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Accepted Article

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To be cited as: *Chem. Asian J.* 10.1002/asia.201700950

Link to VoR: http://dx.doi.org/10.1002/asia.201700950

A Journal of

ACES
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10.1002/asia.201700950

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Synthesis and Configuration of Neomaclafungin A

Shijun Zhu[a] and Yikang Wu*[a]

Dedication ((optional))

Abstract: The relative and absolute configuration of neomaclafungins were impossible to establish by spectroscopic analyses alone because of the lack of exploitable ^{1}H-^{1}H couplings and nOe's between the upper and the lower subunits. This very difficult task now is finally completed by an enantioselective total synthesis of neomaclafungin A (revised) and its diastereomer (reported). The results also provided a key reference for the complete structures for other neomaclafungins and the long-known closely related natural product maclafungin.

Neomaclafungins (**1a-i**, Figure 1) were isolated in 2012 by Sato and coworkers[1] from *Actinoalloteichus* sp. NPS702 (found in marine sediment). In the preliminary testing, **1a-i** showed significant antifungal activity (MIC 1-3 μg/mL) against *Trichophyton* mentagrophytes (ATCC9533). The gross structures of neomaclafungins were assigned on the basis of spectroscopic analyses of neomaclafungin A (the most abundant component), which differ from maclafungin[2] (**2**) only at the C-4 and C-33, with the lower (spiroketal) subunit very similar to that in oligomycin A[3] (**3**). The relative configurations for the upper (C-1 to C-17) and the lower fragments of neomaclafungin A were assigned separately by analysis of the ^{1}H-^{1}H coupling constants. However, lack of any exploitable ^{1}H-^{1}H couplings between the two arrays of stereocenters made it impossible to establish a relative configuration for the whole molecule (cf. configurations of oligomycins were determined by X-ray). To overcome this difficulty, an enantioselective synthesis appeared to be essential

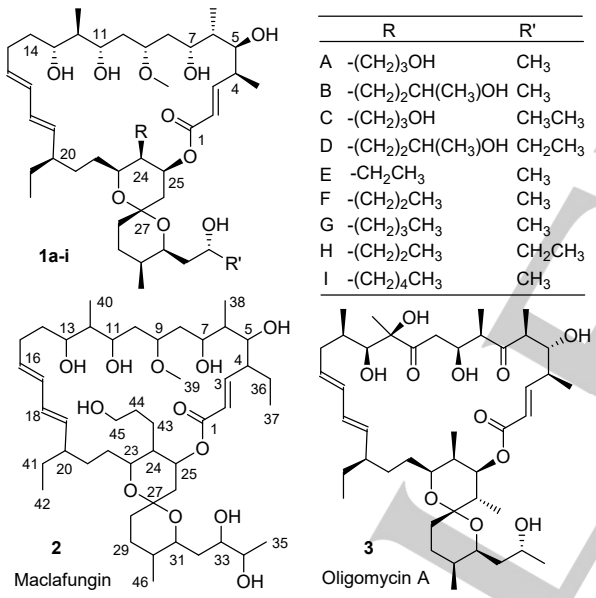
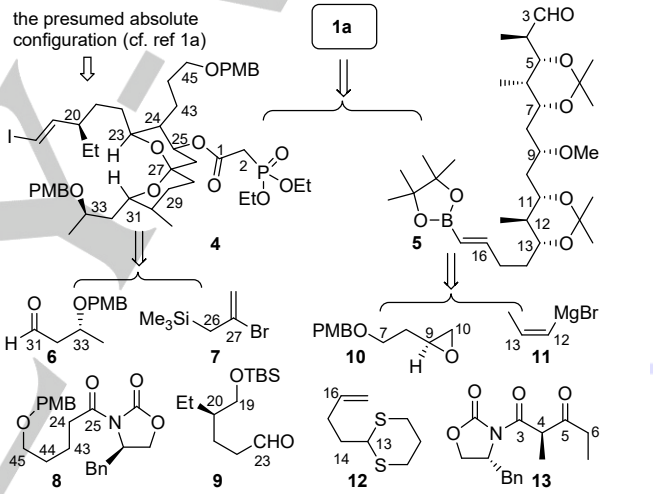
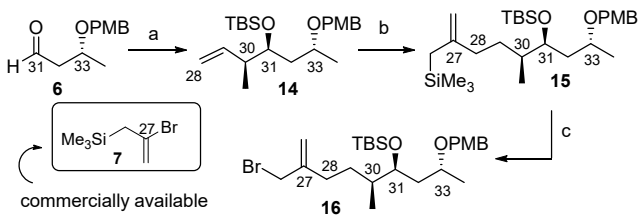


Figure 1. The structures of neomaclafungins A-I (**1a-i**, deduced from ref 1 with correction at C-5; disproved in this work), maclafungin (**2**) and oligomycin A (**3**).



Scheme 1.

Our initial retrosynthetic analysis is shown in Scheme 1. The target **1a** was planned to be disconnected first into the lower fragment **4** and the upper fragment **5**, each of which was then further disconnected into readily accessible fragments **6-13**.



Scheme 2. Reagents and conditions: a) (i) Brown asy. crotylation, (ii) TBSCl, DMAP, imidazole, 70% from **6**; b) (i) 9-BBN, THF, 50 °C, (ii) **7**, DMF, Cs_2CO_3, $Pd(PPh_3)_4$, 50 °C, 90% from **14**; c) NBS, CH_2Cl_2, DMF, propylene oxide, –72 °C, 98%. TBS = *t*-Butyldimethylsilyl, DMAP = 4-(dimethylamino)pyridine, 9-BBN = 9-borabicyclo[3.3.1]nonane, NBS = *N*-Bromosuccinimide.

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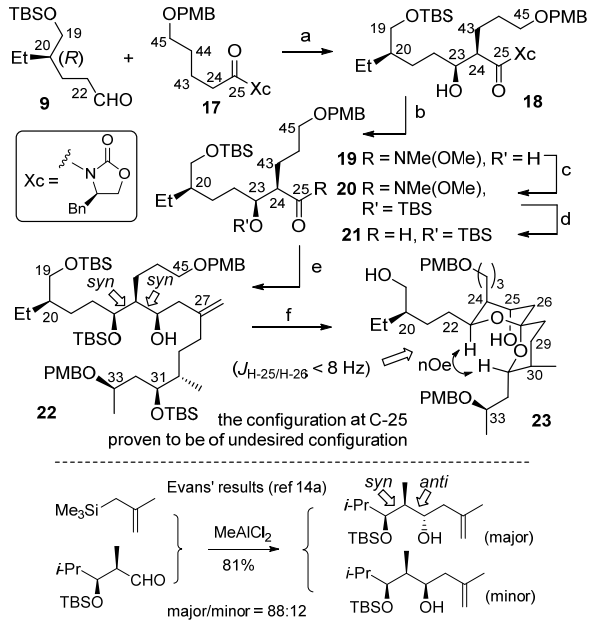
Synthesis of fragment **4** began as shown in Scheme 2. Aldehyde **6**[4] was subjected to Brown[5] crotylation and TBS protection to afford **14**, which on hydroboration with 9-BBN at 50 °C[6] followed by a Suzuki coupling with **7** gave **15**.[7] Further treatment with NBS delivered the corresponding bromide **16**.[8]

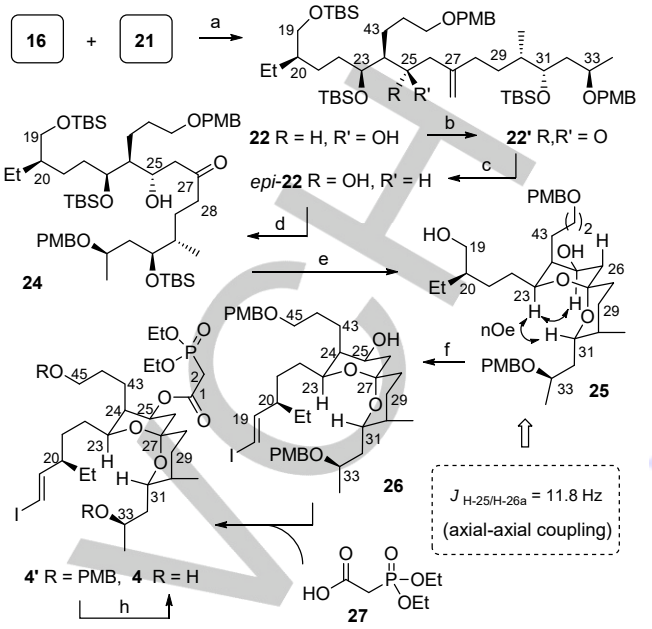


Scheme 3. Reagents and conditions: a) $TiCl_4$, *i*Pr_2NEt, NMP, CH_2Cl_2, –98 °C to 0 °C, 80%; b) MeNH(OMe)·HCl, $AlMe_3$, THF, 0 °C, 86%; c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 88%; d) DIBAL-H, THF, 0 °C, 82%; e) **15**, $EtAlCl_2$, *n*$Bu_4NSiPh_3F_2$, CH_2Cl_2, –78 °C, 47%; f) (i) OsO_4, NMO, $PhI(OAc)_2$, 76%, (ii) aq. $HClO_4$, MeCN-CH_2Cl_2, 0 °C, 58%. NMP = *N*-methylpyrrolidinone, DIBAL-H = diisobutylaluminum hydride.

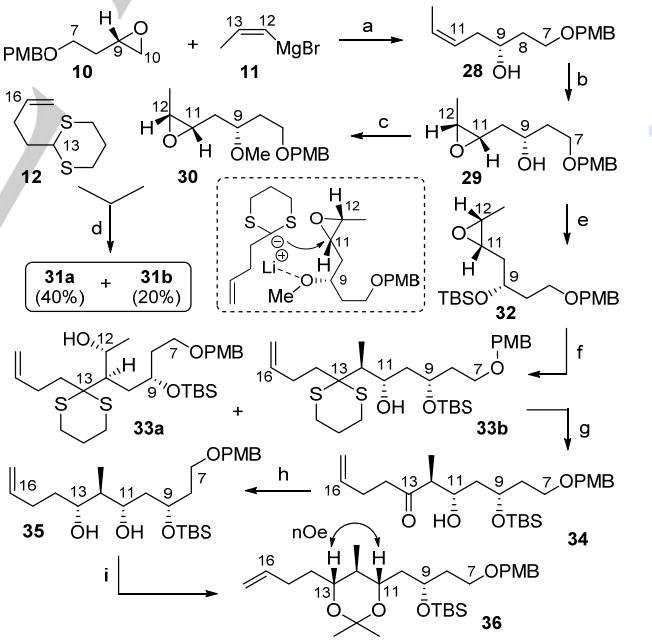
The C-19 to C-25 moiety of fragment **4** was achieved as shown in Scheme 3. Evans aldol condensation of **9**[9] with **17** under the Crimmins[10a] conditions ($TiCl_4$/*i*Pr_2NEt/NMP[10b,11]) at –98 °C gave **18** in 80% yield. Removal of the chiral auxiliary in **18** with MeN(OMe)·HCl/$AlMe_3$[12] afforded **19**, which on TBS protection and DIBAL-H reduction gave **21**.[13] Subsequent coupling with **15** in the presence of $EtAlCl_2$[14a]/*n*$Bu_4NSiPh_3F_2$[14b] afforded **22** (47%), the C-25 configuration of which was determined by the $J_{H\text{-}25/H\text{-}26}$ (< 8 Hz) in **23** (by treatment with first OsO_4 and then $HClO_4$)[15] and opposite to Evans'[14a] results.

Reaction of **16** with **21** mediated by $CrCl_2$/$NiCl_2$[16] (Scheme 4) led to **22** (59%) and *epi*-**22** (19%). The undesired **22** was oxidized and stereoselectively reduced with DIBAL-H (cf $LiAlH_4$ gave a 1:1 mixture) to afford *epi*-**22**, which on sequential exposure to OsO_4/NMO/$PhI(OAc)_2$[17] and CSA[18] gave ketal **25**. It is noteworthy that either $HClO_4$ (worked well for **22**) or HF (worked well[14c] for oligomycin C) resulted in only traces of **25**.

Diol **25**, with its C-25 OH configuration proven by the nOe and $J_{H\text{-}25/H\text{-}26a}$ (11.8 Hz), was then selectively oxidized at C-19 with $RuCl_2(PPh_3)_3$[19a]. The resulting aldehyde reacted with $CrCl_2$/CHI_3[19b,20] to afford **26**. Finally, a Yamaguchi[21] esterification and removal[22] of the PMB furnished the desired lower fragment **4**.

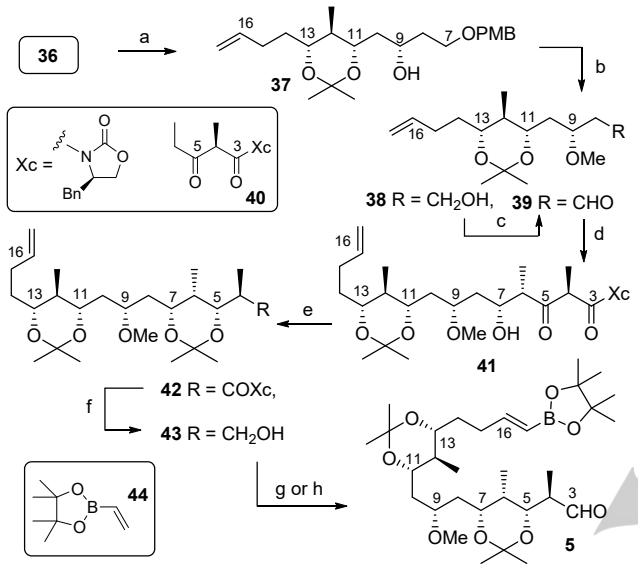


Scheme 4. Reagents and conditions: a) $CrCl_2$, $NiCl_2$, THF, rt, 12 h, 19% for *epi*-**22**, 59% for **22**; b) Dess-Martin oxidation, 89%; c) DIBAL-H, –78 °C, 84%; d) $PhI(OAc)_2$, OsO_4, NMO, acetone-H_2O, 96%; e) CSA, MeCN-H_2O, 58%; f) (i) $RuCl_2(PPh_3)_3$, toluene, rt, 77%, (ii) $CrCl_2$, CHI_3, THF, dioxane, rt, 56%; g) Yamaguchi esterification; h) DDQ, rt, CH_2Cl_2-H_2O, 100%. CSA = D-camphorsulfonic acid, DDQ = 2,3-dicyano-5,6-dichlorobenzoquinone.

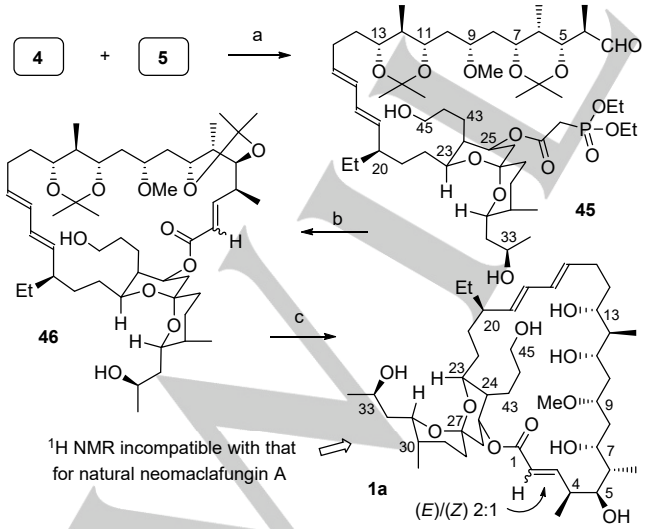


Scheme 5. Reagents and conditions: a) CuBr·Me_2S, THF, –20 °C to 0 °C, 98%; b) $VO(acac)_2$, *t*BuOOH, CH_2Cl_2, 0 °C, 24 h, 87% (dr 20:1); c) NaH, MeI, DMF, 80%; d) *n*BuLi, THF, rt, 40% for **31a**, 20% for **31b**; e) TBSCl, Et_3N, DMAP, 93%; f) *n*BuLi, THF, rt, 30% for **33a**, 68% for **33b**; g) $Hg(ClO_4)_2$, $CaCO_3$, THF-H_2O, 58%; h) (i) *c*Hex_2BCl, Et_3N, Et_2O, –30 °C (dr 20:1), (ii) $LiBH_4$, –78 °C; i) PPTS, $Me_2C(OMe)_2$, 75% from **34**. PPTS = Pyridium *p*-toluenesulfonic acid.

To access fragment **5** (Schemes 5-6), **10**[23] was treated with **11**[24] to afford **28**. Epoxidation of **28** using $VO(acac)_2$/TBHP[25] gave **29** (dr 20:1). The OH in **29** was masked as OTBS (to revert the abnormal regioselectivity observed in reaction of **12**[26] with **30** caused by the OMe, cf the inset in Scheme 5) to provide **33b** in 68%.[27] Treatment of **33b** with $Hg(ClO_4)_2$/ $CaCO_3$[28] furnished **34**. Finally, reduction of **34** with *c*-$hex_2BCl/LiBH_4$[29] and the following acetonization of the diol afforded **36** (the hydroxyl configuration of which was confirmed by the nOe between H-11/H-13).



Scheme 6. Reagents and conditions: a) nBu_4NF, THF, rt, 88%; b) (i) NaH, MeI, DMF, (ii) DDQ, CH_2Cl_2, pH 7 buffer, 91% from **37**; c) Dess-Martin oxidation, 90%; d) (i) **40**, Et_3N, $Sn(OTf)_2$, CH_2Cl_2, –20 °C, (ii) **39**, –78 °C, 88% from **40**, dr 18:1; e) (i) DIBAL-H, Et_2O, –98 °C, (ii) CSA, $Me_2C(OMe)_2$, 74% from **41**; f) $LiAlH_4$, THF, –78 °C, 7 h, 90%; g) (i) **44**, Grubbs I catalyst, CH_2Cl_2, 51%, (ii) Dess-Martin oxidation, 30%; h) (i) Dess-Martin oxidation, 69%, (ii) **44**, Grubbs I catalyst, CH_2Cl_2, 71%. DMF = *N*,*N*-dimethylformamide.

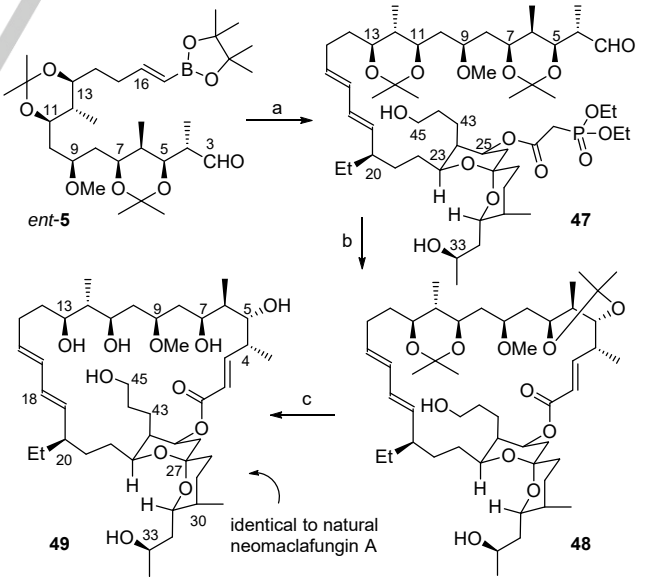


Scheme 7. Reagents and conditions: a) $Pd(PPh_3)_4$, Ag_2O, THF-H_2O, rt, 12 h, 70%; b) K_2CO_3, 18-crown-6, toluene, 48 h, 33%; c) (i) 65% AcOH, rt, 4 h, (ii) 80% AcOH, 80 °C, 30 min, 51% from **46**.

Conversion of **36** into **41** was achieved by removal of the TBS, methylation of the hydroxyl group with MeI/NaH, cleavage of PMB, Dess-Martin oxidation[30] and a tin-mediated[31] Evans aldol condensation (Scheme 6). Reduction of **41** with DIBAL-H[31] at –98 °C (dr > 20:1) followed by acetonide protection gave **42**, which on removal[31] of the chiral auxiliary, oxidation and coupling[32] with **44** afforded the upper fragment **5**.

A Suzuki coupling[33] of **4** with **5** (Scheme 7) was then performed to afford **45**.[34] Subsequent exposure of **45** to K_2CO_3/18-*c*-6/PhMe[35] afforded **46** as a 2:1 mixture of the (*E*)/(*Z*) isomers, which was converted into the end product **1a** using a two-stage[36] hydrolysis strategy (also a 2:1 (*E*)/(*Z*) mixture) after repeated failures[37] using conventional protocols.

Unexpectedly, the ^1H NMR of **1a** was incompatible with that for natural neomaclafungin A. Therefore, *ent*-**5** was next synthesized (cf. Supporting Information) and coupled with **4** in the same manner (Scheme 8). Under the same conditions, **48** formed as a single isomer (rather than an (*E*)/(*Z*) mixture). However, the final hydrolysis became much more difficult (with unidentified side products predominated) than hydrolysis of **46**. Despite our exhaustive efforts, the yield for **49** could not exceed 10%, illustrating a previously unknown differential reactivity caused by the relative configuration between two remotely located subunits. Nevertheless, the ^1H and ^{13}C NMR as well as $[\alpha]_D$ for **49** were consistent with those for natural neomaclafungin A, proving that these two compounds have the same configuration.



Scheme 8. Reagents and conditions: a) $Pd(PPh_3)_4$, Ag_2O, THF-H_2O, rt, 12 h, 77%; b) K_2CO_3, 18-crown-6, toluene, rt, 48 h, 38%; c) (i) 65% AcOH, rt, 4 h, (ii) 80% AcOH, 80 °C, 30 min, 10% from **48**.

In summary, the first synthesis of neomaclafungin A was completed. The relative and absolute configurations for neomaclafungins, which previously were impossible to assign due to lack of exploitable ^{1}H-^{1}H couplings/nOe's between the two major fragments, were eventually established. The results also provided direct configuration reference for other neomaclafungins and maclafungin and offered valuable opportunities to observe the interesting reactivity differences caused by the relative configurations (e. g., between **45** and **47**, also **46** and **48**). The regioselectivity of the opening of epoxides **30** and **32**, the reverted stereoselectivity of addition of **15** to **21**, the various problems caused by a substituent larger than methyl group at the C-24 (compared with oligomycins) and the tricky hydrolysis of the acetonides in **46** and **48** are also noteworthy.

Acknowledgments: Prof. Ang Li (SIOC) and Prof. Zhujun Yao/Dr. Xiaoliang Yang (Nanjing University) are thanked for access to HPLC facility and recording the NMR of **49**, respectively. This work was supported by the NSFC (21372248, 21532002, 21672244) and the Strategic Priority Research Program of the Chinese Academy of Sciences (XDB20020200).

Keywords: Configuration• macrolides • condensation• total synthesis •Natural products

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[13] Addition of the Grignard reagent of **16** to **20** failed.

[14] a) D. A. Evans, B. D. Allison, M. G. Yang, C. E. Masse, *J. Am. Chem. Soc*. **2001**, *123*, 10840-10852; b) The yield for **22** was 20% in the absence of *n*$Bu_4NSiPh_3F_2$ (which has never been reported for this reaction before); c) It is noteworthy that the -$(CH_2)_3$OPMB at the C-24 instead of a Me as in the Evans' case reverted the stereoselectivity. The spiroketal formation was also retarded by the C-24 -$(CH_2)_3$OPMB (compared with the facile synth. of the spiroketal in oligomycins).

[15] Use of $F_3B{\cdot}Et_2O$ to replace $EtAlCl_2$ led to a 1:1 mixture of C-25 epimers in 40% yield. Under the Yamamoto's conditions (see, K. Ishihara, M. Mouri, Q. Gao, T. Maruyama, K. Furuta, H. Yamamoto, *J. Am. Chem. Soc*. **1993**, *115*, 11490-11495), neither **22** nor *epi*-**22** was detected.

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[34] Use of **4'** in Suzuki coupling with **5** led to <10% yields and removal of PMB at a later stage was unfeasible. We are not aware of any precedents involving substrates with an aliphatic aldehyde group.

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[36] Use of PPTS/MeOH-H_2O/rt resulted in a side product (with one less C-C double bond and an extra THP ring). $HS(CH_2)_3SH$/*p*-TsOH/$CHCl_3$ or 60% aq. AcOH/rt gave a mixture (one acetonide remained). 80% aq AcOH/80 °C/30 min led to a side product (same as that obtained with PPTS) but no **1a**. Using the two-stage hydrolysis prevented the formation of the undesired THP ring. Storage of **1a** in $CDCl_3$ at rt for more than 24 h led to significant deterioration.

[37] Either no reaction occurred or a complex mixture was resulted.

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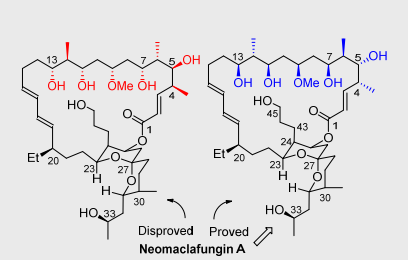
Layout 1:

COMMUNICATION

Although the relative configurations of the upper and lower fragments of neomaclafungin A were assigned, establishment of the configuration for the whole molecule remained impossible because of the lack of exploitable ^{1}H-^{1}H couplings between the two fragments. Now the problem is solved by an enantioselective total synthesis. Some interesting relative configuration dependent reactivity differences were also observed en route to the total synthesis…



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