

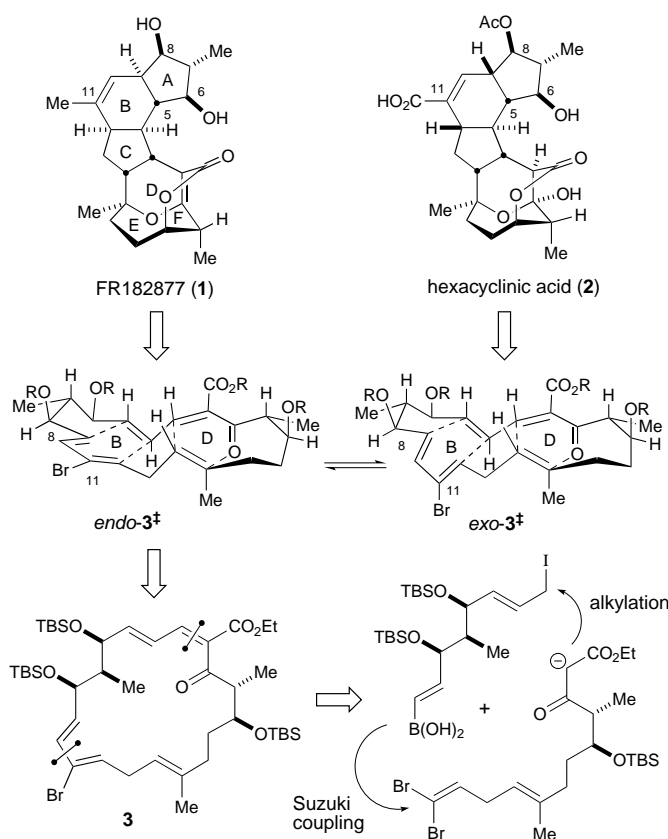


# A Cascade Cycloaddition Strategy Leading to the Total Synthesis of (–)-FR182877\*\*

David A. Evans\* and Jeremy T. Starr

Herein we outline a general strategy for the synthesis of the closely related natural products FR182877 (**1**)<sup>[1]</sup> and hexacyclenic acid (**2**)<sup>[2]</sup> from a common macrocyclic precursor (**3**) by a sequence of transannular [4+2] cycloadditions (Scheme 1).<sup>[3,4]</sup> This approach has been validated by its successful application to the enantioselective synthesis of (–)-FR182877, and provided confirmation of its assigned absolute configuration.

The cytotoxic substance FR182877 (**1**) was isolated from *Streptomyces* sp. No. 9885 in 1998, and at that time was reported as the enantiomer to the illustrated structure (Scheme 1).<sup>[1a]</sup> FR182877 exhibits microtubule stabilizing



Scheme 1. FR182877 and hexacyclenic acid retrosynthesis.

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activity similar to the mode of action of paclitaxel and shows potent cytotoxicity towards multiple tumor cell lines.<sup>[1b, 1c]</sup> The hexacyclic structure includes a bridgehead enol ether and an embedded cyclohexene ring which suggest it originates biosynthetically from a sequence of intramolecular [4+2] cycloaddition events.<sup>[1d]</sup>

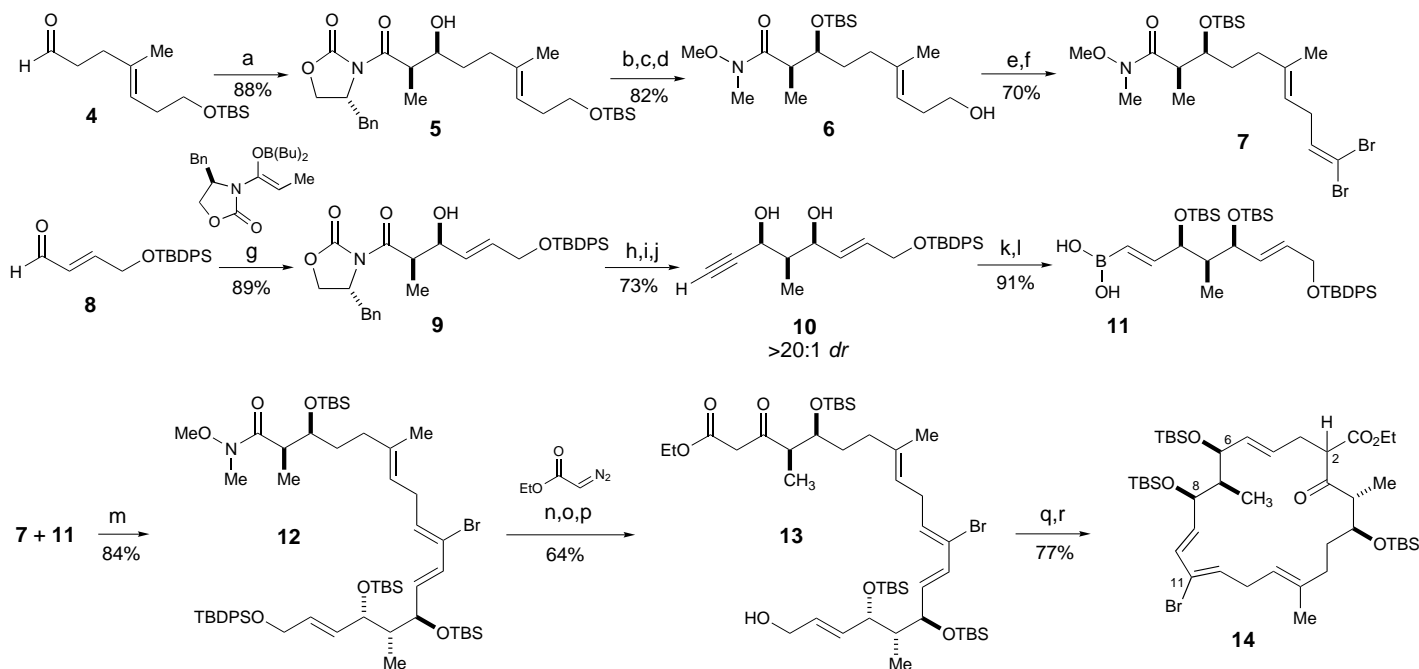
The recently reported hexacyclinic acid (**2**) bears a strong resemblance to **1** and is probably biosynthetically related.<sup>[2]</sup> FR182877 and hexacyclinic acid have common relative and absolute configurations of the C6–C8 substituents as well as of the entire lower DEF ring system. The only important stereochemical difference between **1** and **2** is in the relationships of the ring fusions in the ABC ring system.

The gross structures and relative stereochemistries of **1** and **2** were established by X-ray crystallographic analysis, and the absolute configurations were determined in each case by the Mosher ester method.<sup>[5]</sup> However, on the basis of our own analysis of the reported data for the FR182877 Mosher esters, we suspected its absolute configuration may be opposite to the published assignment and instead be in agreement with the hexacyclinic acid assignment. This suspicion was later confirmed by the recent publication of the structure illustrated in Scheme 1.<sup>[1e]</sup>

The suspected stereochemical relationship between FR182877 and hexacyclinic acid led us to target macrocycle **3** as a precursor common to both natural products. The pivotal transformations associated with both syntheses are the sequential transannular Diels–Alder (TADA)<sup>[3a–c]</sup> and hetero-Diels–Alder<sup>[3d–g]</sup> cycloadditions (Scheme 1). Given the assumption that the transannular Diels–Alder reaction

would be the initiating cycloaddition, the *endo*-**3** transition state should afford the FR182877 skeleton while the diastereomeric *exo*-**3** transition state should afford the hexacyclinic acid ring system. Since we did not know, a priori, the stereochemical outcome of the postulated cyclization events, we designed **3** with a bromine substituent at C11 so that it could serve as a common intermediate for the synthesis of either natural product.

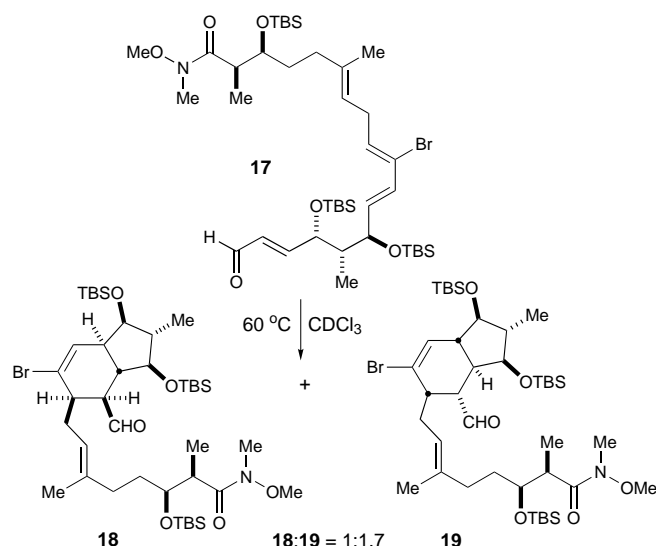
The convergent synthesis of **3** began with the syntheses of two principal fragments **7** and **11** of comparable complexity (Scheme 2). Synthesis of **7** began with an aldol addition of (*R*)-4-benzyl-*N*-propionyl-2-oxazolidinone to **4** mediated by dibutylboron triflate to give *syn* aldol adduct **5** in 88% yield.<sup>[6]</sup> Conversion of **5** into the Weinreb amide (Me<sub>3</sub>Al, MeNH<sub>2</sub>O-MeCl, 96%),<sup>[7]</sup> silylation of the secondary hydroxyl group (TBSCl, 96%), then desilylation of the primary hydroxyl group (1:4 TsOH:*n*Bu<sub>4</sub>NHSO<sub>4</sub>, MeOH, 89%) gave primary alcohol **6**. Oxidation (DMP, 94%)<sup>[8]</sup> and Corey–Fuchs olefination (CBr<sub>4</sub>, PPh<sub>3</sub>, 74%)<sup>[9]</sup> gave the desired vinyl dibromide fragment **7**. The synthesis of **11** began with the same boron-enolate-mediated aldol addition described above to aldehyde **8** to give the expected *syn* aldol adduct **9** in 89% yield. The conversion of **9** into the Weinreb amide (Me<sub>3</sub>Al, MeNH<sub>2</sub>O-MeCl, 97%), was followed by alkynone formation (HCCMgBr, 77%),<sup>[10]</sup> and diastereoselective *syn* reduction by using Kiyooka's method (DIBAL, THF, *dr* > 20:1, 98%),<sup>[11]</sup> to give diol **10**. Double silylation (TBSCl, 94%) was then followed by hydroboration (catecholborane, cat. Cy<sub>2</sub>BH) and saponification (1*N* NaOH, 97%) to give the desired boronic acid fragment **11**.<sup>[12]</sup>



Scheme 2. Reagents and conditions: a) (*R*)-4-benzyl-*N*-propionyl-2-oxazolidinone, Bu<sub>2</sub>BOTf, TEA, 88%; b) MeNHOMe/HCl, Me<sub>3</sub>Al, THF, 96%; c) TBSCl, imid., 96%; d) TsOH:*n*Bu<sub>4</sub>NHSO<sub>4</sub> (1:4), MeOH, 89%; e) DMP, 94%; f) CBr<sub>4</sub>, PPh<sub>3</sub>, 74%; g) (*R*)-4-benzyl-*N*-propionyl-2-oxazolidinone, Bu<sub>2</sub>BOTf, TEA, 89%; h) MeNHOMe/HCl, Me<sub>3</sub>Al, THF, 97%; i) HCCMgBr, THF, 77%; j) DIBAL, THF, *dr* > 20:1, 98%; k) TBSCl, imid., 94%; l) cat. Cy<sub>2</sub>BH, catecholborane then 1*N* NaOH, 97% (crude); m) Pd(PPh<sub>3</sub>)<sub>4</sub>, Ti<sub>2</sub>CO<sub>3</sub>, 84%; n) DIBAL, THF; o) ethyl diazoacetate, cat. SnCl<sub>2</sub>, 70% (2 steps); p) *n*Bu<sub>4</sub>NF, AcOH, 92%; q) I<sub>2</sub>, PPh<sub>3</sub>; r) Cs<sub>2</sub>CO<sub>3</sub>, 77% two diastereomers (1:1); TBS = *tert*-butyldimethylsilyl; Bn = benzyl; TBDPS = *tert*-butyldiphenylsilyl; DIBAL = diisobutylaluminum hydride; TsOH = *p*-toluenesulfonic acid; DMP = Dess–Martin Periodinane; TEA = triethylamine; Tf = trifluoromethanesulfonyl; imid. = imidazole; Cy<sub>2</sub>BH = dicyclohexylborane.

Suzuki coupling of **7** and **11** ( $\text{Ti}_2\text{CO}_3$ ,  $\text{Pd}(\text{PPh}_3)_4$ , 84 %) gave, regioselectively, bromodiene **12**.<sup>[13]</sup> Reduction to the corresponding aldehyde (DIBAL) was followed by a two carbon homologation (ethyl diazoacetate,  $\text{SnCl}_2$ , 70 %, 2 steps)<sup>[14]</sup> and selective removal of the TBDPS group ( $n\text{Bu}_4\text{NF}$  hydrate,  $\text{HOAc}$ , DMF, 92 %) to provide **13**.<sup>[15]</sup> Iodination of **13** ( $\text{I}_2$ ,  $\text{PPh}_3$ ) gave a sensitive allyl iodide that was immediately submitted to macrocyclization conditions ( $\text{Cs}_2\text{CO}_3$ , THF, RT, 77 %, 2 steps) to give **14** as a 1:1 mixture of diastereomers, epimeric at C2.<sup>[16]</sup> It was correctly anticipated that this intermediate, lacking the C2–C3 double bond, would not engage in a transannular Diels–Alder reaction.

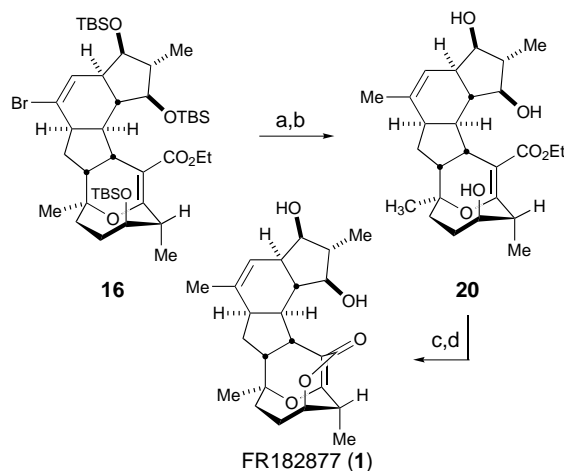
Oxidation of **14** ( $\text{Ph}_2\text{Se}_2\text{O}_3$ , TEA, THF, RT then 50 °C)<sup>[17]</sup> initiated a sequence of transannular cycloadditions (**3** → **15** → **16**) culminating in the formation of **16** as a single diastereomer and the only isolable product (63 % yield; Scheme 3). The macrocyclic conformation of **3** appears to



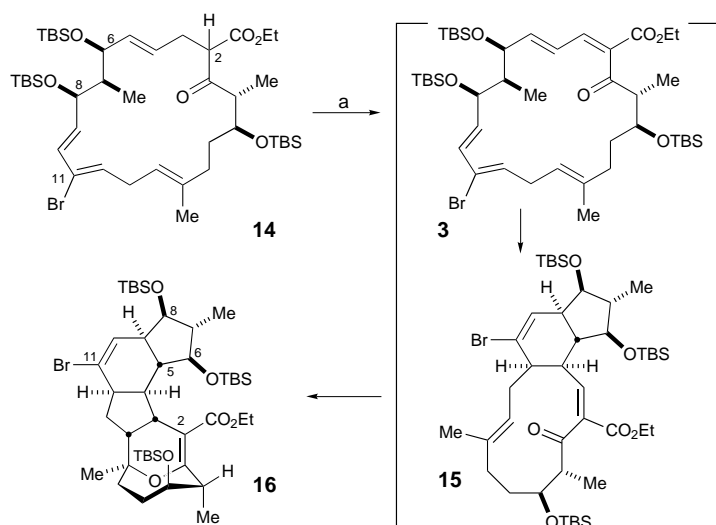
Scheme 4. Open-chain intramolecular Diels–Alder results.

provided qualitative evidence that the substituents at C5 and C9 were *trans* in **16** and corresponded to the ring system of FR182877. This similarity encouraged us to proceed on the premise that a successful synthesis of **1** from **16** would confirm the structure assignment of **16**.

Scheme 5 illustrates the final steps in the synthesis of **1**. Global desilylation of **16** ( $\text{HF}/\text{CH}_3\text{CN}$ , 89 %) was followed by Suzuki methylation by using the recently reported procedure of Gray et al. ( $\text{Me}_3\text{B}_3\text{O}_3$ ,  $[\text{Pd}(\text{dppf})\text{Cl}_2]$ ,  $\text{Cs}_2\text{CO}_3$ , 71 %) to give **20**.<sup>[19]</sup> Saponification of the ethyl ester ( $\text{TMSOK}$ , THF)<sup>[20]</sup> and lactonization (1-methyl-2-chloropyridinium iodide,  $\text{NaHCO}_3$ , 62 %, 2 steps)<sup>[21]</sup> afforded a white solid whose  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra as well as mass spectral characteristics were identical to those published for the natural product.<sup>[22]</sup> In addition, synthetic **1** exhibited an optical rotation of  $[\alpha]_D^{23} = -5^\circ$  while that reported for the natural sample was  $[\alpha]_D^{23} = -3.5^\circ$ . This observation led us to conclude that synthetic **1** was of the same absolute stereochemistry as natural (–)-FR182877, therefore confirming the corrected structure.



Scheme 5. Reagents and conditions: a)  $\text{HF}/\text{CH}_3\text{CN}$  5:95; 89 %; b) trimethylboroxine,  $\text{Cs}_2\text{CO}_3$ ,  $[\text{Pd}(\text{dppf})\text{Cl}_2]$ , DMF, 80 °C, 71 %; c)  $\text{TMSOK}$ , THF; d) Mukaiyama's reagent,  $\text{NaHCO}_3$ , 62 % (2 steps). dppf = 1,1'-bis(diphenylphosphanyl)ferrocene; TMS = trimethylsilyl.



Scheme 3. Reagents and conditions: a)  $\text{Ph}_2\text{Se}_2\text{O}_3$ ,  $\text{SO}_3/\text{pyridine}$ , TEA, THF, RT (2 h) then 50 °C (6 h), 63 %.

predispose the reacting olefin/carbonyl faces to a single orientation, and the resulting high stereoselectivity of the cycloaddition sequence stands in stark contrast to the results obtained by us and Sorensen and co-workers in similar acyclic systems.<sup>[18]</sup> We observed excellent *endo* selectivity in a related acyclic intramolecular Diels–Alder cycloaddition (IMDA) study (Scheme 4), but only 1:1.7 diastereoface selectivity was realized. Sorensen and co-workers observed 1.6:1 diastereoface selectivity in a similar system leading to an analogous pair of *endo* diastereomers.<sup>[18b]</sup>

COSY and NOESY studies established the C5 center of **16** as having the desired configuration relative to the C6–C8 triad, but lacked a suitably diagnostic NOESY crosspeak to assign the C9 and C12 stereocenters unambiguously. Since **1** and **2** have the C5 stereocenter in common, we could only surmise that **16** must correspond to one of the natural product configurations for the ABC system, but the question of which one remained unanswered at this stage. Comparison of the coupling patterns for the C5–C9 protons in the  $^1\text{H}$  NMR spectrum of **16** to the corresponding signals in the  $^1\text{H}$  NMR spectrum of aldehyde **18** obtained in our IMDA study

Efforts are underway to access the alternate transannular [4+2] cycloaddition pathway leading to the hexacyclic acid framework, and will be reported in due course.

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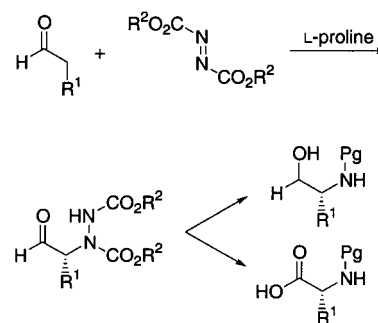
## Direct Organo-Catalytic Asymmetric $\alpha$ -Amination of Aldehydes—A Simple Approach to Optically Active $\alpha$ -Amino Aldehydes, $\alpha$ -Amino Alcohols, and $\alpha$ -Amino Acids\*\*

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One of the ultimate goals and challenges in chemistry is to develop stereoselective transformations for the creation of functionalized optically active molecules with structural diversity from simple and easily available starting materials. Several procedures to generate optically active molecules are known and among these asymmetric catalysis plays an important role.

The importance of optically active  $\alpha$ -amino acids,  $\alpha$ -amino aldehydes, and  $\alpha$ -amino alcohols, formed by asymmetric catalysis,<sup>[1]</sup> has stimulated an enormous development in synthetic strategies, and two different catalytic, enantioselective approaches are attractive: the C–C and the C–N bond-forming reactions. The catalytic enantioselective C–C bond-forming reactions include the addition to imines, such as the Strecker<sup>[2]</sup> and Mannich<sup>[3]</sup> reactions.

The catalytic, enantioselective, direct C–N bond-forming reaction using aldehydes and a nitrogen source, such as azodicarboxylates, would constitute one of the simplest procedures for the construction of a stereogenic carbon center attached to a nitrogen atom (Scheme 1). Recently, we presented the first direct, enantioselective  $\alpha$ -amination of 2-keto esters catalyzed by chiral copper(II)–bisoxazoline complexes.<sup>[4, 5]</sup> This development led to a simple synthetic approach to optically active *syn*- $\beta$ -amino- $\alpha$ -hydroxy esters.



Scheme 1. Pg = protecting group.

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