Natural Product Synthesis

DOI: 10.1002/anie.200802079

The Asymmetric Total Synthesis of (+)-Cytotrienin A, an Ansamycin-Type Anticancer Drug**

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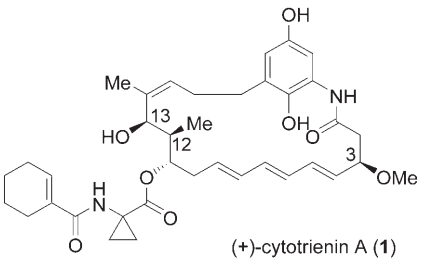
Cytotrienin A (**1**) is a microbial antitumor secondary metabolite that was isolated from the fermentation broth of *Streptomyces sp*. RK95-74 from soil.[1] It possesses an

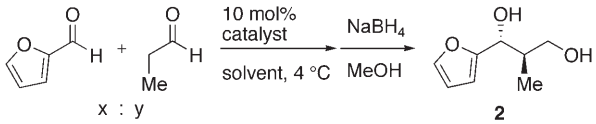


(+)-cytotrienin A (**1**)

E,*E*,*E*-triene motif within a 21-membered cyclic lactam, which also contains four chiral centers. These are common structural features of the ansamycin class of natural products, which include the mycotrienins (or ansatrienins),[2] trienomycins,[2c,3] thiazinotrienomycins,[4] and trierixin.[5] Cytotrienin A, with its unusual aminocyclopropane carboxylic acid side chain, exhibits potent apoptosis-inducing activity on HL-60 cells with an ED_{50} value of 7.7 nM. To facilitate elucidation of its mechanism of action, the development of a method for the total synthesis and derivatization of cytotrienin A is highly desirable. The research groups of Smith and Panek have accomplished the total synthesis of other members of this class of natural products, including trienomycins A and F,[6] mycotrienin A,[7] and thiazinotrienomycin E.[8] Although the macrocyclic core of cytotrienin A has been synthesized in its protected form by Panek et al.[9] and Kirschning et al.,[10] the total synthesis of cytotrienin A, with the side chain attached, has not been reported. The relative and absolute stereochemistry has not been confirmed, but has been assigned based on analogous mycotrienin natural products. Herein we report the first total synthesis of the naturally occurring enantiomer of cytotrienin A, which confirms its relative and absolute stereochemistry.

We envisioned installing the side chain midway through the synthesis and constructing the triene unit at a late stage by ring-closing metathesis (RCM).[11] We reasoned that introduction of the bulky side chain after formation of the macrocyclic core would be difficult, and also, a long sequence of reactions after the construction of the labile triene unit would be avoided. Other noteworthy features of our approach are the use of novel organocatalyzed and proline-mediated enantioselective reactions, both of which have been developed by our research group.[12] Specifically, we planned to form two (C11 and C12) of the three contiguous chiral centers with an aldol reaction by using an organocatalyst, and to control the configuration at C3 by using proline-mediated α-aminoxylation.

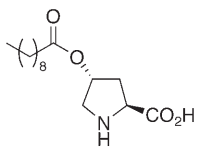
The synthesis started with an organocatalyzed aldol reaction which was found to be problematic. The original procedure[13] which used proline was not practical for large-scale synthesis owing to the excess amount of furfural required (10 equivalents), low yield, and low diastereoselectivity [Eq. (1)]. After some experimentation, diol **2** was obtained in good yield and with good d.e. when the reaction was conducted without solvent using surfactant-proline con-



(1)

proline x/y = 10:1 DMF 32 h 10% *anti/syn* = 1:1

cat. **33** x/y = 1:5 neat 48 h 77% *anti/syn* = 6.2:1, 96% *ee*



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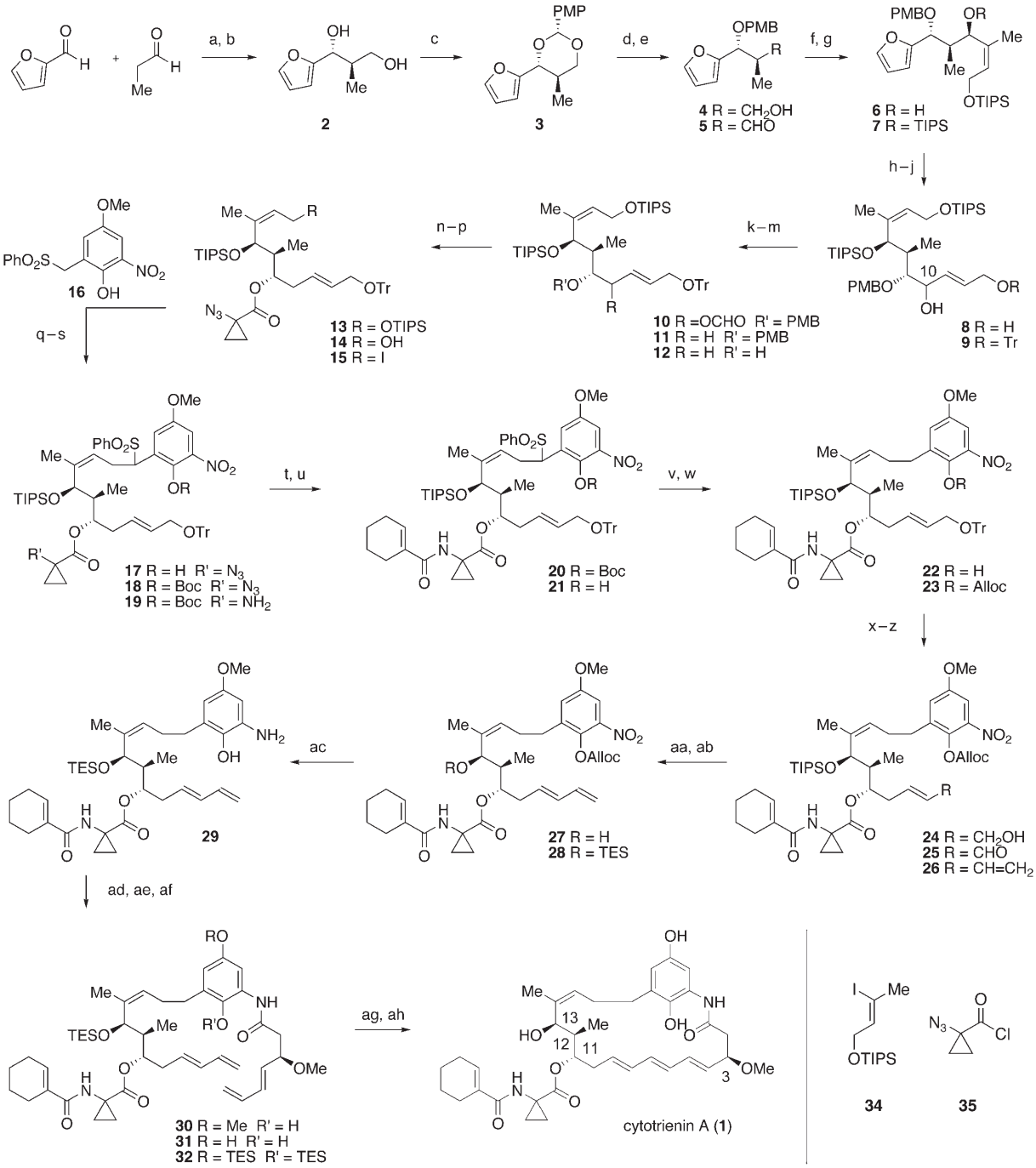
[**] This work was supported by a Grant-in-Aid for Creative Scientific Research from The Ministry of Education, Culture, Sports, Science, and Technology (MEXT).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200802079.



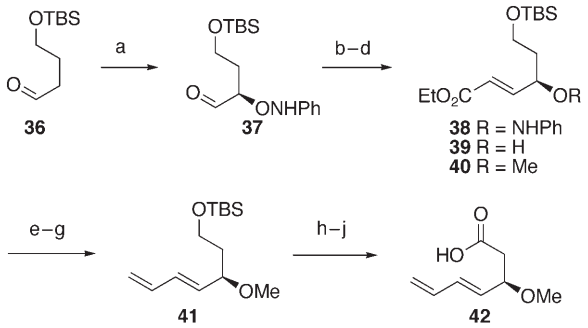
Scheme 1. Reagents and conditions: a) **33**, 4 °C, 48 h; b) $NaBH_4$, MeOH, 0 °C, 1 h (77%, 96% *ee*, *anti*:*syn* 6.2:1); c) *p*-MeOPhCH$(OMe)_2$, PPTS, benzene, 80 °C, 1 h (64%, >99% *ee* after recrystallization); d) DIBAL-H, Et_2O, −78 °C to −10 °C, 128 h [80% (92% brsm)]; e) SO_3·py, DMSO, Et_3N, CH_2Cl_2, 0 °C, 45 min (quant.); f) **34**, *t*BuLi, THF, −78 °C, 1 h; Me_2Zn, 0 °C, 20 min; then **5** at −78 °C; −35 °C, 3 h (79%); g) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 23 h (99%); h) O_2, Rose Bengal, EtCN, *hν*, −78 °C, 8 h; Me_2S, −20 °C, 15 h; DABCO, −20 °C, 2 h; i) $NaBH_4$, $CeCl_3·7H_2O$, EtOH, 0 °C, 20 min (81% from **7**); j) TrCl, Et_3N, CH_2Cl_2, 23 °C, 3 h (93%); k) 1*H*-benzotriazole-1-carbaldehyde, DMAP, CH_2Cl_2, 23 °C, 4 h (quant.); l) $[Pd_2(dba)_3]·CHCl_3$, nBu_3P, HCO_2NH_4, 1,4-dioxane, 23 °C, 67 h (76%); m) DDQ, CH_2Cl_2/pH 7 phosphate buffer, 0 °C, 4 h (96%); n) **35**, DMAP, Et_3N, 0 °C, 20 min (98%); o) py$(HF)_x$, THF, 23 °C, 17 h (84%); p) I_2, Ph_3P, imidazole, benzene, 23 °C, 30 min; q) **16**, LHMDS, THF, −90 °C, 40 min; then **15** at −90 °C; −65 °C, 18 h (78% from **14**); r) $(Boc)_2O$, DMAP, CH_2Cl_2, 23 °C, 30 min (96%); s) 1,3-propanedithiol, Et_3N, MeOH, 23 °C, 18 h (87%); t) 1-cyclohexenecarboxylic acid, EDCI, DMAP, CH_2Cl_2, 23 °C, 21 h (78%); u) pyrrolidine, CH_2Cl_2, 23 °C, 5 h; v) $NaBH_4$, EtOH, 50 °C, 21 h (57% from **20**); w) AllocCl, Et_3N, CH_2Cl_2, 23 °C, 40 min; x) TsOH·H_2O, MeOH, 23 °C, 1 h (94% from **22**); y) MnO_2, CH_2Cl_2, 23 °C, 40 min; z) $[Ph_3P^+CH_3]I^-$, *t*BuOK, THF, 0 °C, 30 min (74% from **24**); aa) 46% HF, MeCN, 23 °C, 16 h [68% (91% brsm)]; ab) TESOTf, *i*Pr_2EtN, CH_2Cl_2, 23 °C, 30 min (99%); ac) $NaBH_4$, S_8, THF, 50 °C, 2.5 h; ad) **42**, BOP-Cl, *i*Pr_2EtN, toluene, 23 °C, 8 h; K_2CO_3, MeOH, 23 °C, 10 min (79% from **28**); ae) MnO_2, CH_2Cl_2, 23 °C, 5 min; $NaBH_4$, MeOH, 0 °C; af) 4-triethylsiloxy-3-penten-2-one, DMF, 23 °C to 50 °C, 9 h (77% from **30**); ag) Grubbs I catalyst (40 mol%), CH_2Cl_2, 23 °C, 71 h [39% (51% brsm)]; ah) Amberlyst 15, THF/H_2O (10:1), 23 °C, 47 h (95%). Definitions of acronyms given in reference [28].

jugated catalyst **33**.[14] This catalyst was developed by us for aldol reactions in the presence of water. As this reaction proceeds without solvent, scale-up and purification are straightforward. Diol **2** was treated with *p*-anisaldehyde dimethyl acetal in the presence of PPTS to provide **3**, which was isolated in diastereomerically and optically pure form (>99% *ee*) after recrystallization (and without the need for column chromatography; Scheme 1).

Reduction of **3** with DIBAL-H gave primary alcohol **4** in 80% yield (92% yield based on recovered starting material (brsm)). Alcohol **4** was oxidized to aldehyde **5** quantitatively. The reaction of **5** with vinyl zincate,[15] prepared from vinyl iodide **34** with *t*BuLi and Me_2Zn, proceeded in a highly diastereoselective manner to afford **6** as a single isomer in 79% yield. Notably, other vinyl metals gave low diastereoselectivities.[16] The secondary hydroxy group of **6** was protected with the TIPS group. The furan ring was cleaved by oxidation with O_2 under irradiation conditions in the presence of Rose Bengal.[17] Subsequent *cis*/*trans* isomerization using DABCO, followed by Luche reduction[18] gave diol **8** as a mixture of diastereomers at C10 in 81% yield (over 3 steps). The primary hydroxy group of **8** was protected as the trityl ether. The free hydroxy group of **9** was converted into formate ester **10**, which was removed by reduction using a palladium–PBu_3 complex with the protocol developed by Tsuji and co-workers [19] to provide **11** as a single isomer without positional or *E*/*Z* isomerization. Removal of the PMB group followed by reaction with acid chloride **35**[20] gave ester **13**. Selective removal of the TIPS group gave primary alcohol **14**, which was transformed into iodide **15** with PPh_3 and I_2. Coupling of fragment **15** and sulfone **16** was successfully performed by the lithiation of hydroxysulfone **16** with LHMDS, followed by alkylation using **15** to afford **17** in 78% yield (over 2 steps). After protection of the phenol of **17** as its Boc derivative, the azide moiety was reduced to an amine with 1,3-propanedithiol,[21] and the amide bond with cyclohexenyl carboxylic acid was constructed to provide **20** in good yield. This completed installation of the side chain.

Carrying out desulfonylation without affecting the nitro group was difficult. After experimentation, a novel method was developed which consisted of removal of the Boc group with pyrrolidine[22] followed by treatment of phenol **21** with $NaBH_4$. This method provided **22** in 57% yield (over 2 steps) through a retro-Michael reaction with SO_2Ph, probably involving *o*-quinonemethide, followed by reduction with $NaBH_4$. The phenol was protected as its Alloc derivative and removal of the Tr group gave alcohol **24** in 94% yield (over 2 steps). Oxidation of **24** with MnO_2, followed by a Wittig reaction gave diene **26** in 74% yield (over 2 steps). As we could not remove the TIPS group after construction of the triene moiety, this protecting group was replaced with the easily removable TES group at this stage. Treatment with HF provided **27** in 91% yield (brsm), then reaction with TESOTf afforded **28** quantitatively. The nitro group was reduced with $NaBH_2S_3$[23] and was accompanied by removal the Alloc group to provide **29**. The amine **29** was treated with carboxylic acid **42** (vide infra) in the presence of BOP-Cl to afford **30** in 79% yield (over 2 steps).

Carboxylic acid **42** was synthesized as shown in Scheme 2. Proline-mediated α-aminoxylation[24] of aldehyde **36** proceeded efficiently to provide **37**. Under Horner–Emmons reaction conditions, a crude sample of **37** was converted into



Scheme 2. Reagents and conditions: a) nitrosobenzene, L-proline, MeCN, −20°C, 24 h; b) triethyl phosphonoacetate, NaH, THF, 23°C, 45 min; c) $CuSO_4$, MeOH, 0°C, 46 h (46% from **36**, 98% *ee*); d) MeI, NaH, DMF, 0°C, 1 h (94%); e) DIBAL-H, CH_2Cl_2, −78°C to −40°C, 2 h; f) MnO_2, CH_2Cl_2, 23°C, 2 h; g) $[Ph_3P^+CH_3]I^-$, *t*BuOK, THF, 0°C, 15 min (66% from **40**); h) py(HF)$_x$, MeCN, 0°C, 1.5 h; i) SO_3·py, DMSO, Et_3N, CH_2Cl_2, 0°C, 50 min; j) $NaClO_2$, NaH_2PO_4·$2H_2O$, 2-methyl-2-butene, *t*BuOH/H_2O (3:1), 23°C, 1 h (56% from **41**).

alcohol **39** by treatment with $CuSO_4$ in MeOH giving 46% yield (over 3 steps) with 98% *ee*. Williamson ether synthesis gave **40** in 94% yield. Diene **41** was synthesized by a three-step procedure: reduction with DIBAL-H, oxidation with MnO_2, and a Wittig reaction ($Ph_3P{=}CH_2$). Carboxylic acid **42** was constructed by removal of the TBS group, oxidation with SO_3·pyridine,[25] and subsequent oxidation by the method of Pinnick and co-workers.[26]

All that remained to complete the synthesis was the crucial ring formation. The protecting group of the phenol was converted from methyl to the more easily removable TES group through an oxidation/reduction sequence: 1) oxidation to the quinone with MnO_2, 2) reduction to hydroquinone **31** with $NaBH_4$, 3) immediate protection of **31** with 4-triethylsiloxy-3-penten-2-one[27] (this was the best silylating reagent in this particular case as low yields were obtained with other reagents because of the facile oxidation of hydroquinone **31** to quinone by adventitious O_2). Next RCM methodology, which had been used by Panek and co-workers in the synthesis of the core lactam of cytotrienin, was employed.[9] This reaction proceeded slowly when catalyzed by the first-generation Grubbs catalyst to afford triene in 39% yield along with recovered starting material **32** (23%), and therefore, a good conversion (51% brsm) was obtained. Removal of the TES group with Amberlyst 15 gave (+)-cytotrienin A (**1**) in 95% yield. Synthetic cytotrienin A exhibited spectroscopic properties identical to those of the natural product[1] (^{1}H NMR and IR spectroscopy, R_f value, optical rotation, and HPLC analysis) which confirms the absolute stereochemistry.

In summary, the first asymmetric total synthesis of (+)-cytotrienin A has been achieved, and its absolute configuration has been confirmed. There are several noteworthy features to this total synthesis: a practical diastereo- and

enantioselective aldol reaction using novel catalyst **33** under solvent-free conditions, highly diastereoselective construction of the three contiguous chiral centers, a deoxygenation reaction without positional or *E*/*Z* isomerization (from **10** to **11**), desulfonylation using $NaBH_4$ (from **21** to **22**), control of the absolute configuration at C3 by proline-mediated α-aminoxylation, and RCM for the formation of the 21-membered macrolactam.

Received: May 2, 2008
Published online: July 21, 2008

Keywords: aldol reaction · asymmetric synthesis · organocatalysis · ring-closing metathesis · total synthesis

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[28] Alloc = allyloxycarbonyl, Boc = *tert*-butyloxycarbonyl, BOP-Cl = bis(2-oxo-3-oxazolidinyl)phosphinic chloride, DABCO = 1,4-diazabicyclo[2.2.2]octane, dba = *trans*,*trans*-dibenzylideneacetone, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIBAL-H = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, LHMDS = lithium hexamethyldisilazaide, PPTS = pyridinium *p*-toluenesulfonate, py = pyridine, TES = triethylsilyl, Tf = trifluoromethanesulfonyl, TIPS = triisopropylsilyl, Tr = trityl, Ts = 4-toluenesulfonyl.

