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Diastereoselective Synthesis of the *Trans-anti-cis*-decahydro-*as*-Indacene Ring System via the Transannular Diels-Alder Reaction of a Functionalized (E,E,E)-Cyclododeca-1,6,8-Triene

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Abstract: A stereoselective synthesis of trans-anti-cis decahydro-as-indacene **5** *is described. The key step of this synthesis is the tandem Claisen ring contraction of the 16-membered macrolactone* **3** *followed by the transannular Diels-Alder reaction of the resulting (E,E,E)-cyclododeca-1,6,8-triene* **4**.
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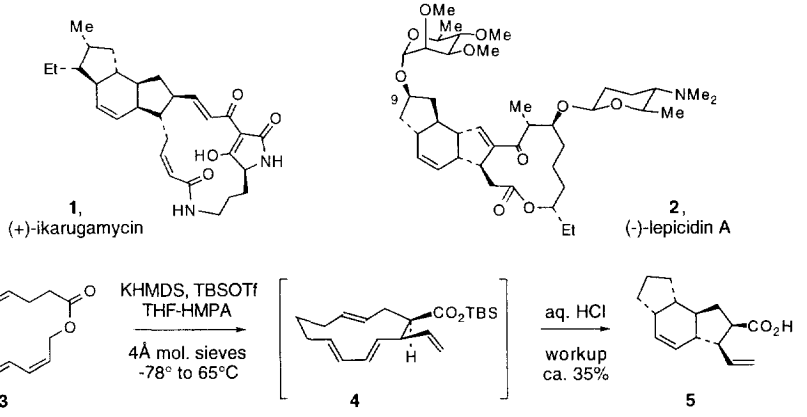
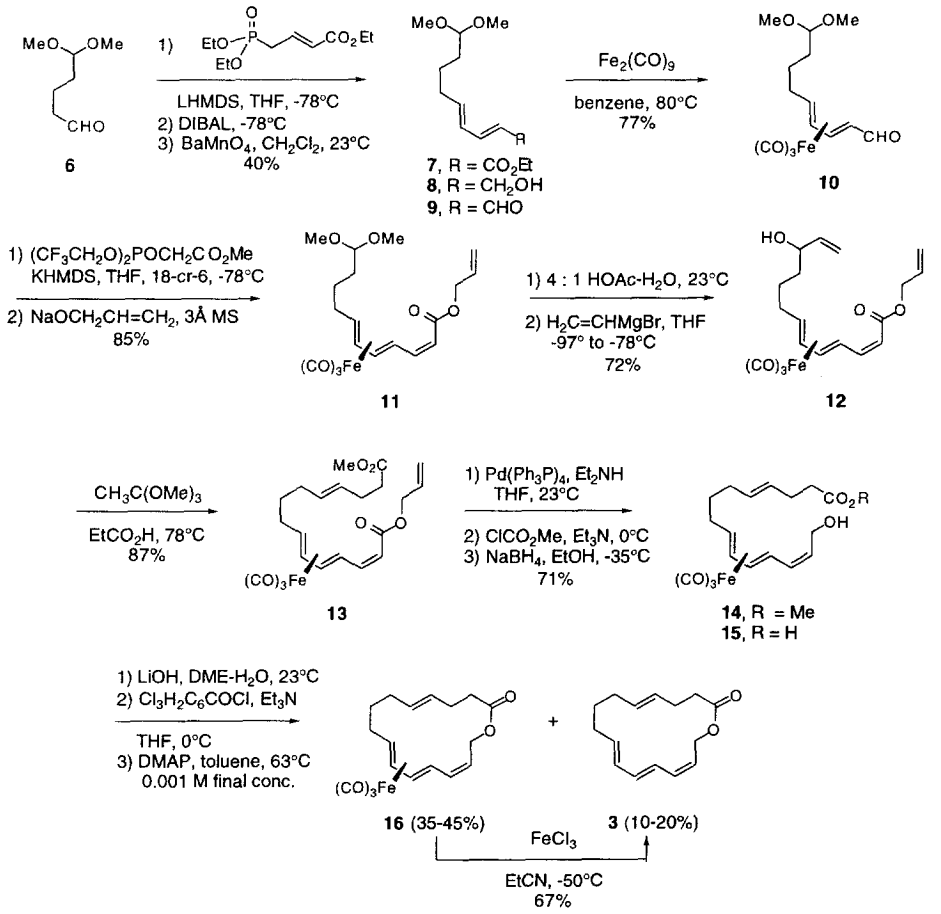
Ikarugamycin (**1**)[1] and lepicidin A (**2**)[2] are members of a relatively small family of natural products that possess perhydro-*as*-indacene ring systems. The unique structural features and the biological properties of these compounds have stimulated considerable interest, and total syntheses of both **1**[3-5] and **2**[6] have been reported. In three of the successful syntheses,[4-7] the *trans-anti-cis* decahydro-*as*-indacene ring systems were constructed by a conventional intramolecular Diels-Alder reaction leading to a *trans*-fused hexahydroindene nucleus,[8] followed several steps later by closure of the final cis-fused five-membered ring. However, we were interested in the possibility, stimulated by the biosynthetic proposal of Ito and Hirata,[1] that the *trans-anti-cis* decahydro-*as*-indacene ring system could be established more directly by a transannular Diels-Alder reaction[9] of an appropriately substituted (E,E,E)-cyclododeca-1,6,8-triene. We report herein the successful demonstration of this plan culminating in the synthesis of **5** via the stereoselective enolate Claisen ring contraction of lactone **3** and the facile cyclization of the *in situ* generated (E,E,E)-cyclododeca-1,6,8-triene **4**.



Our plan for the synthesis of **4** was guided by prior experience that suggested that the (E,E,E)-cyclododeca-1,6,8-triene ring system is relatively strained and therefore correspondingly difficult to prepare. For example, attempts to synthesize substituted (E,E,E)-cyclododeca-1,6,8-trien-3-ones by intramolecular Horner-Wadsworth-Emmons cyclizations proceeded in less than 5% yield.[10,11] Similar results have been reported by

Park who attempted the synthesis of 12-membered (E,E,E)-trienoic lactones.[12] Other work from our laboratory established that the comparatively less strained 14-membered macrocyclic trienes are difficult to prepare by intramolecular Suzuki cross coupling reactions,[13] while Deslongchamps has indicated that closure of 13-membered (E,E,E)-trienes by intramolecular alkylation reactions is difficult as well (unlike the cyclizations leading to 14-membered trienes).[9,14] Accordingly, we decided to approach the synthesis of 12-membered triene **4** by an enolate Claisen ring contraction of a (presumably) more easily synthesized 16-membered lactone, **3**.[15-17] This strategy has previously been used with great success for the synthesis of strained carbocycles.[18]

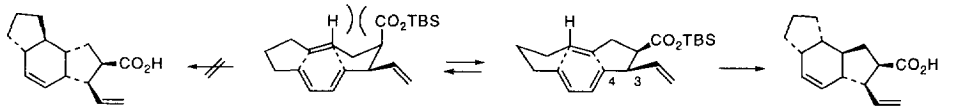
The synthesis of macrocyclic lactone **3** commenced with the vinylogous Horner-Wadsworth-Emmons olefination of 5,5-dimethoxypentanal (**6**)[19] with triethyl phosphonocrotonate (61% yield).[20] Reduction of **7** with DIBAL (2.25 equiv., toluene, -78°C, 71% yield) and re-oxidation of the resulting alcohol **8** with $BaMnO_4$ (1.4 equiv.) in CH_2Cl_2 then provided diene aldehyde **9** in 93% yield (40% overall from **6**).[21] Treatment of **9** with $Fe_2(CO)_9$ (3.9 equiv., in five portions over 5 h) in benzene at 80°C then provided the iron(tricarbonyl)-complexed diene **10** in 77% yield.[22] At the outset, we had hoped that use of a chiral diene-$Fe(CO)_3$ complex would provide



a means of controlling the stereochemistry of the enolate Claisen rearrangement (e.g., **17** → **4**-$Fe(CO)_3$) with respect to remote stereocenters (e.g., C(9) of **2**) present in more fully functionalized synthetic intermediates.[5,23] Unfortunately, all attempts to perform the enolate Claisen ring contraction with **17** as substrate were unsuccessful. Nevertheless, the -$Fe(CO)_3$ unit still played a significant role in the present synthesis, since the efficiency of the macrolactonization of **16** was considerably better than with the analogous $Fe(CO)_3$-free seco acid.[24]

Aldehyde **10** was converted via Still's procedure to the corresponding (Z)-α,β-unsaturated methyl ester (>95% yield),[25] which was trans-esterified by treatment with 0.6 M $NaOCH_2CH{=}CH_2$ in allyl alcohol (23°C), thereby giving allyl ester **11** in 85% overall yield. Standard hydrolysis of the dimethyl acetal and careful, low temperature (-97°C for 20 min; -90°C for 10 min; -78°C for 2 h) addition of $H_2C{=}CHMgBr$ to the aldehyde provided allylic alcohol **12** in 72% yield. This intermediate was then subjected to a modified Johnson orthoester Claisen rearrangement ($MeC(OMe)_3$ as solvent, cat. $EtCO_2H$, 78°C, 2 days), which provided the differentiated diester **13** in 87% yield. Relatively mild reaction temperatures were required here in order to minimize decomposition of the sensitive triene-$Fe(CO)_3$ complex. The allyl ester was deprotected by using $Pd(PPh_3)_4$ (0.04 equiv.) in the presence of Et_2NH (5 equiv.),[26] and the resulting carboxylic acid was reduced by way of the mixed anhydride (71% yield of **14**). Hydrolysis of **14** (6 equiv. LiOH, 4 : 1 DME-H_2O, 23°C, 5 h) provided the very sensitive seco acid **15** that was immediately subjected to macrolactonization conditions.[27] The best yields of **16** were obtained by slow addition (12 h) of a -78°C solution of **15** in toluene to a solution of DMAP (25 mM) and the peptide coupling agent PyBroP (12 equiv., 10 mM),[28] which provided **16** in 48% yield with no detectable amounts of decomplexed lactone **3** present. Unfortunately, the thermal instability of **15** complicated the scale-up of this reaction. As an alternative, we found that the Yonemitsu variant of the Yamaguchi lactonization provided **16** in 35-45% yield.[29] This involved generation of the mixed anhydride with trichlorobenzoyl chloride (1.2 equiv.) and Et_3N (3 equiv.) at 0°C in THF. This mixture was filtered to remove Et_3NHCl, diluted with toluene and added over 6 h to a 63°C solution of DMAP (29 mM) in toluene (0.001 M final concentration). Although the mixed anhydride was more stable than **15**, the temperature (63°C) required for the lactonization resulted in partial decomplexation of **16**, leading to the isolation of 10-20% of **3** in addition to **16** (45-55% combined yield of **3** and **16**).[24] Finally, treatment of **16** with $FeCl_3$ (10 equiv.) in EtCN at -50°C provided **3** in 67% yield.

With macrolactone **3** in hand, we examined the key enolate Claisen ring contraction-transannular Diels-Alder sequence. Thus, a solution of **3** in THF-HMPA at -78°C was treated with TBSOTf (1.05 equiv.) and KHMDS (1.05 equiv.) in the presence of crushed, activated 4Å molecular sieves. The mixture was immediately allowed to warm to ambient temperature and then was heated at 65°C overnight. This provided a 4-5 : 1 mixture of tricycle **5** and a second diastereomer[30] in ca. 35% yield following acidic workup, from which **5**, m.p. 127-128°C, was isolated by crystallization from ether-hexanes. Also obtained was ca. 30% of recovered **3**; macrocycle **4** was not detected at any stage of the reaction. The stereochemistry of **5** was determined by single crystal X-ray analysis.[31] These results indicate that the enolate Claisen rearrangement of **3** provides macrocycle **4** with cis stereochemistry of the two substituents, and that the transannular Diels-Alder reaction proceeds preferentially by way of transition state **A**. The stereochemical control elements responsible for production of **5** as the predominant product evidently are the syn relationship[8] between the C(3)-vinyl substituent and C(4)-H (also present in t.s. **B**) and especially the pseudoequatorial geometry of the carboxyl substituent in t.s. **A**.



17 ts. **B** ts. **A** **5**

In conclusion, we have demonstrated that the tandem enolate Claisen ring contraction of **3** and the subsequent transannular Diels-Alder of triene **4** constitutes a viable strategy for the stereoselective synthesis of *trans-anti-cis* decahydro-*as*-indacene **5**. Further developments of this methodology for application towards the total synthesis of ikarugamycin, lepicidin A and related structures will be reported in due course.

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