunately, this effect is also observed for mammalian cells so that these antibiotics are too toxic for clinical use. Nevertheless its complex molecular architecture renders **2** an attractive target for a total synthesis.

The retrosynthetic disconnection of **2** immediately reveals the diketo mono seco acid **33** which can be further disconnected into fragments **34-36** by two aldoltype additions. The first subgoal was to develop efficient syntheses for the major fragments **34** and **35**, respectively.

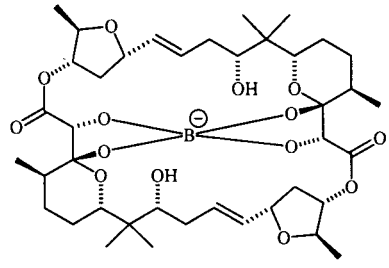
Structurally Related Antibiotics



Tartrolon B, 2



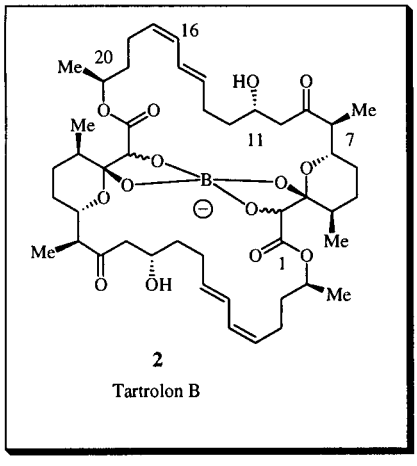
Boromycin



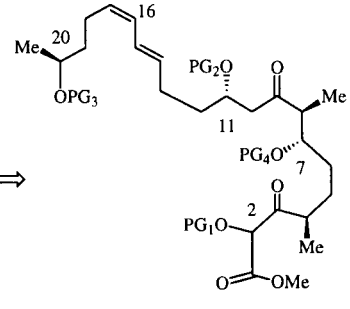
Aplasmomycin

Formula 14.

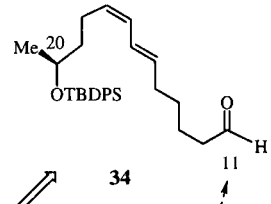
Retrosynthetic Disconnection



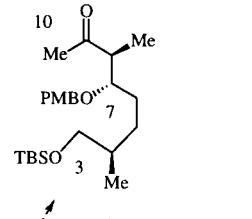
2
Tartrolon B



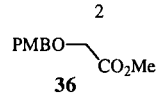
Diketo-
Mono- Seco Acid
33



34



35



36

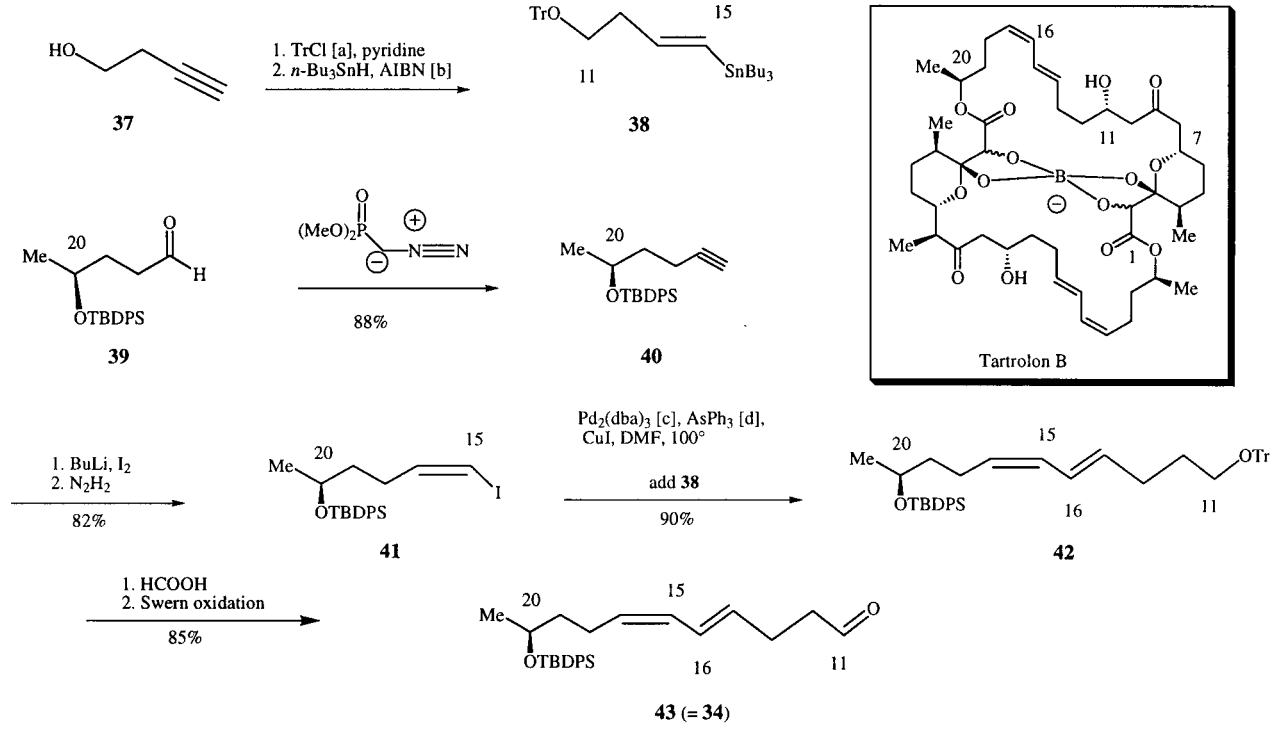
10,11-aldol

2,3-aldol

Formula 15.

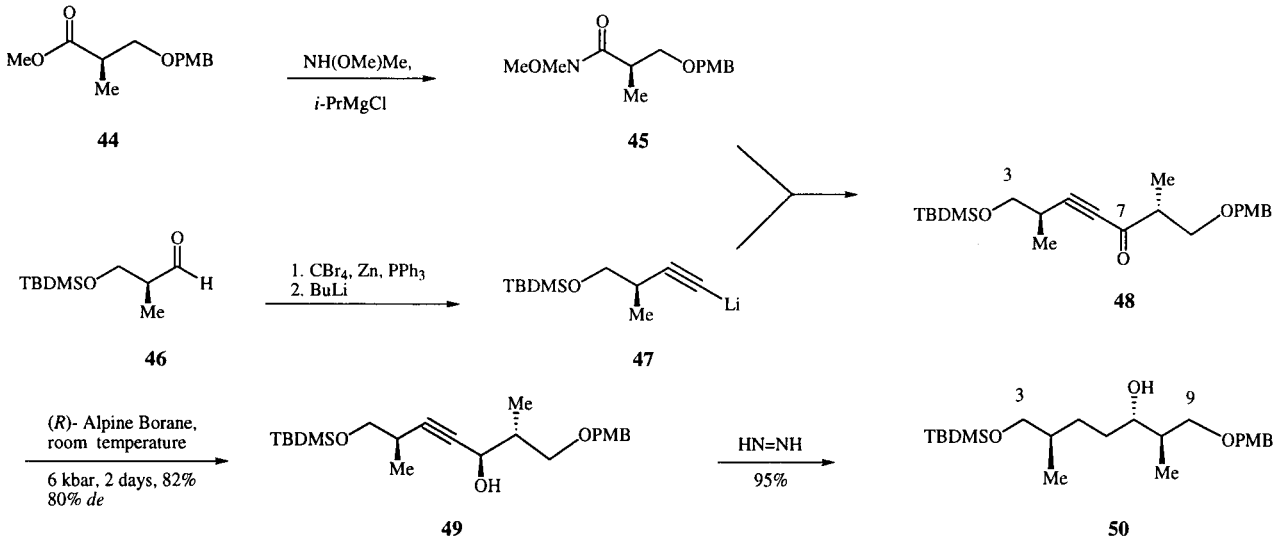
Aldehyde **35** was prepared by a Sonogashira coupling of vinystannane **38** and vinyliodide **41** both available from simple precursors. The coupling proceeded with complete retention of the double bond configurations to produce the (*Z*,*E*)-diene **42** in 90% yield which was selectiviely deprotected at O-11 and oxidized to the aldehyde **43** (= **34**). The C-1-C-9 fragment **50** was composed from the (*R*)- and (*S*)-Roche's ester derivatives **44** and **46**, respectively, by an acetylide-Weinreb amide-coupling to give alkynone **48** from **45** and **47**. Diastereoselective carbonyl reduction with alpine borane [8] gave the alkynol **49** which was reduced with diimide to give fragment **50** as desired.

The Stille Approach to the C-11-C-20 Diene Fragment **34**



Formula 16. [a] TrCl: Trityl Chloride; [b] AIBN: 2,2'-Azobisisobutyronitrile; [c] $Pd_2(dba)_3$: Tris(dibenzylideneacetone)dipalladium(0); [d] $AsPh_3$: Triphenylarsine.

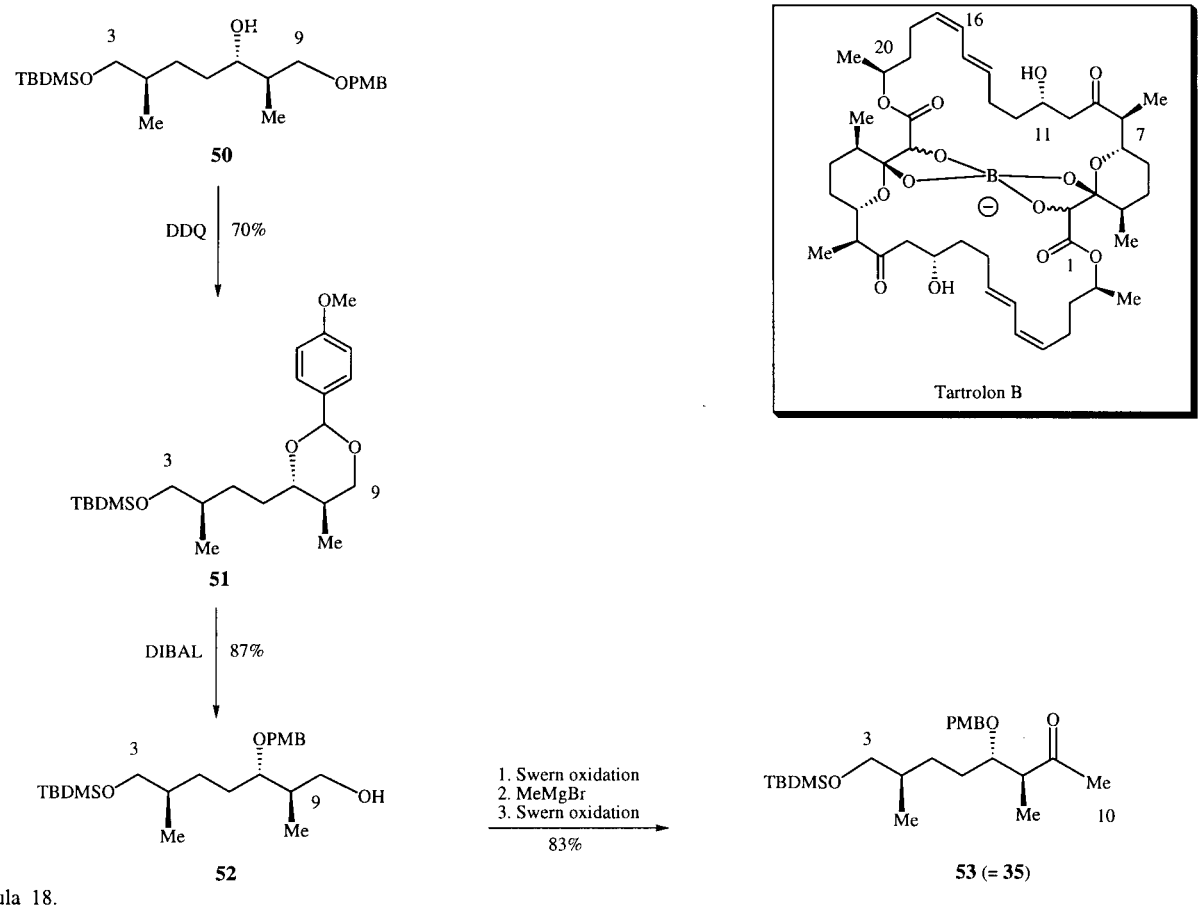
Alkynone Approach to C-3-C-9-Fragment
Alpine Borane Reduction at C-7



Formula 17.

Chain elongation by one carbon led from C-9 alcohol **50** to methyl ketone **53** (= **35**) uneventfully, which was then used in an aldol addition to aldehyde **34**. In this way the C-3-C-20 carbon skeleton of the mono seco acid is generated in form of the aldol **54**. By application of Paterson's modification [9] of the Mukaiyama aldol addition the diastereoselectivity was raised to 10:1.

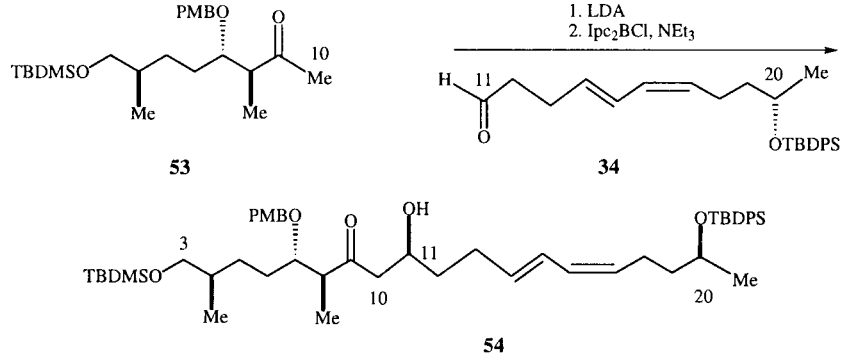
Chain Elongation from C-9 to C-10, Synthesis of Fragment **35**



50 **51** **52** **53 (= 35)**

Formula 18.

Aldol Additions C-10 to C-11



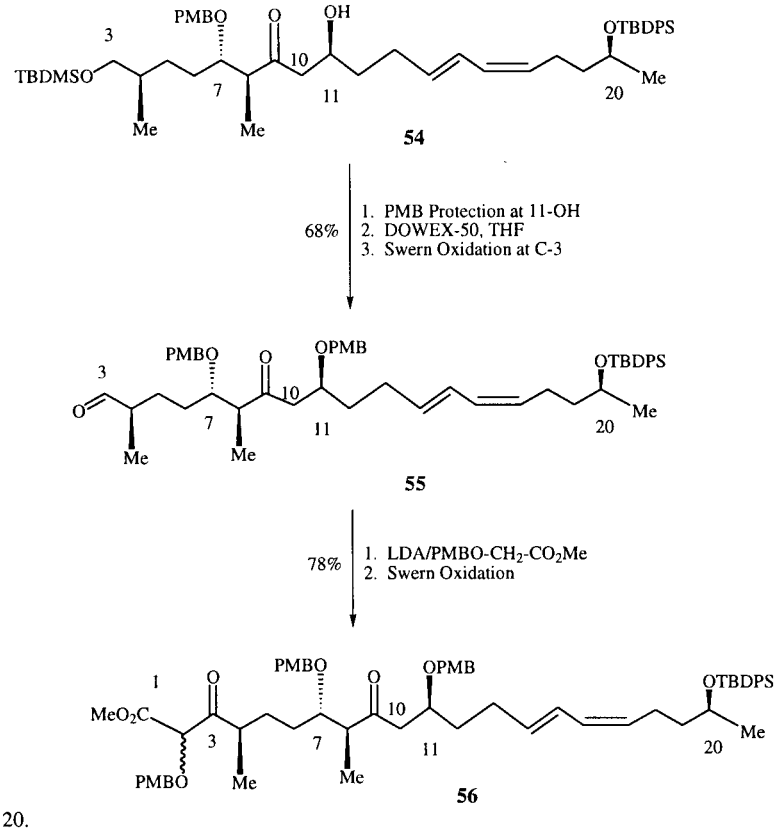
53 **34** **54**

S/*R* ratio at C-11		
	without Ipc_2BCl	1:1
	(+)-Ipc_2BCl	10:1
	(-)-Ipc_2BCl	10:1

Formula 19.

The missing carbon atoms C-1-C-3 were introduced *via* a second aldoltype addition of OPMB-glycolester enolate to aldehyde **55**. The protected mono seco acid **56** was generated in good yield as a mixture of C-2 epimers. Deprotection of O-20 and saponification of the ester led to seco acid **58** which failed to lactonize under a wide variety of conditions (*e.g.*, the Corey-Nicolaou protocol using 2,2'-dipyridyl disulfide **59** [10]).

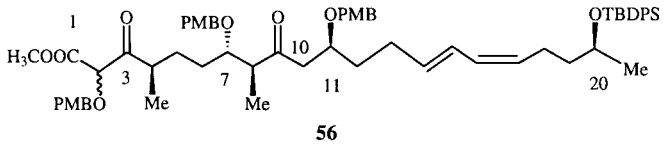
Synthesis of a Protected Seco Acid



Formula 20.

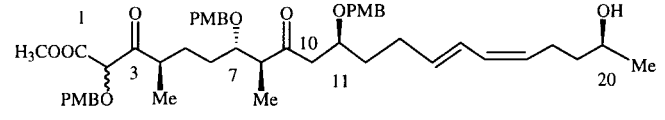
This observation prompted us to reconsider the entire retrosynthetic scheme. In place of the unprotected diketo seco acid **58** a non-keto precursor **60** (masked as a C-9 alcohol and C-3 ketal) should be used in the lactonization step. Additionally the formation of the diolide was to be performed in two steps, first dimerization *via* chemospecific esterification and then ring closure by lactonization. Seco acid **60**, in turn, should be assembled by an aldol type addition of ketone **61** to aldehyde **34** which had been used previously.

Attempted Diolide Cyclization Using the Corey-Nicolaou-Method



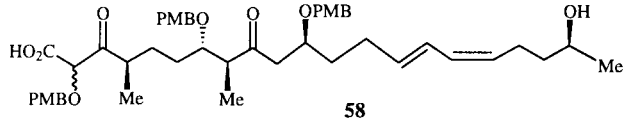
56

HF, CH_3CN, H_2O, 3 days
65%

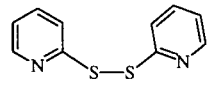


57

LiOH, MeOH, THF, H_2O
85%



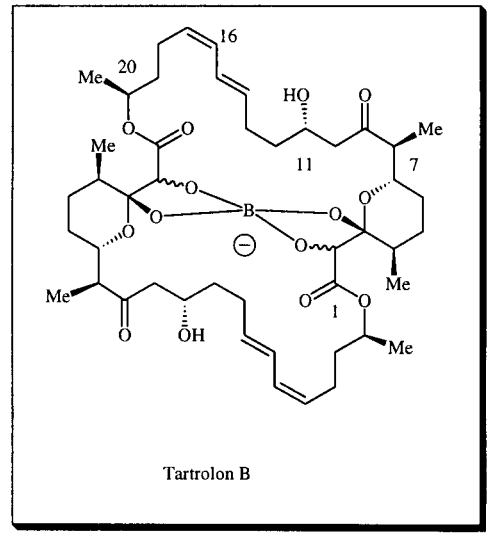
58



59

PPh_3, toluene

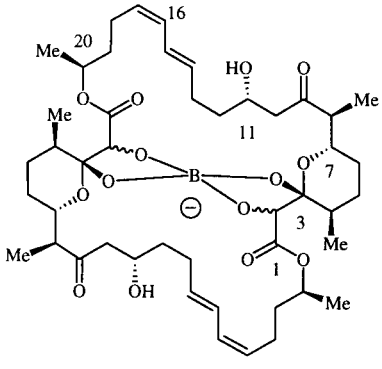
No defined products!



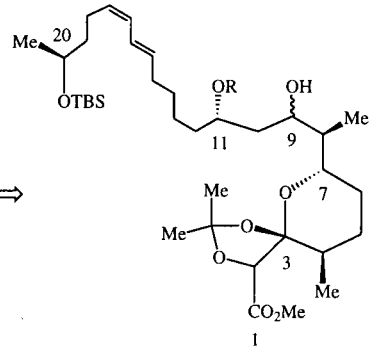
Tartrolon B

Formula 21.

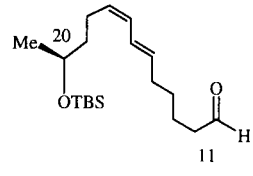
Modified Retrosynthetic Analysis



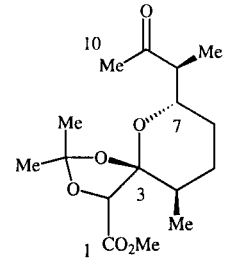
Tartrolon B



60



34
unchanged



61, new

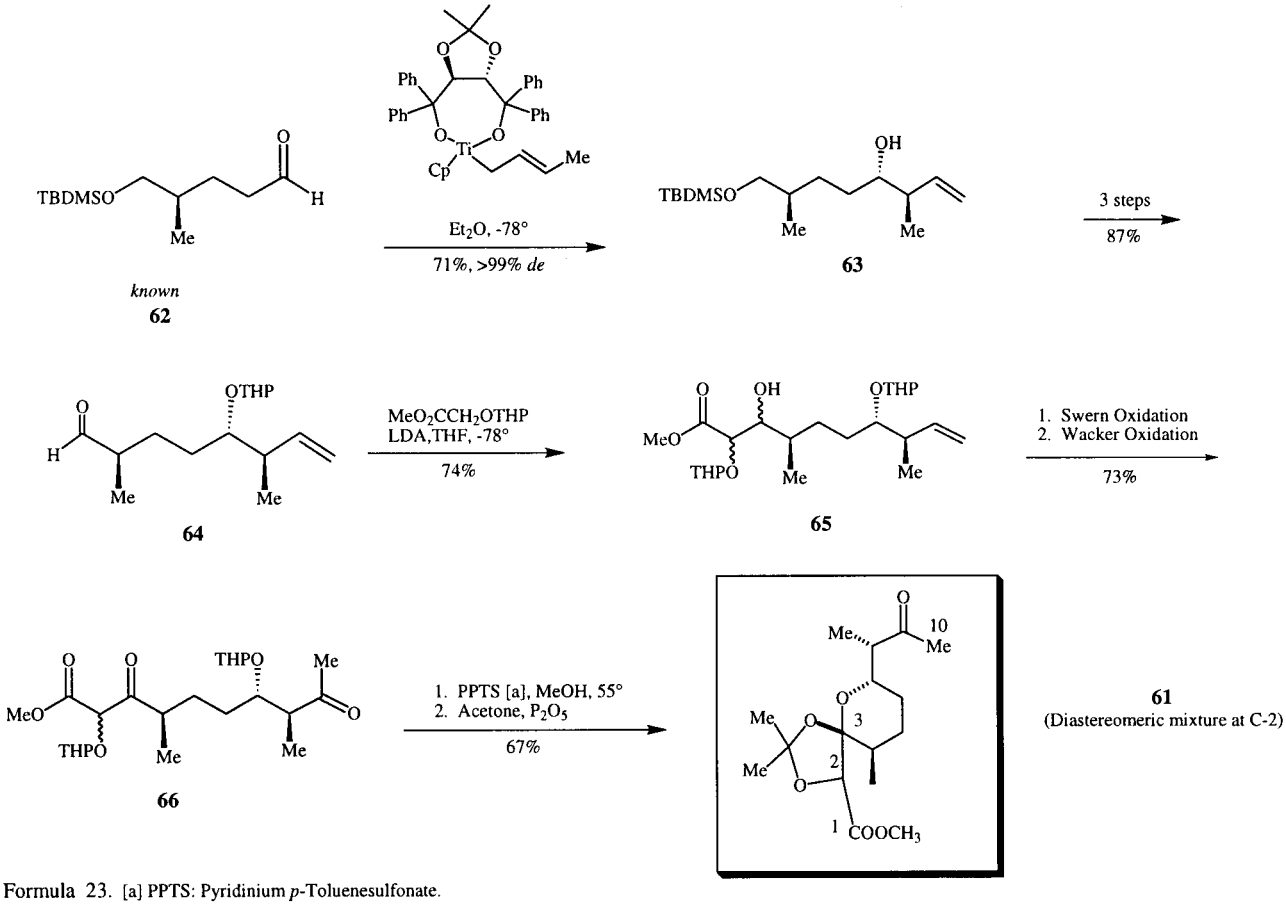
Formula 22.

For the synthesis of methyl ketone **61** a new route was devised starting with the known aldehyde **62** [11], availabe from (*S*)-Roche's ester in four simple steps. Duthaler-Hafner crotylation of **62** [12] produced the *anti*-diastereomer **63** with high absolute and relative stereoselectivity which was converted into aldehyde **64** and then treated with the glycolester enolate as before. Hydroxy ester **65** was obtained which was transformed into methyl ketone **66**. Ketalization gave the envisaged C-1-C-10 fragment **61**.

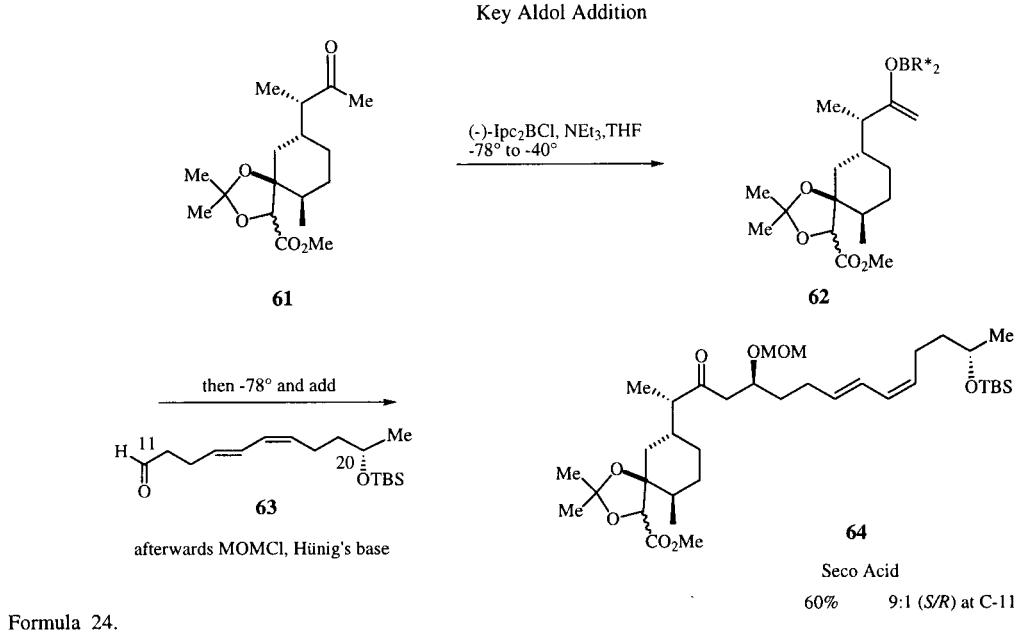
The key aldol addition was performed as before, but now using components **61** and **63**, respectively, to obtain adduct **64** in acceptable yield and stereoselectivity.

The protected seco acid **64** was reduced at C-9 to give alcohol **65** as a 1:1 epimeric mixture which was converted into alcohol **66** and acid **67** separately to set the stage for the ensuing Yamaguchi dimeriziation which gave the complete seco acid **68**. Deprotection of the O-20 and selective saponification of the methyl ester allowed macrolactonization, again under Yamaguchi's conditions, to give the 42-membered macrolactone **69** which was converted into tartrolone B by reoxidizing the 9-OH's, removing the acetal functions and inserting the boron. The product thus obtained was indistinguishable from an authentic sample according to its ^{1}H- and ^{13}C-nmr, ir and ms spectra including HRMS and the HPLC R_f value. The absolute configuration of our synthetic sample was confirmed to be correct by comparing the CD spectrum with one of the natural material [13].

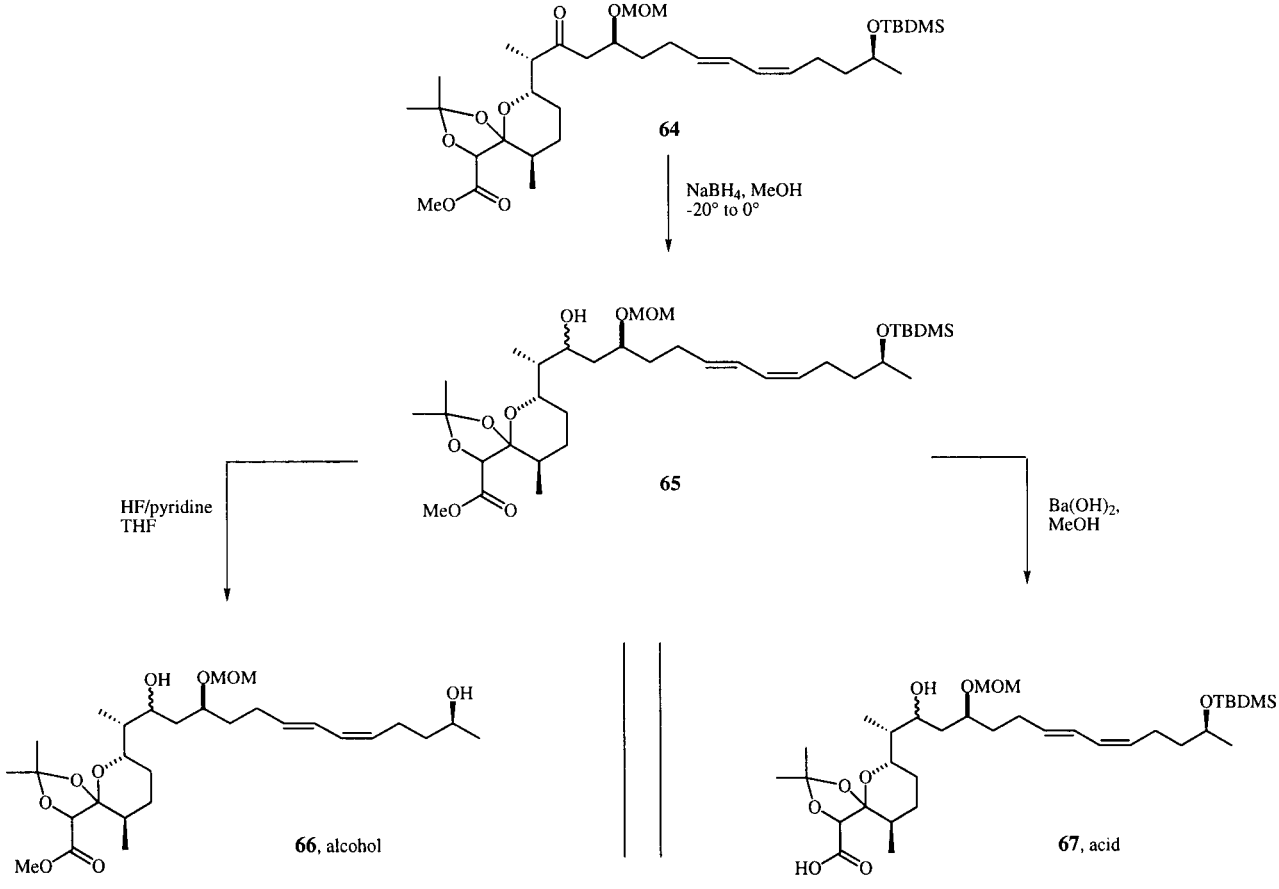
Synthesis of Modified C-1 - C-10- Fragment **61**



Formula 23. [a] PPTS: Pyridinium *p*-Toluenesulfonate.

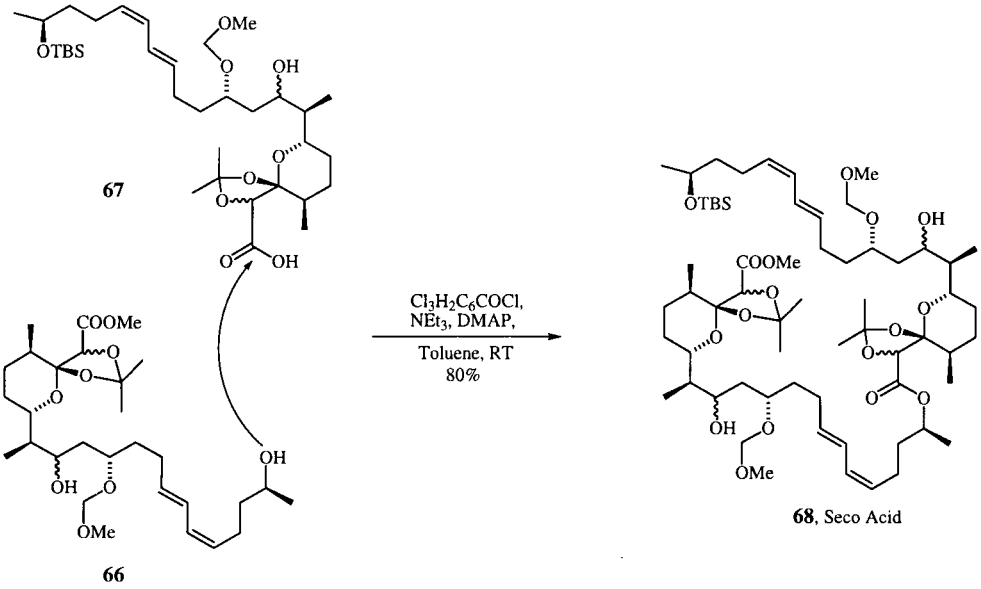


Formula 24.



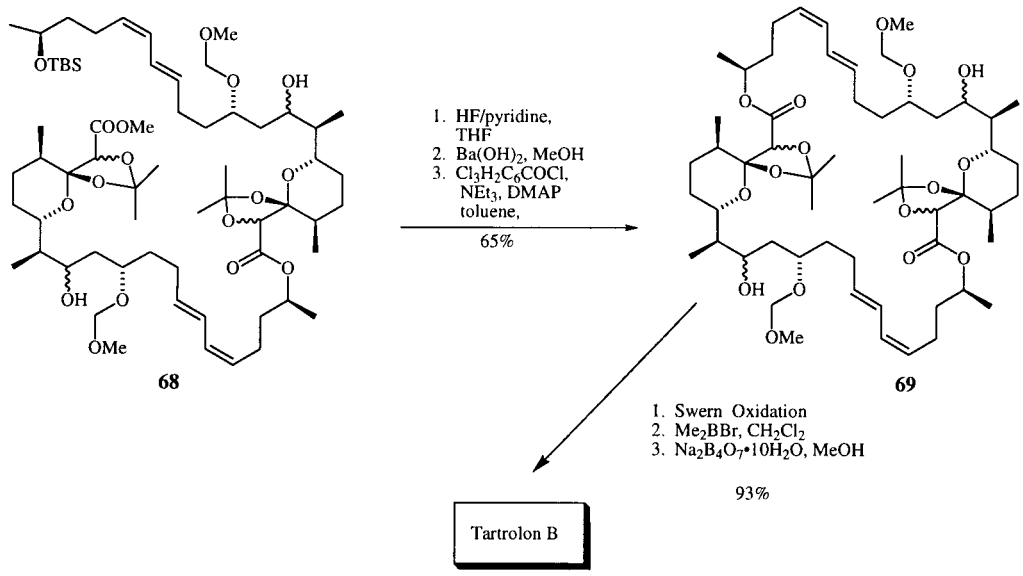
Formula 25.

Yamaguchi Dimerization



Formula 26.

Endgame



Formula 27.

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