Natural Products Synthesis

Total Synthesis of Antascomicin B**

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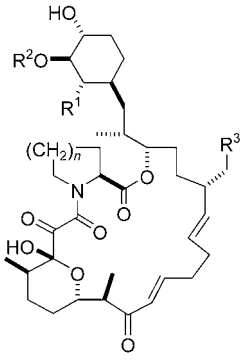
In 1996, a search for novel materials that might elicit similar biological effects to rapamycin and FK506 was initiated at Sandoz.[1] The immunophilin FKBP12 (the primary target for rapamycin and FK506) was used and the degree of binding to substrates in competition with FK506 was measured to evaluate metabolites from over 12000 strains of *Actinomycetes*. Alongside the known immunophilin-binding compounds rapamycin, ascomycin,[2] and meridamycin,[3] the novel antascomicin family was discovered.

It was found that, despite the strong levels of binding to FKBP12 of all these compounds, only rapamycin and ascomycin show immunosuppressive properties in vitro and in vivo, whereas meridamycin and the antascomicins show none.[1,3] Specifically, the antascomicins bind FKBP12 to the same degree as do FK506 and rapamycin (1.1 and 0.6 nM, respectively, in the same binding assay) and antagonize both immunosuppressants. It has been demonstrated by Schreiber and co-workers that it is the fate of the ligand–FKBP12 complex, rather than solely ligand binding to FKBP12, that determines the immunosuppressive effect.[4,5] Subsequently, the significantly higher levels of FKBP12 found in the brain, rather than in the immune system,[6] stimulated work on the effects of rapamycin and FK506 complexes with FKBP12 in the treatment of neurodegenerative diseases.[7] However, the immunosuppressive effects of these complexes became a liability,[8] thus pushing nonimmunosuppressive FKBP ligands to the fore. Further results demonstrated the ability of synthetic FKBP ligands to promote not only regrowth of damaged nerves in the peripheral nervous system, but also the regeneration of damaged neurons in the central nervous system.[9]



Antascomicin	R^1	R^2	R^3	n	FKBP12 binding IC_{50} (nM)
A	H	H	H	2	2.0
B	OH	H	H	2	0.7
C	OH	Me	H	2	1.0
D	H	H	H	1	5.2
E	H	H	OH	2	0.7

The wealth of biological and chemical attention attracted by other FKBP12 ligands prompted us to initiate a program aimed at the total synthesis of antascomicin B, as it combined both structural complexity and the most potent FKBP12 binding ability. Antascomicin B is an enticing target for the synthetic organic chemist as it has a complex polyketide structure that includes both lactol and lactam functionalities, 12 stereogenic centers, and a masked 1,2,3-tricarbonyl unit. A recent synthetic study described the stereoselective synthesis of the C18–C34 fragment of antascomicin A;[10] however, no total synthesis of any member of the antascomicin family has been disclosed. Examination of the structure of antascomicin B (**1**) suggested disconnection to three major fragments (Scheme 1).

Construction of the C10–C34 carbon framework was envisaged through the coupling of a C24 anion (via an intermediate sulfone on fragment **III**) with the epoxide functionality at C25 in fragment **II**, followed by esterification with pipecolic acid fragment **I**. The installation of all but two of the carbon atoms present in the natural product would then set the stage for the key macrocyclization and tricarbonyl-generation steps. Enone formation (C16) and deprotection would then be all that was required to complete the synthesis.

Fragment **II** could be constructed by a ring-closing metathesis of diene **2**, which could be derived by addition of the allyl stannane **4** to a butanediacetal-protected aldehyde **3** (Scheme 2).

By utilizing work developed in our group on the use of desymmetrized butanediacetal-protected tartrates as building blocks for *anti*-1,2-diols,[11–13] diacetal **6** was easily prepared from dimethyl D-tartrate **5** in large quantities and converted into protected aldehyde **3** via protected tetrol **7** (Scheme 3). It

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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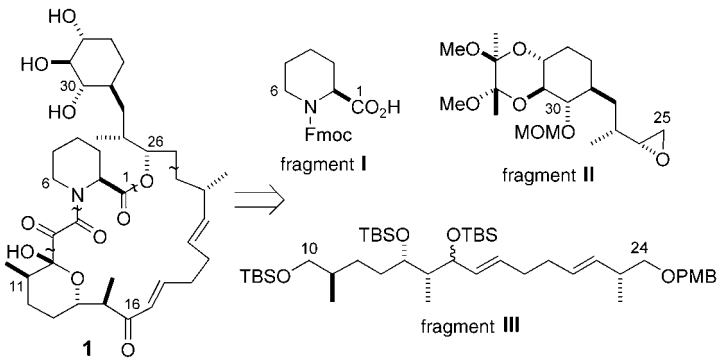
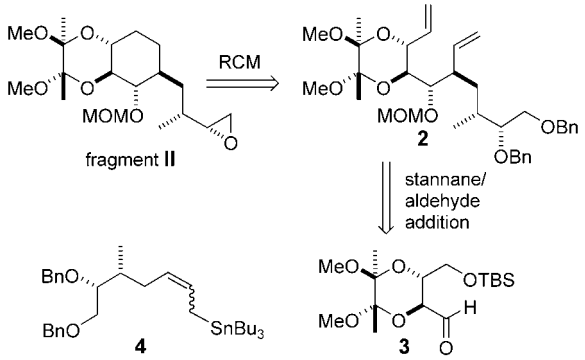
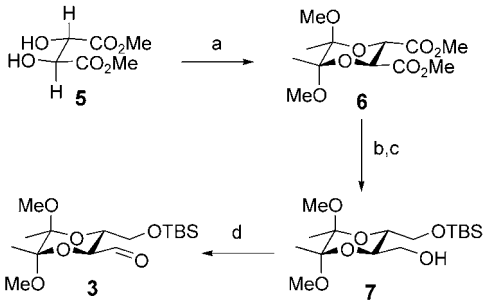


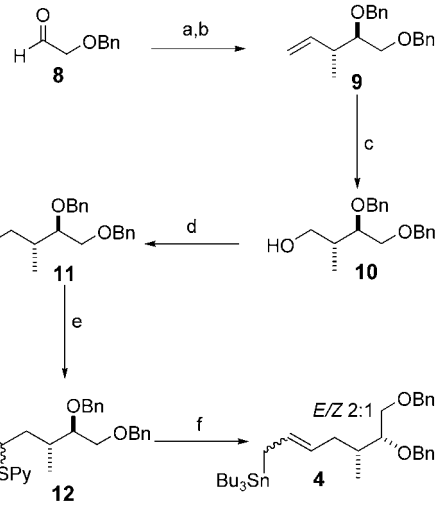
Scheme 1. Disconnection of antascomicin B. Fmoc = 9-fluorenylmethyloxycarbonyl; MOM = methoxymethyl; TBS = *tert*-butyldimethylsilyl; PMB = *p*-methoxybenzyl.



Scheme 2. Retrosynthetic analysis of fragment **II**. Bn = benzyl.



Scheme 3. Reagents and conditions: a) MeCOCOMe, CSA, $CH(OMe)_3$, MeOH, 68%; b) $LiAlH_4$, THF, 99%; c) NaH, TBSCl, 87%; d) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N. CSA = (+/−)-camphorsulfonic acid; DMSO = dimethyl sulfoxide.



Scheme 4. Reagents and conditions: a) 1. (*E*)-Butene, KO*t*Bu, *n*-BuLi, THF, −78 °C; 2. (+)-$(Ipc)_2BOMe$, Et_2O, $BF_3{\cdot}OEt_2$, aldehyde, −78 °C; b) BnBr, NaH, DMF, 62% over two steps; c) 1. O_3, CH_2Cl_2, −78 °C; then PPh_3, 2. $NaBH_4$, MeOH, 90% over two steps; d) I_2, PPh_3, imidazole, CH_2Cl_2, 90%; e) allylpyridylsulfide, *t*BuLi, THF, −78 °C, 95%; f) Bu_3SnLi, CuBr, THF, −78 °C, 98%. Ipc = isopinocampheyl; DMF = *N*,*N*-dimethylformamide.

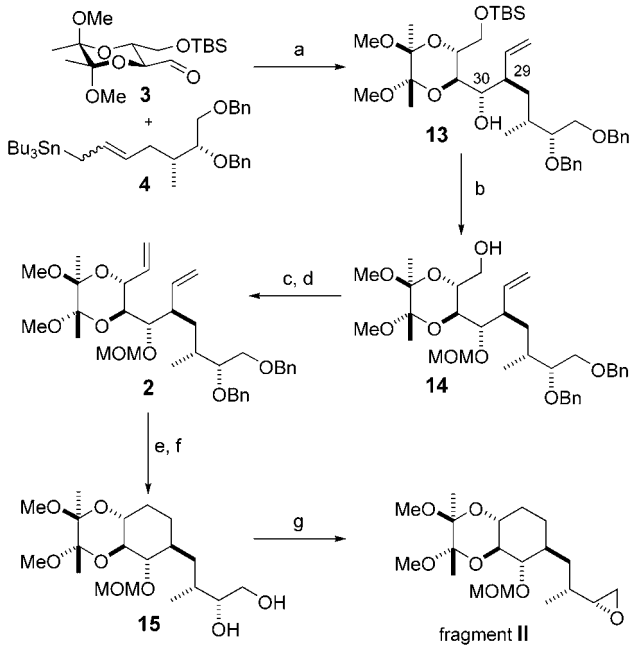
was found that butanediacetal-protected aldehyde **3** was most effective when used crude in subsequent reactions.

After some encouraging results with model studies on the addition of allyl stannanes to aldehyde **3**, work began on the synthesis of the fully substituted allyl stannane **4** (Scheme 4). The two stereogenic centers in allyl stannane **4** were installed through asymmetric crotylation of commercially available benzyloxyacetaldehyde (**8**) to give the secondary alcohol with 97% *ee*, under conditions originally developed by Brown and Bhat.[14] Benzylation to provide alkene **9** and reductive ozonolysis afforded primary alcohol **10**. Owing to the stability of the ozonide to reduction by sodium borohydride, it was necessary to form the aldehyde initially en route to the alcohol. This was achieved with triphenylphosphane, and the transformation remained a one-pot procedure. Subsequent conversion into iodide **11** and displacement by allylpyridylsulfide provided substrate **12**. The allyl stannane functionality was subsequently installed through an anionic cuprate procedure to give stannane **4**.[15]

A variety of conditions were examined for the aldehyde/stannane addition, with the optimum selectivity arising from the use of zinc iodide in CH_2Cl_2 to give **13** with near total diastereoselectivity at C30 and in a 7:1 ratio at C29 in favor of the desired isomer (Scheme 5). It was found that the *E*/*Z* ratio of the stannane had only a minor effect on the diastereoselectivity of the subsequent addition.

Modeling studies and precedent for stannane additions suggest the mechanism and transition state shown in Figure 1.[16,17] It is believed that chelation between the carbonyl group and the axial lone pair of electrons on the α-oxygen atom of the butanediacetal group through the Zn^{2+} permits attack of the stannane to occur onto only one face of the carbonyl group. The allyl stannane attacks in an antiperiplanar orientation, with the vinylic hydrogen substituent being placed over the chelate ring.

Protection of the newly formed hydroxy group as a MOM ether and removal of the TBS protecting group yielded alcohol **14**, which upon completion of a Swern–Wittig protocol, provided access to the ring-closing-metathesis precursor **2**. Portionwise addition of Grubbs second-generation imidazolidine catalyst[18] to the substrate in refluxing toluene enabled the substituted cyclohexene to be formed in 95% yield. Treatment with hydrogen in the presence of palladium on carbon resulted in the reduction of the C33–C34 double bond and the simultaneous removal of both benzyl



Scheme 5. Reagents and conditions: a) ZnI_2, CH_2Cl_2 −78 °C→RT, 85% over two steps, *syn*/*anti* 6:1 at C29–C30; b) 1. MOMCl, DIPEA, CH_2Cl_2; 2. TBAF, THF, 89% over two steps; c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; d) $MePPh_3Br$, BuLi, THF, −78 °C→RT, 87% over two steps; e) 1,3-(bis-(mesityl)-2-imidazolidinylidene) dichloro(phenylmethylene) (tricyclohexylphosphane) ruthenium (3×3.5 mol%), toluene, reflux, 95%; f) H_2, Pd/C, EtOH, 96%; g) NaH, 2-(2,4,6-triisopropylbenzenesulfonyl)-imidazole, THF, 88%. DIPEA = diisopropylethylamine; TBAF = tetrabutylammonium fluoride.

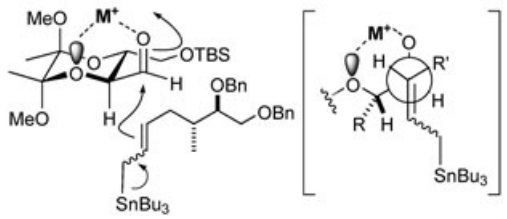


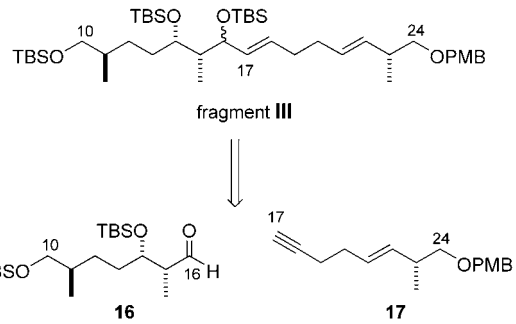
Figure 1. Suggested mechanism and transition state for stannane additions.

groups to give diol **15**, which was transformed in one step to the epoxide, fragment **II** (Scheme 5).

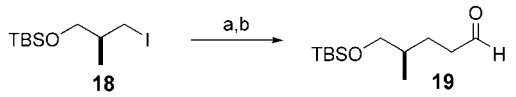
The synthesis of fragment **III** centered on the construction of aldehyde **16** and alkyne **17** and on their coupling through a hydrozirconation protocol to create the C10–C24 allylic alcohol (Scheme 6).

Synthesis of the C10–C16 aldehyde **16** started from iodide **18**, which is available in two steps from commercially available (*2S*)-3-bromo-2-methylpropan-1-ol by silylation and halide exchange. Displacement with allylmagnesium chloride in the presence of copper iodide gave the terminal olefin-bearing compound that underwent ozonolysis with reductive workup to afford the aldehyde **19** in an overall yield of 79% for the two steps (Scheme 7).

The C14–C15 stereogenic centers were introduced through an asymmetric aldol reaction by using the Evans

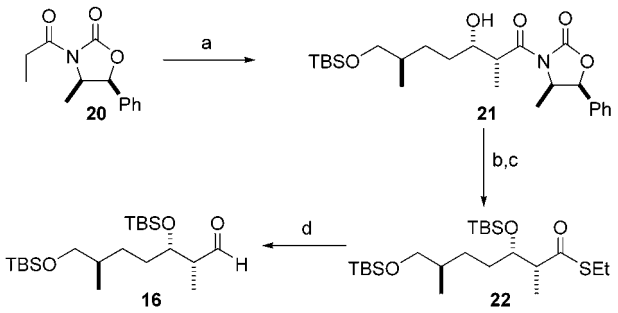


Scheme 6. Retrosynthetic analysis of fragment **III**.



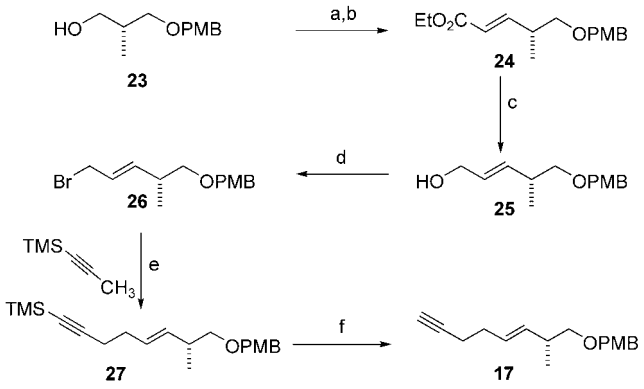
Scheme 7. Reagents and conditions: a) AllylMgCl, CuI, THF, 90%; b) O_3, CH_2Cl_2, −78 °C; then PPh_3, 88%.

chiral auxiliary.[19] Addition of the boron enolate of oxazolidinone **20** to aldehyde **19** gave aldol adduct **21** in high yield as a single diastereoisomer after recrystallization. Protection of the C14 hydroxy group as a silyl ether, and removal of the auxiliary via thioester **22**[20,21] gave the desired aldehyde **16** (Scheme 8).



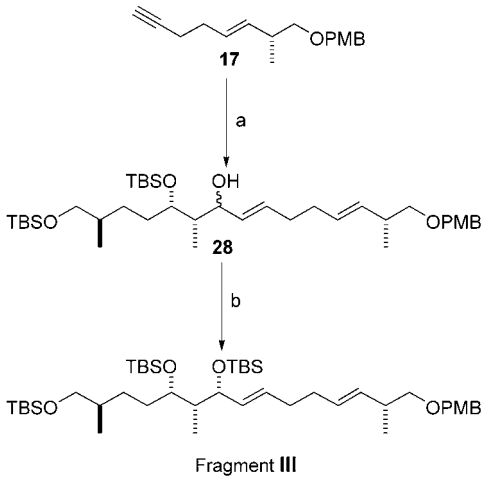
Scheme 8. Reagents and conditions: a) Bu_2BOTf, Et_3N, CH_2Cl_2, **19**, −80 °C, 60 h; then pH 7.2 phosphate-buffered MeOH, H_2O_2, 94% (single isomer); b) TBSCl, imidazole, DMF, 100%; c) EtSH, BuLi, THF, −78 °C, 99%; d) Et_3SiH, Pd/C, acetone, 99%. Tf = trifluoromethanesulfonyl.

The synthesis of alkyne **17** started from primary alcohol **23**, which is available in four steps from Roche ester ((*S*)-3-hydroxy-2-methylpropionic acid methyl ester). Swern oxidation followed by Wittig reaction was used to establish the C21–C22 *trans* olefin **24** with exceptionally high selectivity (Scheme 9). Reduction with DIBAL-H to alcohol **25** and conversion into bromide **26** enabled introduction of the alkyne functionality in its TMS-protected form to give protected alkyne **27** in 88% yield. A minor allene side product (8%), which arises from S_E2' attack of the TMS-propargyl organolithium reagent, was also isolated. Desilylation under basic conditions completed the synthesis of alkyne **17** in this high-yielding series of steps.



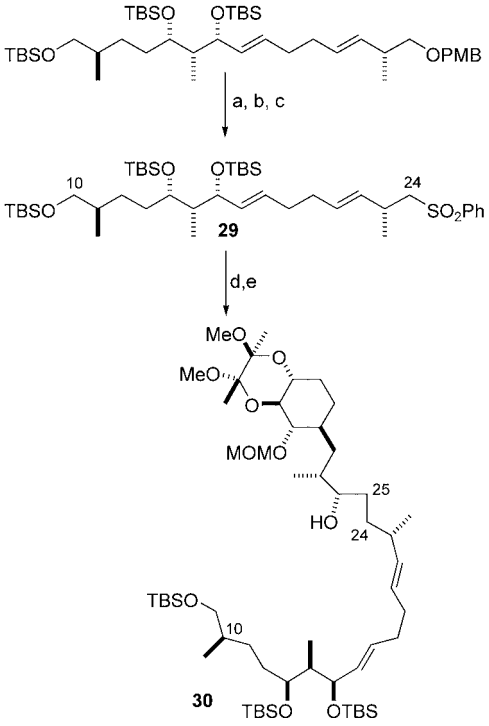
Scheme 9. Reagents and conditions: a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 95%; b) Ph_3PCHCO_2Et, CH_2Cl_2, 0°C→RT, 2 days, 98%, *E*/*Z* 99:1; c) DIBAL-H, PhMe, −78°C, 1.5 h, 93%; d) Ph_3P, CBr_4, CH_2Cl_2, 95%; e) BuLi, THF, −78°C, 1 h, 88%; f) aqueous NaOH (10%), 2 days, 99%. DIBAL-H = diisobutylaluminum hydride.

Cis-specific hydrozirconation of alkyne **17** with freshly prepared Schwartz reagent[22] afforded a vinylzirconium species[23] that underwent silver perchlorate mediated addition to aldehyde **16** in 96% yield.[24,25] The resultant secondary alcohol **28** was formed as a 1:1 mixture of separable diastereoisomers; the stereoselectivity is unimportant at this stage as the alcohol functionality at C16 is ultimately oxidized. After separation (for analytical convenience), silylation of the secondary alcohol completed the synthesis of fragment **III** (Scheme 10).



Scheme 10. Reagents and conditions: a) 1. $[Zr(Cp)_2(H)(Cl)]$, CH_2Cl_2, −78→0°C; 2. **16**, $AgClO_4$, CH_2Cl_2, 96%, (1:1 mixture, separable); b) 1. separation; 2. TBSCl, imidazole, DMF, 93%.

To couple with fragment **II**, the 16*R* diastereoisomer of fragment **III** was converted into the C24 sulfone (Scheme 11). Oxidative removal of the PMB protecting group and direct conversion into the sulfide was followed by selective oxidation of the sulfur function by using diphenyldiselenide and hydrogen peroxide to give sulfone **29**.[26] Addition of the α-lithiated sulfone to fragment **II** was then carried out in THF and HMPA to give two diastereoisomeric γ-hydroxysulfones,

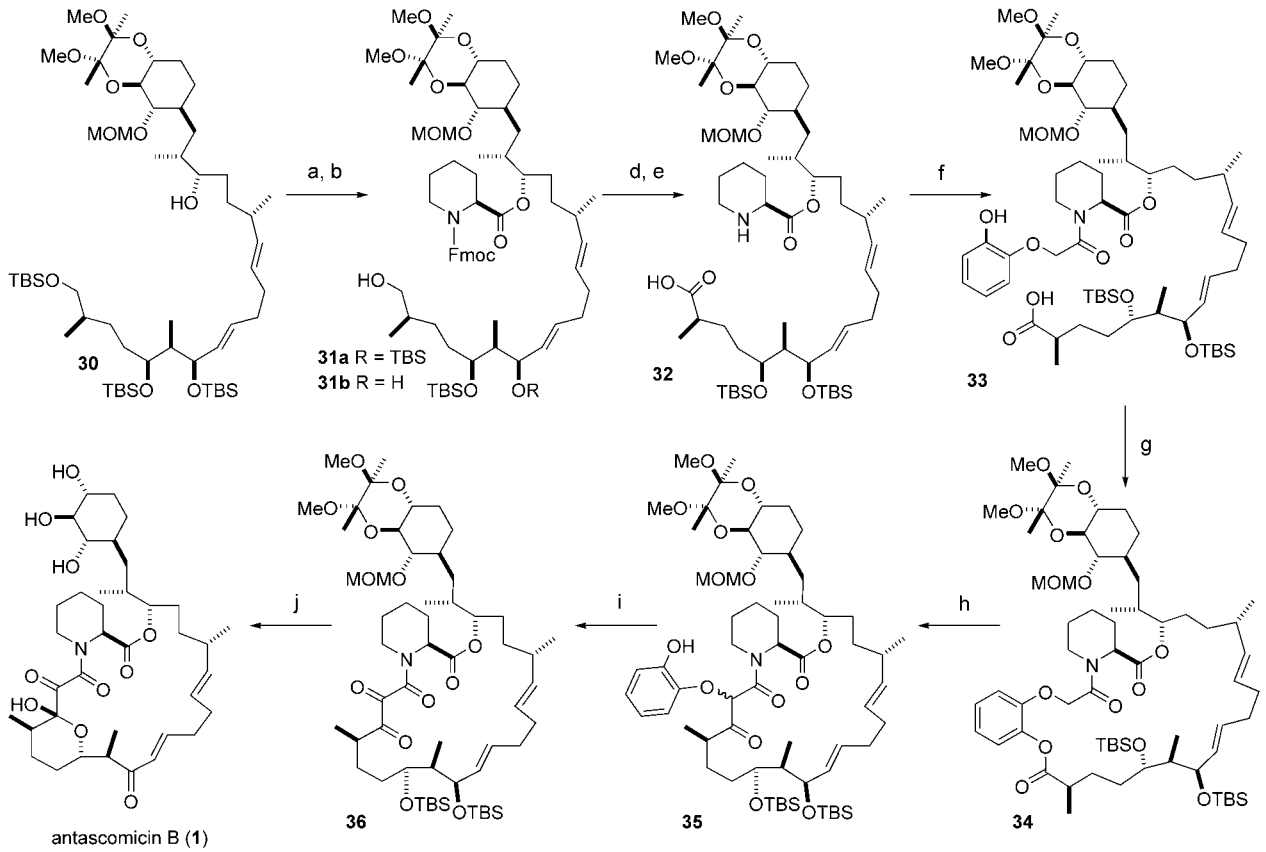


Scheme 11. Reagents and conditions: a) DDQ, CH_2Cl_2, H_2O; b) PhSSPh, PBu_3, py, 95% over two steps; c) PhSeSePh, H_2O_2, Et_2O, 88%; d) BuLi, HMPA, THF, −78°C; then fragment **II** at −20°C, 70%; e) lithium 4,4-di-*tert*-butylbiphenyl, THF, −78°C, 78%. DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone; HMPA = hexamethylphosphoramide.

epimeric at C24, which were reductively desulfonylated with excess lithium in the presence of 1.5 equivalents of 4,4-di-*tert*-butylbiphenyl to give alcohol **30**.[27–29] This was subsequently esterified with *N*-Fmoc-protected pipecolic acid, fragment **I**, and the primary TBS group was removed by using camphorsulfonic acid in methanol to give late-stage intermediate **31a** (Scheme 12).

As this desilylation was not completely selective, a small proportion (25%) of bisdeprotected product **31b** was also formed. This was easily recycled by protection with TBSCl to regenerate the fully protected triol **30**. The C10-OH group was oxidized to carboxylic acid through a two-step TPAP[30]–Pinnick protocol[31] in 76% yield over two steps.

Despite employing a disconnection across the C9–C10 carbon–carbon bond, it was envisaged that macrocyclization could be effected by exploiting the relative ease of carbon–heteroatom bond formation and the entropic advantage of using a tether. With this in mind, the Fmoc group on the pipecolic acid moiety was removed to afford the free amine **32**, which was treated with benzo[1,4]dioxin-2-one to form amide **33** with the first carbon–heteroatom bond. High-dilution macrolactonization (0.001M) with EDCI then formed the second carbon–heteroatom bond to generate catechol-tethered macrocycle **34**. Treatment with LHMDS in THF led to the formation of the required C9–C10 bond, presumably through a kinetic C9 deprotonation followed by a transannular Dieckmann-type condensation onto the C10 ester to give macrocycle **35**. The effectiveness of this transformation



Scheme 12. Reagents and conditions: a) EDCI, DMAP, CH_2Cl_2, fragment **I**, −5 °C, 95%; b) CSA, MeOH, CH_2Cl_2, −15 °C 62%; c) TBSCl, imidazole, DMF, 98%; d) 1. TPAP, NMO, CH_2Cl_2, 2. $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, *t*BuOH, 76% over two steps; e) piperidine, DMF; f) benzo-[1,4]dioxin-2-one, DMAP, CH_2Cl_2, 87% over two steps; g) EDCI, CH_2Cl_2, 71%; h) LHMDS, THF, 68%; i) DMP, H_2O, CH_2Cl_2, py, 80%; j) 1. HF·py, py, THF, 4 days; 2. DMP, CH_2Cl_2, py; 3. TFA, H_2O, 10 min, 13% over three steps. EDCI = 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride; DMAP = 4-dimethylaminopyridine, TPAP = tetra-*n*-propylammonium perruthenate; NMO = *N*-methylmorpholine *N*-oxide; LHMDS = lithium hexamethyldisilazide; DMP = Dess–Martin periodinane; TFA = trifluoroacetic acid.

lies in the simplified requirements of its six-membered transition state. Oxidation[32,33] with the Dess–Martin reagent[34] in the presence of water[35] cleaved the catechol tether and directly furnished the desired tricarbonyl **36**, which contains the complete carbon framework of antascomicin B (**1**). Medium-ring ketones have been synthesized by the Ohtsuka group in a related approach by using lactam sulfoxides followed by a reductive tether cleavage;[36–38] this method has been applied to the preparation of a taxane skeleton.[39]

Removal of the TBS protecting groups at C16 and C14 with pyridine-buffered HF·pyridine complex was slow but effective and led to the spontaneous formation of the six-membered C10 lactol. The C16 allylic alcohol was then oxidized under Dess–Martin conditions to generate the corresponding α,β-unsaturated carbonyl compound. Simultaneous deprotection of the MOM and butane diacetal groups under acidic conditions afforded the natural product, which was demonstrated to be identical to an authentic sample.[40,41–48]

The challenge posed by the total synthesis of antascomicin B has been met through the combination of established synthetic procedures and our research group methods, including the use of butanediacetal as both a protecting and a stereodirecting functionality, and the development of novel transformations including a transannular Dieckmann oxidation protocol to access the vicinal tricarbonyl functionality. Completion of the synthesis in a total of 52 synthetic steps from commercially available starting materials (longest linear sequence: 23 steps) demonstrates the utility of these methods in the synthesis of complex natural products.

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