DOI 10.5012/bkcs.2010.31.03.653

Enantioselective Total Synthesis of (-)-Clavosolide A and B†

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Received November 14, 2009, Accepted November 23, 2009

Enantioselective total synthesis of (-)-clavosolide A and B was reported in full including the synthesis of proposed structure of (-)-clavosoldie A (**1**), revised structure of (-)-clavosoldie A (**5**), and revised structure of (-)-clavosoldie B (**6**). The relative and absolute stereochemistries of the natural products were confirmed unambiguously by comparing the optical rotation values and ^{1}H and ^{13}C NMR spectra of them.

Key Words: Enantioselective total synthesis, Clavosolide A, Clavosolide B

Introduction

Marine sponges have provided an inexhaustible supply of bioactive metabolites.[1] In 1998, Fu isolated the clavosines A-C,[2] a potent cytotoxin and inhibitor of protein phosphatase 1 and 2A, from the crude extract of the sponge *Myriastra clavosa* collected from Palau. In 2002, Faulkner isolated a suite of unusual metabolites, clavosolides A (**1**, 4.3×10^{-3}% wet wt) and B (**2**, 1.4×10^{-3}% wet wt),[3] from the crude extract of the sponge *Myriastra clavosa* from the Philippines and proposed their structures based on the extensive spectroscopic experiments and molecular modeling studies (Figure 1). These structures, further supported from the independent research by Erickson in 2002,[4] are quite unique because they are not related to any known sponge metabolites so far.

However, ^{1}H NMR spectra of the natural clavosolide A (**1**) and synthetic compound of the proposed structure obtained by Willis[5] were not identical, especially in the region around the cyclopropane signals, which were later supported by Chakraborty[6,7] and us.[8] Willis also proposed a revised structure **5** for the natural clavosolide A[5] and our group confirmed the relative stereochemistry of clavosolide A (**5**) by stereoselective total synthesis (Figure 2).[8a] Subsequently, Smith,[9] Willis,[10] and Chakraborty[11] unambiguously determined the absolute stereochemistry of (-)-clavosolide A (**5**) by comparison of the optical rotation.

In a similar manner, the enantioselective synthesis of the revised structure **6** for the natural (-)-clavosolide B was recently completed by our group[12] and the comparison of the optical rotation values confirmed the absolute stereochemistry of the natural (-)-clavosolide B (**6**) as expected. In this full paper, we report the whole story covering the stereoselective synthesis of the proposed sturcutre (**1**) and of the revised structure (**5**) for the natural clavosolide A, and the enantioselective synthesis of the revised structure (**6**) for the natural (-)-clavosolide B.

The revised (-)-clavosolide A (**5**) and B (**6**) are 16-membered diolides with two highly substituted tetrahydropyran rings, two *trans*-disubstituted cyclopropyl rings, and 22 stereogenic centers. They differ only in the substitution pattern on the one sugar moiety (-OMe for clavosolide A *vs*. -OH for clavosolide B). This difference makes the (-)-clavosolide A (**5**) and (-)-clavosolide A (**6**) to be a C2-symmetric dimer and asymmetric molecule, respectively.

Results and Discussion

Synthesis of proposed Clavosolide A (1). The retrosynthetic analysis for the proposed clavosolide A (**1**) is illustrated in Scheme 1. Completion of the synthesis of **1** required the coupling of diol **35** and the activated sugar moiety **31** *via* a Schmidt-type glycosylation. The C_2-symmetric nature of the intermediate

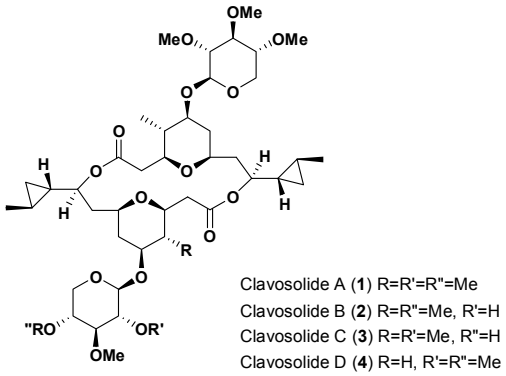


Figure 1. Proposed structures for clavosolide A-D (1-4)[3].

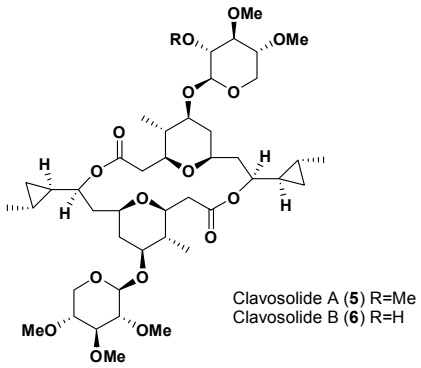
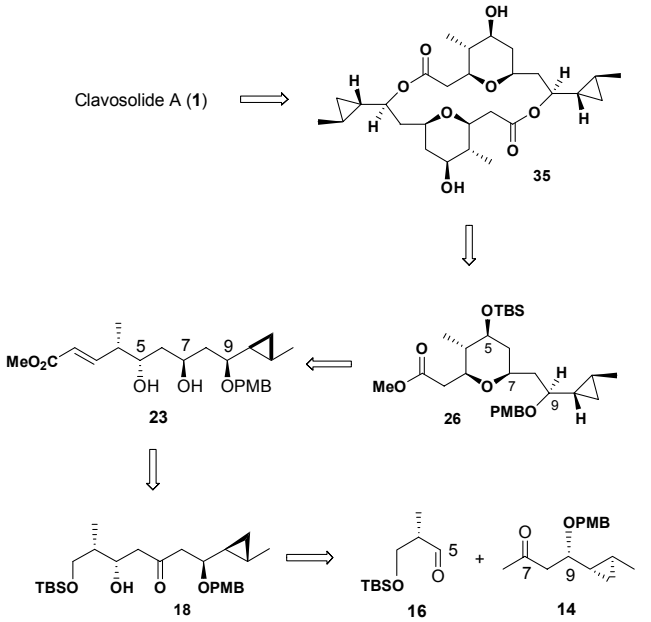
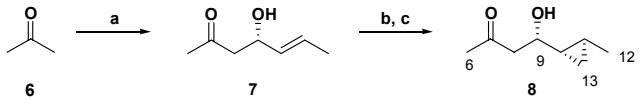


Figure 2. Revised structures for (-)-clavosolide A (5) and B (6).

†This paper is dedicated to Professor Sunggak Kim on the occasion of his honorable retirement.



Scheme 1. Retrosynthetic analysis of proposed clavosolide (**1**)



Scheme 2. Synthesis of C6-C13 fragment **14**. (a) (+)-DIPCl, TEA, crotonaldehyde, ether, −78 °C, 96%. (b) Et_2Zn, CH_2I_2, CH_2Cl_2, −10 °C to 0 °C, 82%

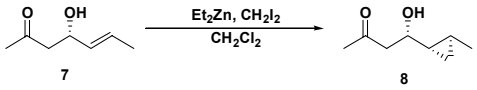
35 allowed us sequential disconnection of the two ester linkages to a key intermediate **26** with all the substituents at the equatorial position in the tetrahydropyran ring. Intermediate **26** would then be constructed *via* intramolecular 1,4-addition of C7-hydroxyl group to the conjugated ester **23**. The protocol for stereoselective 1,3-*anti* reduction should be successful for the conversion of **18** into **23**. The ketone **18** would be constructed efficiently by a diastereoselective aldol reaction of the methyl ketone **14** with chiral aldehyde **16**.

Initial attempt for the synthesis of methyl ketone **14** was summarized in Scheme 2. Asymmetric boron-mediated aldol reaction of acetone with crotonaldehyde provided β-hydroxyketone **7** in 96% yield and 75% ee,[13] which was determined unambiguously by 500 MHz ^{1}H NMR spectra of the corresponding Mosher ester.[14] Hydroxy group-directed cyclopropanation of allylic alcohol **7** proceeded in 82% yield with moderate selectivity (*syn* : *anti* = 11 : 1).[15]

Different sets of reaction conditions were investigated for the hydroxy group-directed cyclopropanation of allylic alcohol (Table 1). Five equivalents of Et_2Zn-CH_2I_2 were necessary to maximize the ratio of isomers and to obtain complete consumption of the olefin. Moreover, the yield turned out to be highly dependent on temperature.

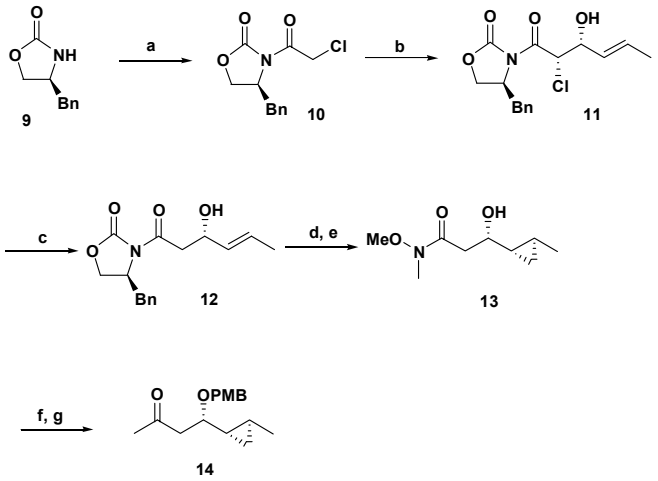
However, due to the low diastereomeric ratio at C9, an alternative route was required. First, Evans oxazolidinone **9** was treated successively with *n*-BuLi and chloroacetyl chloride to afford the carboximide **10** in good yield. Enolization of **10** with

Table 1. Cyclopropanation of chiral allylic alcohol **8**



Et_2Zn (eq)	CH_2I_2 (eq)	Condition	Results
2.5	3	−20 °C, 20 h	21%[a]
5	5	−10 ~ rt, 4 h	58% (*syn* : *anti* = 11 : 1)[b]
5	5	−10 ~ 10 °C, 3 h	84% (*syn* : *anti* = 11 : 1)

[a]Isolated yield of chromatographically pure mixture of isomers. [b]Diastereoselectivities were determined by ^{1}H NMR.

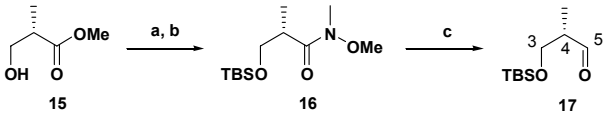


Scheme 3. Alternative enantioselective synthesis of **14**. (a) Chloroacetyl chloride, *n*-BuLi, THF, −78 °C, 98%; (b) Bu_2BOTf, Hunig's base, crotonaldehyde, CH_2Cl_2, -78 °C to rt, 58%; (c) Zinc, NH_4Cl, MeOH, rt, 59%; (d) Et_2Zn, CH_2I_2, CH_2Cl_2, −10 °C to 0 °C, 93%; (e) $HN(CH_3)OCH_3$·HCl, $AlMe_3$, THF, 0 °C to rt, 96%; (f) PMBO(C=NH)CCl_3, TsOH(*cat*), *c*-Hexane-CH_2Cl_2(2 : 1), rt, 95%; (g) MeMgCl, THF, −78 °C to 0 °C, 73%

Bu_2BOTf and Hunig's base was followed by reaction with crotonaldehyde to provide the *syn*-aldol product **11** with 97 : 3 diastereoselectivity.[16] Treatment with zinc dust in methanol then removed the extraneous chlorine to give **12** in 59% yield. Hydroxy group-directed cyclopropanation of allylic alcohol **12** proceeds in 93% yield with moderate selectivity (*syn* : *anti* = 11 : 1), which was successively treated with *N*,*O*-dimethylhydroxylamine hydrochloride and $AlMe_3$ to give the Weinreb amide **13** in 96% yield. The hydroxy group was protected as PMB ether, and the weinreb amide was treated with methylmagnesium chloride to provide the desired methyl ketone **14**.

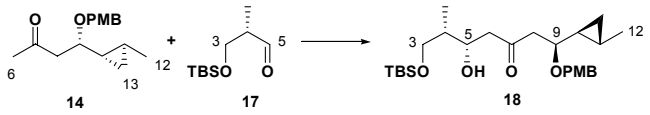
Aldehyde **17**[17] was prepared starting from the commercially available methyl (2*S*)-3-hydroxy-2-methylpropionate (**15**) *via* three-step sequences (Scheme 4). First, protection of the hydroxyl group of **15** with TBSCl gave the silyl ether in good yield, and the ether was treated with *N*,*O*-dimethylhydroxylamine and *i*-PrMgCl in THF to afford the Weinreb amide **16**[18] in 95% yield. Amide was then converted to aldehyde **17** by reduction with DIBAL-H.

High levels of 1,5-stereoinduction were usually obtained in the boron-mediated aldol reactions of methyl ketones with alde-



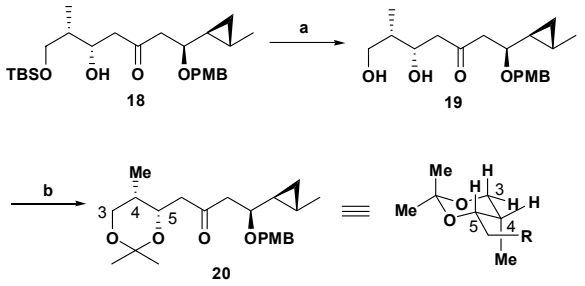
Scheme 4. Synthesis of C3-C5 fragment **17**. (a) TBSCl, DMAP, TEA, CH_2Cl_2, rt, 100%; (b) Me(OMe)NH·HCl, *i*-PrMgCl, THF, −20 °C, 95%; (c) DIBAL, CH_2Cl_2, −78 °C, 99%

Table 2. 1,5-*Anti* aldol reaction with methyl ketone **14** and aldehyde **17**



Reagent	Base	Results
(+)-DIPCl	TEA	59%[a] (ds = 86 : 14)[b]
(−)-DIPCl	TEA	60% (ds = 75 : 25)
n-Bu_2BOTf	*i*-Pr_2NEt	92% (ds = 88 : 12)

[a]Isolated yield after silica gel flash chromatography. [b]Ratio determined by ^{1}H NMR analyses of the diastereomeric mixture of adducts.



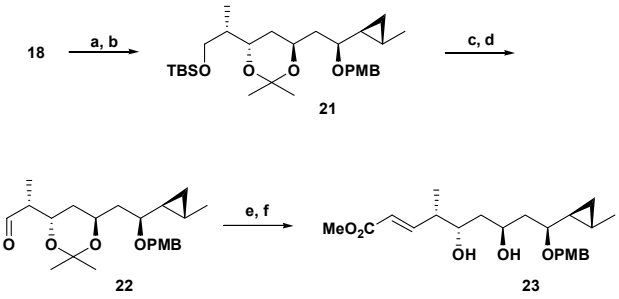
Scheme 5. Determination of relative stereochemistry of 1,5-*anti* aldol product **18**. (a) TBAF, THF, 0 °C, 60%; (b) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 90%

hydes, as described earlier by Paterson[19] and Evans.[20]

Therefore, 1,5-*anti* stereochemical induction in the aldol reaction of methyl ketone **14** containing a PMB-protected β-hydroxy group, with aldehyde **17** were explored (Table 2). Use of (+)- DIPCl seemed to be worst in yield and moderate in diastereoselectivity (ds = 86 : 14). When (-)-DIPCl was used, diasteroselectivity of the product was reduced to 75 : 25, and utilization of *n*-Bu_2BOTf provided the desired product with the best yield (92%) and diastereoselectivity (88 : 12).

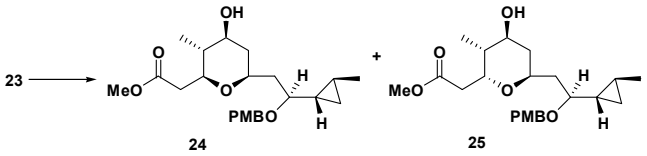
The relative stereochemistry of 1,5-*anti* aldol product **18** was determined unambiguously from ^{1}H NOE and ^{13}C NMR experiments[21] of the acetonide **20**. Acetonide **20** was obtained *via* deprotection of silyl ether and acetal formation of the diol with 2,2-dimethoxypropane. NOESY correlation was observed between C3-axial H and C5-axial H, which confirmed the *syn* relationship between C3-axial H and C5-axial H.

After 1,5-*anti* aldol reaction, a hydroxy group-directed 1,3-*anti*-reduction of **18** with $Me_4NB(OAc)_3H$[22] was followed by protection of the resultant diol with 2,2-dimethoxypropane to produce acetonide **21** in good yield (Scheme 6). The TBS group



Scheme 6. Synthesis of diol **23**. (a) $Me_4NB(OAc)_3H$, −20 °C, 97%; (b) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, rt, 99%; (c) TBAF, THF, rt, 99%; (d) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, −78 °C, 98%; (e) trimethyl phosphonoacetate, *i*-Pr_2NEt, LiCl, MeCN, 0 °C to rt, 92% (*E* : *Z* = 12 : 1); (f) CSA, MeOH/H_2O, rt, 100%

Table 3. Stereoselective intramolecular 1,4-addition



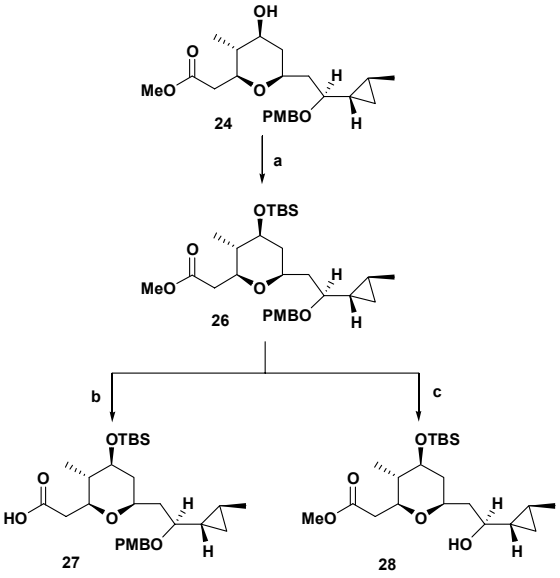
Condition	T, °C	Time	Product[a] (yield)[b]
t-BuOK (1.5 eq)	−40	3 h	Only-**25** (68%)
t-BuOK (0.1 eq)	0	10 min	Only-**25** (79%)
t-BuOK (0.1 eq)	rt	1.5 h	**25** major
NaH (1 eq)	0	4.5 h	**24** : **25** = 1 : 5
NaH (1 eq)	rt	1 h	**24** : **25** = 1 : 1.5
NaH (1.5 eq)	rt	3 h	**24** : **25** = 8 : 1 (78%)
DBU (20 eq)c	95	22 h	**24** : **25** = 2 : 1 (44%)

[a]Ratio determined by ^{1}H NMR analyses of the diastereomeric mixture of adducts. [b]Isolated yield after silica gel flash chromatography. [c]*J. Org. Chem.* **2000**, *65*, 8730-8736.

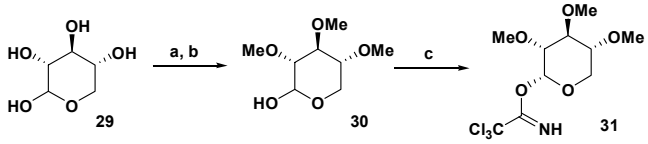
of **21** was deprotected with TBAF, and the resulting primary alcohol was oxidized by Swern protocol[23] into the aldehyde **22** in 98% overall yield. The aldehyde **22** was converted to (*E*)-α,β-conjugated ester using Horner-Wadsworth-Emmons[24] protocol, and the removal of acetonide protecting group under acidic condition provided the diol **23** in excellent yield.

In order to optimize the reaction conditions for the intramolecular Michael cyclization of the diol **23**,[25] the diol **23** was subjected to the various reaction conditions (Table 3).

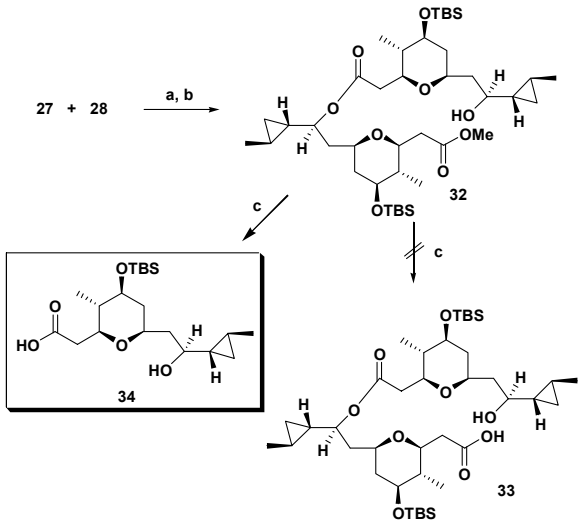
When *t*-BuOK (1.5 eq) was employed in THF at −40 °C,[26] the undesired 2,6-*trans* tetrahydropyran **25** was obtained in 68% yield as a single isomer. Use of catalytic amount of *t*-BuOK (0.1 eq) at 0 °C and room temperature still afforded the undesired isomer **25** as the only product. Treatment of **23** with one equivalent of NaH in THF at 0 °C or at room temperature led quickly to a 1 : 5 and 1 : 1.5 mixture of the isomers, respectively. Reaction of the diol **23** with 1.5 equivalent of NaH in THF at rt for 3 h turned out to be the most effective to provide the desired product **24** in 78% yield as a 8 : 1 diastereomeric mixture.[27] Use of DBU as an alternative base did not show any advantage over



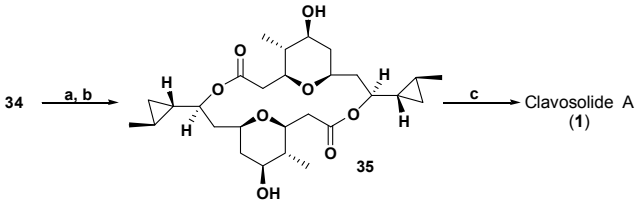
Scheme 7. Synthesis of monomers **27** and **28**. (a) TBSOTf, TEA, CH_2Cl_2, 0 °C, 88%; (b) aq. LiOH, THF-H_2O-MeOH(10/1/1), rt, 93%; (c) DDQ, CH_2Cl_2/H_2O, rt, 84%



Scheme 8. Synthesis of imidate **31**. (a) 50% aq. NaOH, MeI, DMSO, rt, 53 %; (b) 1,4-dioxane/2N HCl, 105 °C, 60%; (c) NaH, Cl_3CCN, CH_2Cl_2, rt, 81%



Scheme 9. Synthesis of hydroxyl acid **34**. (a) DIC, DMAP, CH_2Cl_2, 0 °C to rt, 83%; (b) DDQ, CH_2Cl_2/H_2O, rt, 91%; (c) excess $Ba(OH)_2 \cdot 8H_2O$, MeOH, rt, 97%



Scheme 10. Total synthesis of **1**. (a) 2,4,6-$Cl_3PhCOCl$, TEA, THF, rt, then DMAP, PhMe, reflux; (b) TBAF, THF, 0 °C, 25% (2 steps); (c) **31**, $BF \cdot OEt_2$, 4 Å MS, CH_2Cl_2, −78 °C to rt, 11%

the previous case either. It is clear that the isomer **24** with all the substituents in the equatorial position should be more stable than the isomer **25**. And therefore, the isomers **24** and **25** would be formed under the thermodynamically- and kinetically-controlled reaction conditions, respectively.

Following the successful 1,4-intramolecular cyclization reaction, the secondary hydroxyl group in **24** was treated with TBSOTf and TEA in CH_2Cl_2 to afford the silyl ether **26** in 88% yield (Scheme 7). Basic hydrolysis of ester **26** in THF-H_2O-MeOH produced carboxylic acid **27** in 93% yield and deprotection of PMB group of **26** using DDQ and H_2O gave the secondary alcohol **28** in 84% yield.

Activated sugar moiety **31** was prepared as follows (Scheme 8). D-Xylose (**29**) was treated with excess MeI in DMSO to give per-methylated derivative[28] as a mixture of epimers ($\beta : \alpha = 3 : 1$), which was subsequently brought to hemiacetal **30** under strongly acidic condition. The free hydroxy group in **30** was further activated to imidate derivative **31**, again as a mixture of epimers ($\beta : \alpha = 1 : 3$).

We are now in a position of the final stages in the synthesis of **1** (Scheme 9). The carboxylic acid **27** and the secondary alcohol **28** were coupled successfully with the aid of DIC and DMAP in 83% yield. After cleavage of the PMB protecting group by DDQ in CH_2Cl_2-H_2O, selective hydrolysis of methyl ester was persued. However, to our surprise, we could not achieve this simple transformation under various hydrolysis conditions (LiOH, $Ba(OH)_2 \cdot 8H_2O$, Me_3SnOH). Cleavage of the internal ester linkage and the methyl ester group competed efficiently to give a very complex mixture of products and use of excess base led to the complete hydrolysis of both esters to give the key monomeric hydroxy acid **34**.

Fortunately, direct dimerization of the monomer **34** using slightly modified-Yamaguchi macrolactonization condition[29] was successful and the TBS protecting group on the sugar moiety was removed by treatment of TBAF to provide the diol **35** in 25% 2-steps yield (Scheme 10). Finally, Lewis acid-assisted glycosylation[30] of **35** with the activated imidate **31** in the presence of molecular sieves proceeded smoothly to afford the target molecule **1** as a white solid[31] in 11% yield.

However, comparison of the ^1H NMR spectra between the isolated compound and the synthetic compound **1** showed clearly that the two compounds were not identical (Figure 3). Most of the peaks derived from the macrocyclic ring and sugar moiety were likely to match quite well both in chemical shifts and in the coupling patterns. The only differences in the spectra were found in the peaks around δ 0-1 range, which was expected from the cyclopropane ring protons and substituents.

In the original paper by Faulkner, determination of the relative stereochemistry around the cyclopropane ring was based on the combination of spectroscopic data and molecular model-

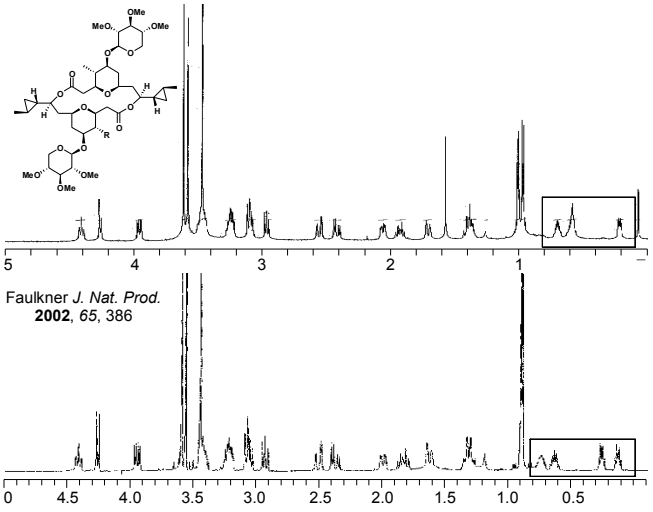
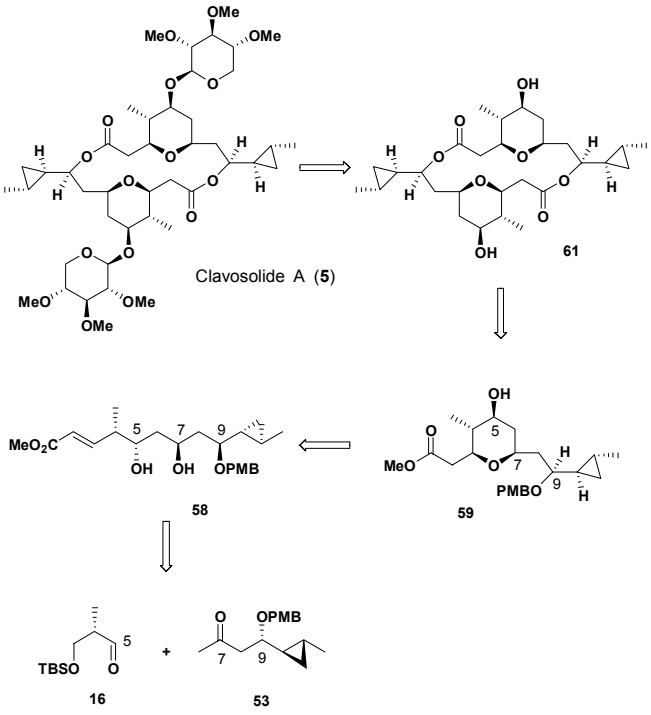


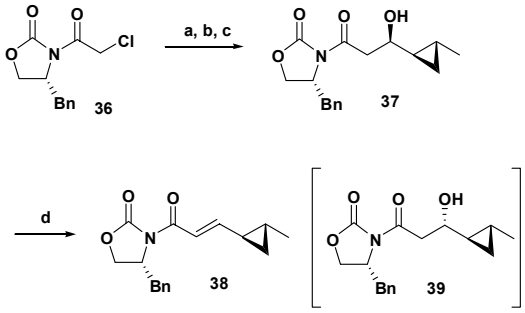
Figure 3. ^{1}H NMR comparison for clavosolide A (**1**).



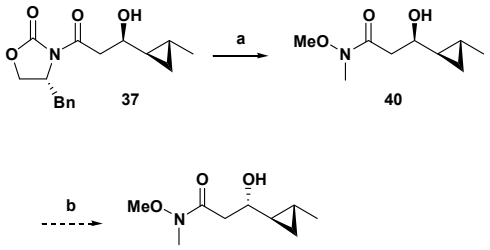
Scheme 11. Retrosynthetic analysis of revised structure **5**

ing studies, and a closer look at the way how they approached in the molecular modeling study led us to think that the evidence might not be conclusive as written in the reference. Therefore, we came to the conclusion that the overall structure of the macrocyclic ring and the sugar moiety must be corrected and that the corrections should be made in the cyclopropane ring structure. We proposed a new revised structure **5** for clavosolide A and started a new journey immediately for the enantioselective synthesis **5**.

Synthesis of revised clavosolide A (5). Retrosynthetic analysis for the revised structure **5** was illustrated in Scheme 11. The basic scheme was the same as that of the proposed structure



Scheme 12. Mitsunobu route to methyl ketone **53**. (a) *i*-Pr_2NEt, Bu_2-BOTf, crotonaldehyde, CH_2Cl_2, −78 °C to rt, 52%; (b) Zinc, NH_4Cl, MeOH, rt, 73%; (c) Et_2Zn, CH_2I_2, CH_2Cl_2, 0 °C, 97%. (d) Benzoic acid, PPh_3, DEAD, THF, 0 °C



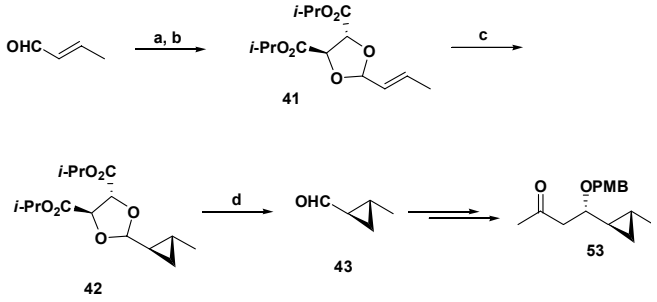
Scheme 13. Diastereoselective reduction route to methyl ketone **53**. (a) MeNH(OMe)-HCl, $AlMe_3$, THF, 63%; (b) DMSO, $(COCl)_2$, CH_2-Cl_2, TEA, 35%; (c) K-selectride, CH_2Cl_2

1 in Scheme 1, except the stereochemical relationship in the cyclopropane ring system. In other words, synthesis of the chiral cyclopropane unit **53** bearing two adjacent carbon substituents in a *trans* relationship became crucial to success of this scheme.

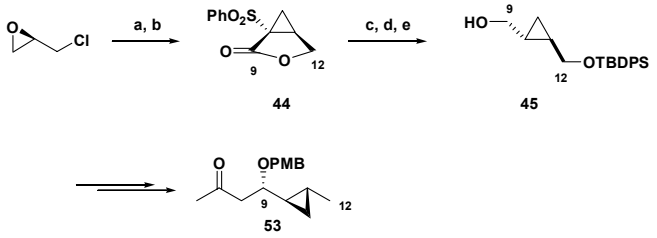
The simplest way to get the methyl ketone **53** was to carry out the hydroxy-directed cyclopropanation to afford the cyclopropyl carbinol with a 1,2-*cis* relationship as usual, and then apply the Mitsunobu protocol to invert the C9 hydroxy group as shown in Scheme 12. Therefore, aldol reaction of carboximide **36** with crotonaldehyde in 52% yield (ds = 95 : 5) and the reductive dechlorination of the *syn*-aldol product by zinc dust in 73% yield were followed by the hydroxy-directed cyclopropanation in 97% yield to provide the precursor **37** as a 11 : 1 ratio of diastereomers. However, reaction of **37** under the standard Mitsunobu condition provided the dehydrated product **38** instead of the inverted alcohol **39**.

Alternatively, the 1,2-*syn* cyclopropylcarbinol **37** was converted into the Weinreb amide **40** in 63% yield (Scheme 13). After oxidation of the amide **40** in 35% yield by Swern protocol, the ketone was reduced diastreoselectively by K-selectride without any fruitful result at all under different reaction conditions.

Next, aldehyde **43** was prepared as a precursor for the chiral boron-mediated methallyation reaction (Scheme 14). Crotonaldehyde was converted into the dimethyl acetal using trimethylorthoformate and the two methoxy groups of the resulting acetal were replaced by the diol moiety of the (*R*,*R*)-tartarate to afford the chiral acetal **41**. Asymmetric Simmons-Smith cyclopropanation of **41** was carried out using Yamamoto's protocol[32] in 88% yield, and the product **42** was hydrolyzed under



Scheme 14. Chiral auxiliary-assisted cyclopropanation route to methyl ketone **53**. (a) triethyl orthoformate, cat. NH_4NO_3, EtOH, 68%; (b) DIPT, PPTS, benzene, reflux, 55%; (c) Et_2Zn, CH_2Cl_2, 0 °C, 88%, TsOH, reflux, THF/H_2O; (d) TsOH, THF/H_2O, reflux



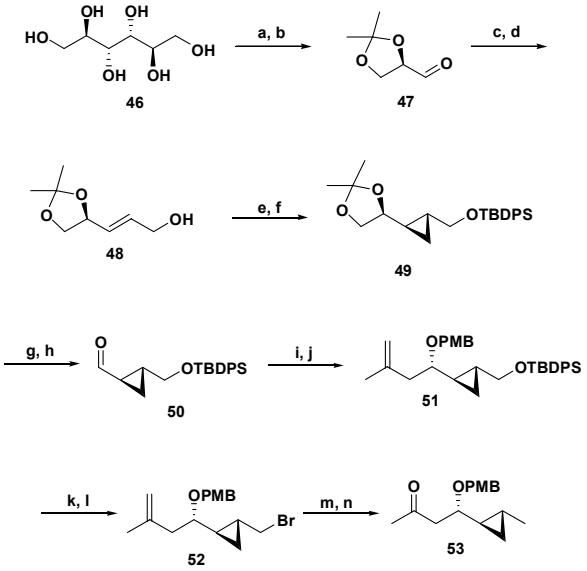
Scheme 15. Diastereoselective cyclopropanation route to methyl ketone **53**. (a) NaOEt, EtOH, $PhSO_2CH_2CN$, 12 h, rt; (b) aq AcOH, 12 h, rt, 38%; (c) $NaBH_4$, MeOH/THF, rt, 12 h, 83%; (d) TBDPSCl, imidazole, DMF, −20 °C, 5 h, 84%; (e) Mg, MeOH, 50 °C, 24 h, 13%

acidic condition. However, isolation of the desired compound **43** was not possible due to the high volatility of the material.

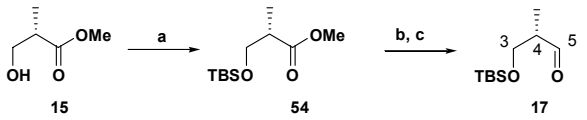
We turned our attention to the Kazuta protocol (Scheme 15).[33] Reaction of epichlorohydrin and phenylsulfonylaceonitrile in the presence of sodium ethoxide, and the acidic hydrolysis *in situ* cyclization provided the lactone **44** in 38% overall yield. Subsequently $NaBH_4$-induced reduction of **44** to 1,4-diol, selective protection of the less hindered primary alcohol, and final desulfonylation by Mg in MeOH provided the alcohol **45**. Although conversion of **45** to the methyl ketone **53** would be possible, however, this route was abandoned again due to the low yield (38% and 13%) in two reaction steps.

Finally, we were pleased to find the successful route to methyl ketone **53** as follows (Scheme 16). Protection of D-mannitol (**46**) with 2,2-dimethoxypropane in the presence of a catalytic amount of $SnCl_2$ in 35% yield was followed by the cleavage of the resulting diol by lead tetraacetate to give the glyceraldehyde acetonide **47**[34] in 86% yield. Horner-Wadsworth-Emmons olefination of aldehyde **47** with triethyl phosphonoacetate and the subsequent reduction of the conjugate ester by DIBAL provided the allylic alcohol **48** in excellent yield. After quantitative protection of the hydroxy group in **48** with TBDPSCl, diastereoselective cyclopropanation using Et_2Zn and CH_2I_2 was carried out to afford the product **49** as a single isomer in 90% yield.

Acetonide **49** was treated with PPTS in MeOH to give the diol in 67% yield, which was cleaved under standard periodate condition to provide the aldehyde **50** in 98% yield. Brown's asymmetric methallylation[35] of aldehyde **50** produced homoallylic alcohol (>97 : 3 by 1H NMR) in 75% yield, and the product was



Scheme 16. Synthesis of methyl ketone **53**. (a) cat. $SnCl_2$, 2,2-dimethoxypropane, 1,2-dimethoxyethane, reflux, 35%; (b) $Pb(OAc)_4$, ethyl acetate, rt, 86%; (c) triethyl phophonoacetate, NaH, THF, −78 °C, 63%; (d) DIBAL, CH_2Cl_2, rt, 91%; (e) TBDPSCl, DMAP, TEA, CH_2Cl_2, 0 °C to rt, 100%; (f) Et_2Zn, CH_2I_2, CH_2Cl_2, −10 °C, 90%; (g) PPTS, MeOH, rt, 67%; (h) $NaIO_4$, THF/H_2O, 0 °C, 98%; (i) isobutylene, TMEDA, n-BuLi, (-)-Ipc_2BOMe, ether, −78 °C; 3N NaOH, H_2O_2, 75%; (j) PMB-imidate, TsOH, CH_2Cl_2/c-Hexane, rt, 76%; (k) TBAF, THF, rt, 93%; (l) CBr_4, PPh_3, THF, rt, 89%; (m) LAH, THF, rt, 96%; (n) O_3, pyridine, MeOH, −78 °C; DMS, rt, 96%

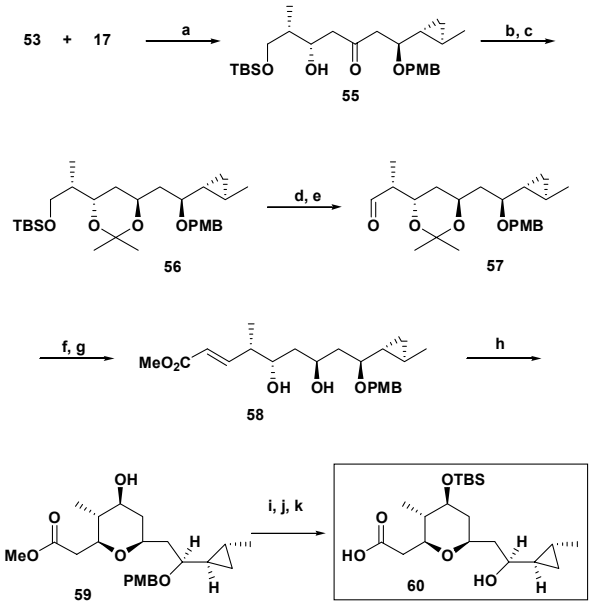


Scheme 17. Synthesis of C3-C5 fragment **17**. (a) TBSCl, DMAP, TEA, CH_2Cl_2, rt, 100%; (b) DIBAL, THF, rt, 67%; (c) DMSO, $(COCl)_2$, TEA, CH_2Cl_2, −78 °C, 99%

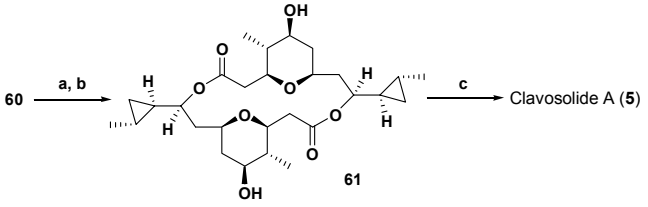
treated with PMB imidate to afford the PMB ether **51**. Deprotection of the TBDPS group in **51** followed by bromination of the primary alcohol afforded the bromide **52**. Finally, reduction[36] of the bromide **52** with LAH in 96% yield and ozonolysis of the double bond in the presence of pyridine provided the desired ketone **53** in 96% yield.

A new route to aldehyde **17** was also utilized starting from the aldehyde **15** *via* the three-step sequences (Scheme 17). Protection of the hydroxy group of the β-hydroxy ester with *tert*-butyldimethylsilyl chloride, reduction of the ester by DIBAL, and Swern oxidation. This route had several advantages over the previous one in Scheme 4. Specifically, the aldehyde **17** was higher in purity and the purity of **17** seemed to be very critical to the success of the next diastereoselective 1,5-*anti* aldol reaction, one of the most important key transformations throughout.

Synthesis of the key monomeric intermediate **60** starting from methyl ketone **53** and aldehyde **17** was summarized in scheme 18. The overall transformations (**53** and **17** to **60**) were basically the same as that in the the synthesis of the proposed clavosolide A (**1**) (**14** and **17** to **26**), which was already described in detail



Scheme 18. Synthesis of monomer hydroxy Acid **60**. (a) *i*-Pr_2NEt, Bu_2BOTf, ether, −78 °C, 93%; (b) $Me_4NB(OAc)_3H$, −20 °C, 95%; (c) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, rt, 83%; (d) TBAF, THF, rt, 99%; (e) Dess-Martin periodiane, $NaHCO_3$, rt, 83%; (f) trimethyl phosphonoacetate, *i*-Pr_2NEt, LiCl, MeCN, 0 °C to rt, 89% (*E* : *Z* = 12 : 1); (g) CSA, MeOH/H_2O, rt, 97%; (h) NaH, THF, rt, 82%; (i) TBSOTf, TEA, CH_2Cl_2, 0 °C, 69%; (j) DDQ, CH_2Cl_2/H_2O, rt, 88%; (k) aq. LiOH, THF/H_2O/MeOH, rt, 81%



Scheme 19. Total synthesis of clavosolide A (**5**). (a) 2,4,6-$Cl_3PhCOCl$, TEA, THF, rt; then add DMAP, PhMe, reflux; (b) TBAF, THF, 0 °C, 41% (2 steps); (c) **31**, $BF_3{\cdot}OEt_2$, 4 Å MS, CH_2Cl_2, −78 °C to rt, 11%

(Table 2 and 3, and Scheme 5, 6, 7).

Boron-mediated diastereoselective aldol reaction of methyl ketone **53** and aldehyde **17** in ether at −78 °C afforded the β-hydroxy ketone **55** (ds ≥ 96 : 4 by ^1H NMR) in 93% yield. 1,3-*Anti*-selective reduction of **55** using tetramethylammonium triacetoxyborohydride in MeCN-AcOH was followed by treatment of the 1,3-*anti*-diol with 2,2-dimethoxypropane in the presence of catalytic PPTS to produce acetonide **56**.

The aldehyde **57** could be constructed from the acetonide **56** *via* deprotection of the primary silyl ether followed by Swern oxidation of the hydroxy group. However, Dess-Martin oxidation in the presence of the $NaHCO_3$ at room temperature turned out to be the reagent of choice because the labile epimerization of aldehyde at C4 occurred during under the Swern oxidation. The aldehyde **57** was then converted into the conjugated ester by a HWE reaction and the acetonide protecting group was cleaved under the acidic condition to provide the 1,3-diol **58**. The (*E*) : (*Z*) ratio was approximately 12 : 1 as determined by ^1H NMR spectroscopy.

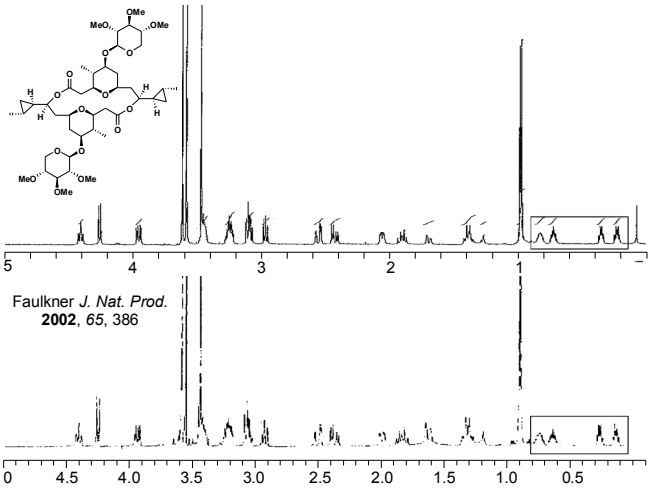


Figure 4. ^1H NMR spectra of synthetic compound **5** and isolated compound **1**.

Intramolecular conjugate addition of C7-hydroxy group in **58** using sodium hydride in THF afforded the 2,6-*cis*-pyran **59** with a moderate diastereoselectivity (2,6-*syn* : 2,6-*anti* = 11 : 1) in 82% yield. The key intermediate **60** was synthesized from **59** by a three-step sequence : protection of secondary alcohol with TBSOTf, deprotection of PMB group using DDQ in CH_2Cl_2, and basic hydrolysis of ester group in THF-H_2O-MeOH.

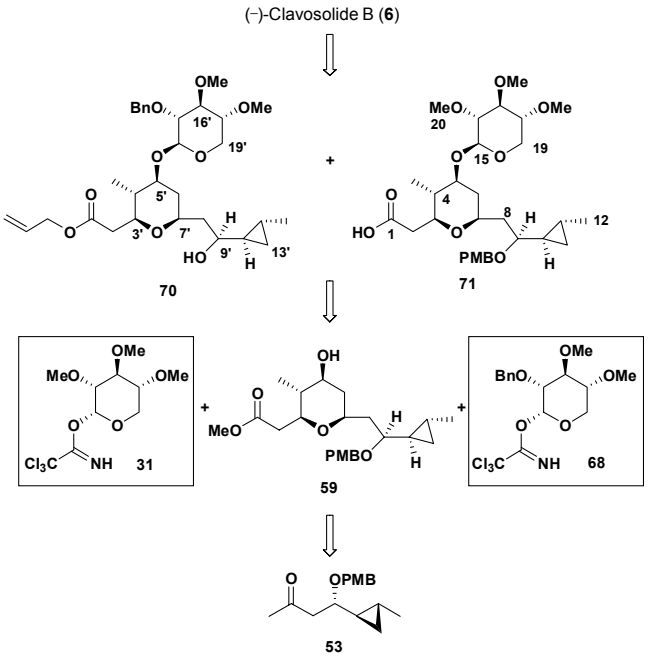
With a key building block **60** in our hands, we moved on directly to the final stage for the synthesis of **5** (Scheme 19). Dimerization of hydroxyl acid **60** was conducted under slightly modified-Yamaguchi macrolactonization condition, and the TBS protecting group on the sugar moiety was removed by treatment of TBAF to provide the diol **61** in 41% two-step yield. Finally, Lewis acid-assisted glycosylation of **61** by the activated imidate **31** in the presence of molecular sieves proceeded smoothly to afford the target molecule **5** as a white solid in 11% yield.

The ^1H NMR spectra of the isolated compound by Faulkner and synthetic compound **5** are identical in all respects including chemical shifts, coupling constants and patterns (Figure 4). Also, the chemical shifts in ^{13}C NMR spectra of the natural and the synthetic materials are indistinguishable. This information confirms the relative stereochemical relationship for the natural clavosolide A as (**5**).

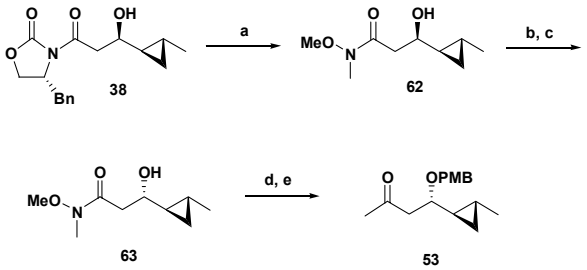
Following our reports on the structure of the revised clavosolde A (**5**), Smith,[37] Willis,[38] and Chakraborty[39] unambiguously determined the absolute stereochemistry of (-)-clavosolide A as (**5**) by comparison of the optical rotation values.

Synthesis of revised clavosolide B (6). From the previous work, it was quite obvious that the proposed structure of clavosolide B (**2**) would be assigned incorrectly and that the isolated clavosolide B should have the same stereochemical relationship as that of the clavosolide A (**5**). Therefore, we proposed a revised structure for clavosolide B as **6** and started the enantioselective synthesis of **6** to clarify this issue.

Retrosynthetic analysis for the revised clavosolide B (**6**) was illustrated (Scheme 20). In contrast to the retrosynthesis of the



Scheme 20. Retrosynthesis of revised clavosolide B (**6**)

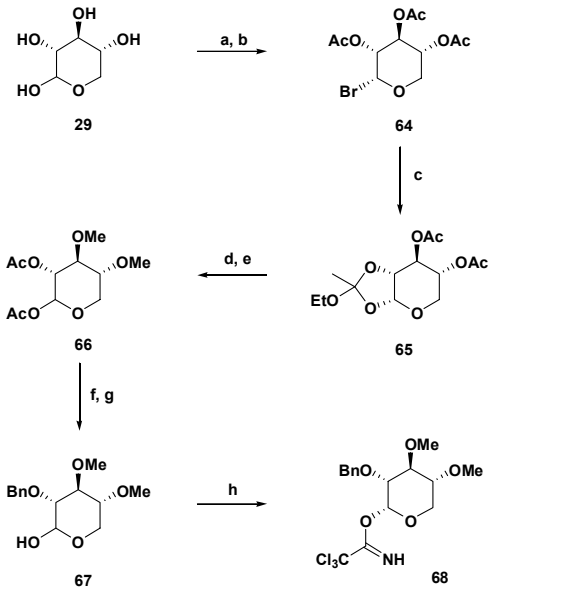


Scheme 21. Alternative synthesis of methyl ketone **53**. (a) Me(OMe)NH·HCl, $AlMe_3$, THF, 0 °C to rt, 96%; (b) PPh_3, DIAD, AcOH, toluene, −45 °C, 61%; (c) K_2CO_3, MeOH, 0 °C, 68%; (d) PMBO(C=NH)CCl_3, TsOH, rt, 83%; (e) MeMgCl, THF, −78 °C to 0 °C, 86%

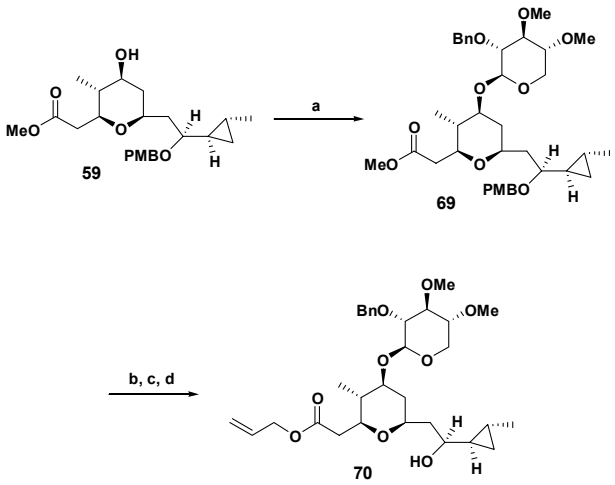
proposed and the revised clavosolide **A** in Scheme 1 and 13, sequential disconnection of the two ester linkages in **6** was necessary due to the asymmetric nature of **6** in structure. Fragments **70** and **71** would be derived from the coupling of the common intermediate **59** and two activated sugar moieties **31** and **68** *via* a Schmidt-type glycosylation.

Although pyran **59** was prepared previously from methyl ketone **53** by us,[8a] a new and simpler sequence has been implemented to synthesize the ketone **53** based on the Smith procedure (Scheme 21).[9]

In Scheme 15, application of the Mitsunobu reaction for the carboximide **38** resulted in dehydration of C9 hydroxy group. However, to our surprise, Mitsunobu inversion of the Weinreb amide **62** with AcOH at −45 °C, obtained by transamination of **38** with *N*,*O*-dimethylhydroxylamine hydrochloride and $AlMe_3$, gave the acetate in 61% yield as a 7 : 1 ratio of diastereomers and the ester was treated with K_2CO_3 in MeOH to provide the required alcohol **63** in 68% yield. Finally, the methyl ketone **53** was prepared in two steps from **63** *via* PMB-protection of secondary alcohol with 4-methoxybenzyl trichloroacetimidate



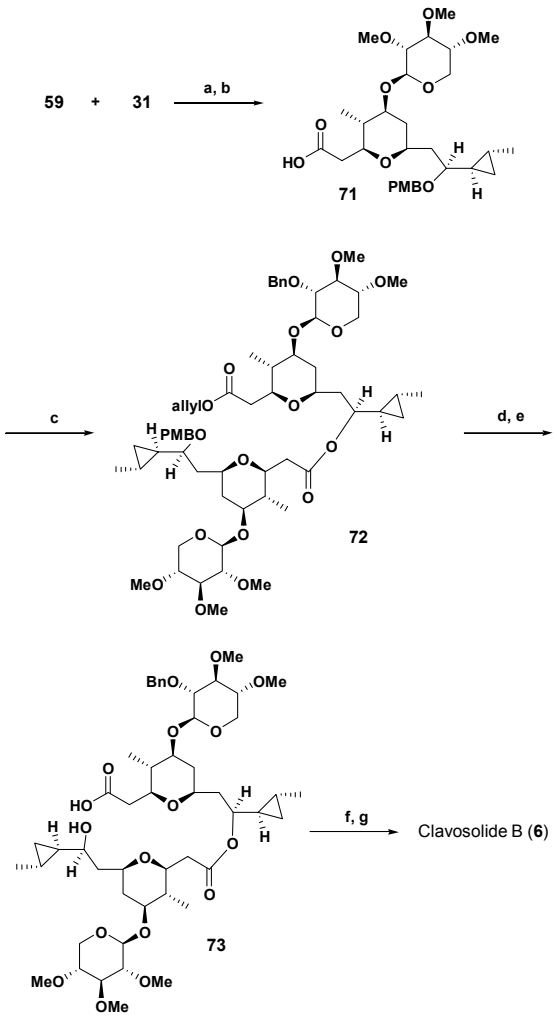
Scheme 22. Synthesis of imidate **68** from D-xylose. (a) Ac_2O, pyridine, 100%; (b) HBr/AcOH, 91%; (c) 2,6-lutidine, Bu_4NBr, CH_2Cl_2, EtOH, rt, 90%; (d) NaOMe, MeOH; NaH, MeI, DMF, 93%; (e)AcOH, rt; Ac_2O, pyridine, rt, 98%; (f) NaOMe, MeOH; NaH, BnBr, DMF, 73%; (g) 1,4-dioxane/2N HCl, 105 °C, 52%; (h) NaH, CCl_3CN, CH_2Cl_2, rt, 89%



Scheme 23. Synthesis of top half segment **70**. (a) **68**, TMSOTf, 4 Å MS, CH_2Cl_2/MeCN(1 : 1), −50 °C, 47%; (b) LiOH, THF/H_2O/MeOH; (c) allyl bromide, K_2CO_3, 53% (2 steps); (d) DDQ, H_2O, rt, 89%

and conversion of Weinreb amide with methylmagnesium chloride.

Preparation of activated sugar imidate **68** was based on the Kochetkov[40] protocol and summarized in Scheme 22. D-Xylose (**29**) was treated with acetic anhydride in pyridine to give peracetated derivative,[41] and the product was treated with hydrogen bromide in acetic acid to provide the α-bromide **64** as the only product. Although reaction of the bromide **64** with *n*-Bu_4NBr and *syn*-collidine in acetonitrile and EtOH was not successful, reaction of the bromide **64** with *n*-Bu_4NBr and 2,6-lutidine in EtOH afforded the orthoester **65** in 98% yield.[42] After mild basic



Scheme 24. Synthesis of bottom half Segment **71** and total synthesis of (-)-claovosolide B (**6**). (a) TMSOTf, 4 Å MS, CH_2Cl_2/MeCN (1 : 1), −50 °C, 47%; (b) LiOH, THF/H_2O/MeOH, rt; (c) **70**, DIC, DMAP, CH_2Cl_2, 54% (2 steps); (d) DDQ, CH_2Cl_2, H_2O, 70%; (e) $Pd(PPh_3)_4$, morpholine, THF, rt; (f) 2,4,6-Cl_3PhCOCl, TEA, THF, rt; DMAP, PhMe, reflux, 52% (2 steps); (g) Pd/C, MeOH, rt, 78%

hydrolysis of two acetate groups in **65**,[43] the hydroxy groups were subjected to methylation using NaH and MeI in 93% overall yield, and the product was treated with glacial acetic acid and acetic anhydride-pyridine system to induce cleavage of the orthoester protecting group and *in situ* acetylation of the diol to give the diacetate **66** in 98% yield.[44] Removal of two acetyl groups in 3- and 4-position of **66** using NaOMe in MeOH as before and benzylation of two hydroxy groups by NaH-BnBr allowed the synthesis of dibenzyl ether, which was converted into the hemiacetal **67** under acidic condition. Treatment of the hemiacetal **67** with trichloroacetonitrile and NaH afforded the imidate **68** in 89% yield as a mixture of epimers (α : β = 6 : 1).

The synthesis of the top half segment **70** was summarized in Scheme 23. Transformation of methyl ketone **7** into the key intermediate **53** was accomplished following the same procedure reported earlier in the synthesis of (-)-clavosolide A (**1**).[8a] Since the methyl and benzyl groups at the C2 position of imidates **31** and **68** would not exert anchimeric assistance in the glycosylation reaction, the selectivity for the required β-glucoside must be ensured by the proper choice of promoter and solvent. After several model studies, we found that Schmidt-type glycosylation[45] of the alcohol **59** with an activated sugar imidate **68** in the presence of TMSOTf and molecular sieves in CH_2Cl_2/MeCN(1 : 1) produced a mixture of isomers (α : β = 1 : 1) and the desired β-isomer **69** was separated by silica gel column chromatography in 47% yield. Alcohol **70** was then prepared in a three-step sequence from **69**, *via* the hydrolysis of methyl ester by LiOH, esterification of carboxylic acid with allyl bromide and K_2CO_3, and deprotection of PMB ether by DDQ.

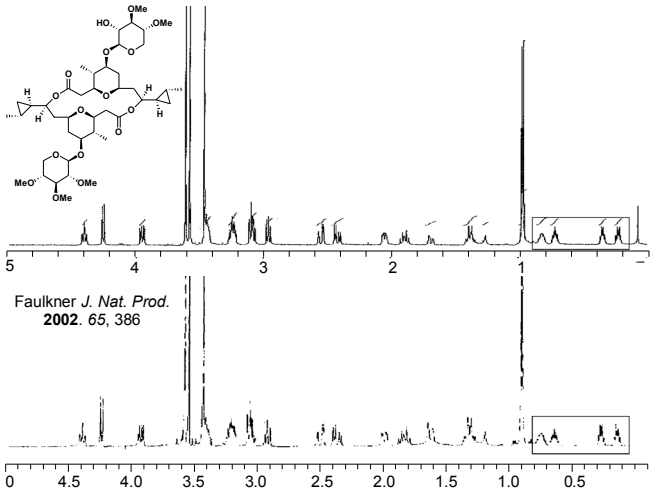


Figure 5. ^{1}H NMR comparison for clavosolide B.

The bottom half segment **71** was also synthesized in a similar manner (Scheme 24). Schmidt glycosidation of alcohol **59** with the activated sugar moiety **31** in the presence of TMSOTf and molecular sieves in CH_2Cl_2/MeCN(1 : 1), exactly the same reaction condition used in scheme 25, provided a mixture of isomers (α : β = 1 : 1). After separation of the desired β-isomer in 47% yield, the β-isomer was treated with LiOH to produce carboxylic acid **71**.

With two key intermediates **70** and **71** in our hands, total synthesis of proposed clavosolide B (**2**) was persued immediately. Alcohol **70** and carboxylic acid **71** were coupled with the aid of DIC and DMAP to provide the ester **72** in 54% yield over two steps from the glycosylation reaction of **59**. Selective cleavage of PMB protecting group by DDQ in CH_2Cl_2-H_2O and of allyl ester protecting group with $Pd(PPh_3)_4$ furnished the hydroxy acid **73**. Macrolactonization of **73** using Yamaguchi protocol under slightly modified condition proceeded smoothly and final deprotection of the benzyl group with Pd/C in MeOH provided the target compound **6** as a white solid in 78% yield.

Comparison of the ^{1}H NMR and ^{13}C NMR spectra of the isolated and synthetic compounds showed clearly that the two compounds are identical (Figure 5) except for the signals from the impurites contained in the isolated natural product.[46] This result led to the correction of the relative stereochemistry of clavosolide B as **6**. as expected from the beginning of the synthesis.

Optical rotation of the synthetic compound was also measured to be $[\alpha]_D$ −47.2 (*c* 0.4, $CHCl_3$), which is similar to the report-

ed value of $[\alpha]_D$ −41.0 (*c* 0.5, $CHCl_3$) for the natural compound, therefore establishing the absolute stereochemistry of clavosolide B (**6**) as shown in Figure 2.

Conclusion

We have successfully synthesized the proposed structure of clavosolide A (**1**). However, the assignment of the relatavtive stereochemistry induced independently by Faulkner and Erickson was not correct, and we proposed a new revised structure **5** for the natural clavosolide A. First total synthesis of the the revised structure **5** was achieved and comparison of the the ^{1}H NMR and ^{13}C NMR spectral data of the isolated and synthetic compounds eventaully confirmed the natural clavosolide A as **5.**

Similarly, we proposed a new revised structure **6** for the clavosolide B. We synthesized the revised clavosolide B (**6**) again and found the identity of the natural and synthetic compounds, proving the relative stereochemistry of the natural clavosolide B. Comparison of the optical rotation values further verified unambiguously the absolute structure of the natural clavosolide B as **6**.

In synthetic point of view, synthesis of the common pyran intermediate (**34**, **59**), activated sugar moiety (**31**, **68**), and glycosylation for the β-isomer constituted the main frame of the synthesis. The synthesis is relatively simple and convergent. Especially, *syn*-selective aldol, hydroxy-directed cyclopropanation, Mitsunobu inversion at C9 position, a Schmidt-type glycosylation, and macrolactonization reactions in a one-pot or stepwise manner were used commonly in the synthesis of all three compounds **1**, **5**, and **6**.

Experimentals

All the information including experimental procedures and spectroscopic data is available in the supporting information.

(-)-Clavosolide A (5). mp 256.8 °C; $[\alpha]_D^{25} = -39.7$ (*c* = 0.055, $CHCl_3$) IR (film): $\tilde{\nu}$ = 3065, 2928, 2855, 1740, 1092 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.41 (t, *J* = 9 Hz, 2 H), 4.26 (d, *J* = 8 Hz, 2 H), 3.95 (dd, *J* = 5, 11.5 Hz, 2 H), 3.61 (s, 6 H), 3.58 (s, 6 H), 3.46 (s, 6 H), 3.43 (m, 2 H), 3.42 (m, 2 H), 3.24 (t, *J* = 11.5 Hz, 2 H), 3.24 (td, *J* = 8.5, 5 Hz, 2 H), 3.09 (t, *J* = 8.5 Hz, 2 H), 3.08 (dd, *J* = 8.5, 11.5 Hz, 2 H), 2.95 (t, *J* = 8.5 Hz, 2 H), 2.54 (dd, *J* = 3, 17 Hz, 2 H), 2.41 (dd, *J* = 6.5, 17 Hz, 2 H), 2.04 (dd, *J* = 4.5, 11.5 Hz, 2 H), 1.88 (dt, *J* = 9, 15 Hz, 2 H), 1.68 (br d, *J* = 15 Hz, 2 H), 1.38 (m, 2 H), 1.37 (q, *J* = 11.5 Hz, 2 H), 0.96 (d, *J* = 6.5 Hz, 6 H), 0.81 (m, 2 H), 0.71 (tt, *J* = 5, 9 Hz, 2 H), 0.34 (dt, *J* = 5, 8.5 Hz, 2 H), 0.22 (dt, *J* = 5, 8.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 105.7, 85.7, 84.0, 83.4, 79.5, 77.2, 77.0, 75.0, 63.4, 61.0(2), 59.0, 42.7, 41.4, 40.9, 39.4, 24.9, 18.7, 12.8, 12.1, 11.1; HRMS: *m*/*z* calcd for $C_{44}H_{72}NaO_{16}$ $[M+Na]^+$ 879.4718, found 879.4718.

(-)-Clavosolide B (6). mp 205 - 207 °C; $[\alpha]_D^{25} = -47.2$ (*c* = 0.4, $CHCl_3$) (Lit. $[\alpha]_D^{25} = -41.0$ (c = 0.5, $CHCl_3$)); IR (film): $\tilde{\nu}$ = 3465, 2951, 2858, 1731, 1434, 1375, 1254 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.43 (br t, *J* = 8.5 Hz, 2 H), 4.37 (d, *J* = 7 Hz, 1 H), 4.27 (d, *J* = 7 Hz, 1 H), 4.03 (dd, *J* = 4.5, 11.5 Hz, 1 H), 3.97 (dd, *J* = 4.5, 11.5 Hz, 1 H), 3.62 (s, 3 H), 3.61 (s, 3 H), 3.59 (s, 3 H), 3.48 (s, 6 H), 3.48-3.43 (m, 5 H), 3.30 (m, 1 H), 3.25 (dt, *J* = 5, 8 Hz, 2 H), 3.25 (dd, *J* = 8, 11 Hz, 1 H), 3.23 (m, 1 H), 3.21 (t, *J* = 8 Hz, 1 H), 3.10 (t, *J* = 8.5 Hz, 1 H), 3.09 (dd, *J* = 9, 11 Hz, 1 H), 2.97 (t, *J* = 8.5 Hz, 1 H), 2.55 (dt, *J* = 3.5, 17.5 Hz, 2 H), 2.42 (dd, *J* = 6.5, 17.5 Hz, 2 H), 2.05 (dd, *J* = 4.5, 12.5 Hz, 2 H), 1.90 (dt, *J* = 6.5, 15 Hz, 1 H), 1.89 (dt, *J* = 6.5, 15 Hz, 1 H), 1.68 (br d, *J* = 15 Hz, 2 H), 1.40 (m, 2 H), 1.38 (m, 2 H), 0.98 (d, *J* = 6.5 Hz, 9 H), 0.95 (d, *J* = 6.5 Hz, 3 H), 0.83 (m, 2 H), 0.72 (tt, *J* = 4.5, 9 Hz, 2 H), 0.35 (dt, *J* = 4.5, 8.5 Hz, 2 H), 0.23 (dt, *J* = 4.5, 8.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.17, 171.14, 105.7, 104.8, 85.7, 84.0, 83.5, 83.4, 83.1, 79.6, 79.1, 77.14, 77.11, 75.04, 75.01, 73.0, 63.4, 62.6, 61.0, 60.4, 59.0, 58.6, 42.7, 42.5, 41.4, 40.9, 40.7, 39.4, 24.9, 18.7, 13.1, 12.8, 12.1, 11.1; HRMS: *m*/*z* calcd for $C_{44}H_{72}NaO_{16}[M+Na]^+$ 865.4562, found 865.4563.

Acknowledgments. This research was assisted financially by the Korea Research Foundation (KRF-2007-314-C00162). BK21 postdoctorial fellowship grant to J. B. Son, BK21 graduate fellowship grants to M. Hwang and W. Lee, and Seoul Science Fellowship grant to M. Hwang are gratefully acknowledged. The instrument facilities of the Organic Chemistry Research Center (OCRC) in the chemistry department of Sogang University were also helpful.

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