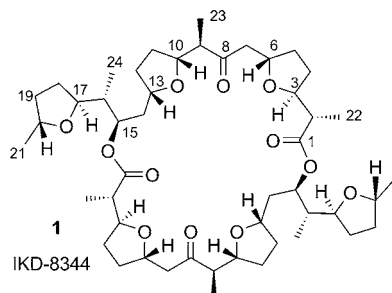


Three Rings in One Step: A Quick Approach to IKD-8344**

Yang Zou and Yikang Wu*

IKD-8344 (**1**, Scheme 1) was first isolated from an unidentified alkalophilic *Actinomyces* (strain no. 8344) in the early 1990s by Nishii and co-workers,^[1] and later from *Streptomyces*



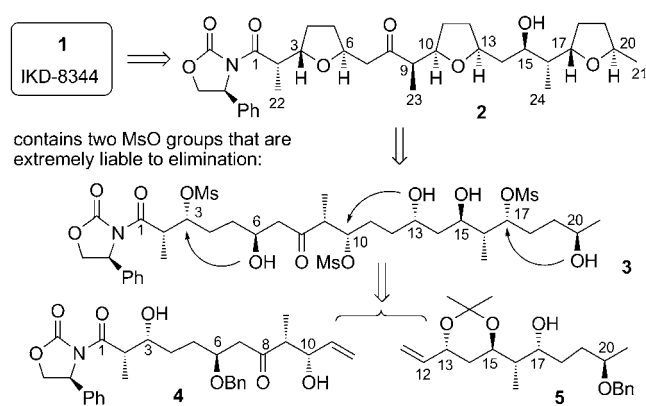
Scheme 1. The structure of IKD-8344 with the relative configuration determined by single crystal X-ray crystallography and the absolute configuration depicted arbitrarily (Ref. [1b]).

sp. A6792 by Kim and co-workers.^[2] This natural dilactone, which contains a 28-membered ring, represents a worthy target for synthetic studies, because of its intriguing molecular architecture and the potent activities against mouse leukemia (IC₅₀ 0.54 ng mL⁻¹) and *Trichinella spiralis*.^[3]

The most striking structural motifs in IKD-8344 are the 2,5-disubstituted THF rings with one of the two substituting carbon atoms being part of a hidden aldol unit. These structural motifs are similar to those found in nonactin and pamamycins. In previous studies^[4,5] on the synthesis of similar THF-containing targets, we developed a novel route to enantiomerically pure THF rings by using an S_N2 type intramolecular O alkylation at a sterically hindered carbon atom in β position to a carbonyl group. Such an S_N2 reaction would normally be considered hopeless, because it competes with the normally very facile α racemization and β elimination. In the beginning, en route to a synthesis of nonactin, we realized the formation of one ring at a time. Later, in the synthesis of pamamycin 621A, we achieved the formation of two rings in one step. Encouraged by these results, we decided

to take up an even greater challenge with the concurrent formation of three THF rings from a highly sensitive linear precursor. Such an approach would also circumvent the undesired complications^[3] encountered in the assembly of the preformed single THF ring containing fragments in the previous total synthesis.

The outline of our retrosynthetic analysis is shown in Scheme 2. We planned to use Evans' asymmetric aldol reaction to establish the C2/C3 aldol motif and to form the



Scheme 2. The main features of our retrosynthetic analysis. Bn = benzyl, Ms = methanesulfonyl.

THF rings in the presence of the Evans auxiliary. The most convenient precursor for the *seco* acid would be the oxazolidinone-masked hydroxy acid (**2**), which in turn was expected to form from the highly sensitive/unstable linear precursor **3**, which contains two carbonyl groups, three leaving groups, and four hydroxy groups, and is thus a compound that may readily undergo a range of side reactions. The C1 to C21 chain was planned to be assembled from two smaller fragments, alkenes **4** and **5**, through a cross metathesis reaction.

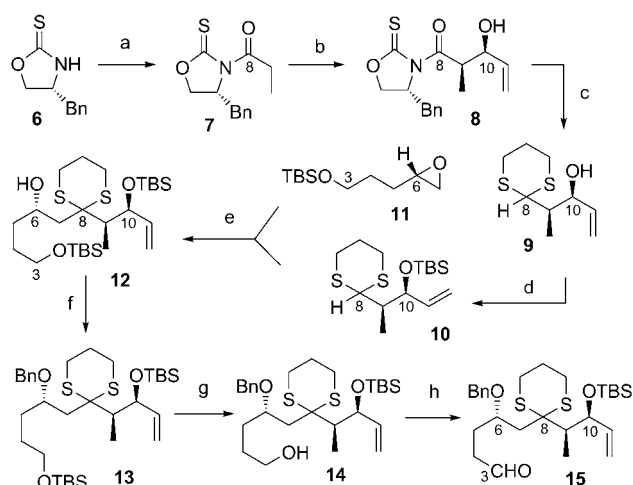
We started the synthesis with the construction of the C3 to C11 unit (Scheme 3). The asymmetric aldol reaction between **7** (readily derived from **6**^[6]) and acrolein under the conditions described by Crimmins et al.^[7] afforded the desired enantiopure **8** in 86% yield of isolated product. Subsequent cleavage of the chiral auxiliary with DIBAL-H^[7] followed by reaction with HS(CH₂)₃SH in the presence of BF₃·Et₂O gave dithiane **9**. The free OH group was then masked as TBS ether before deprotonation of the dithiane with *t*BuLi and reaction with epoxide **11** to give alcohol **12**. Use of *n*BuLi instead of *t*BuLi led to lowered yields for **12** (42%) in this case. However, this disadvantage was partially compensated by the convenience of performing the reaction at ambient temperature without the need to add HMPA.

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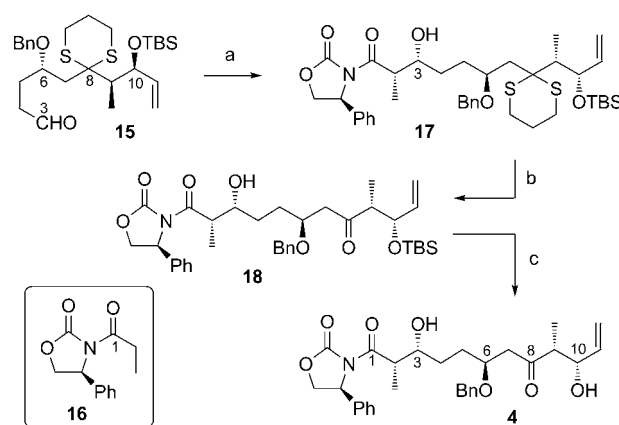
Scheme 3. Synthesis of **15**. Reagents and conditions: a) EtCO₂H, EDCI, DMAP, CH₂Cl₂, 96%; b) TiCl₄, (–)-sparteine, acrolein, CH₂Cl₂, 0°C, 86%; c) 1) DIBAL-H, CH₂Cl₂, –78°C; 2) HS(CH₂)₃SH, BF₃·Et₂O, 69% from **8**; d) TBSOTf, Et₃N, CH₂Cl₂, 0°C, 90%; e) *t*BuLi, THF, HMPA, –78°C, 71%; f) BnBr, NaHMDS, THF, DMF, 90%; g) CSA, MeOH, –10°C, 93%; h) SO₃·py, DMSO, Et₃N, CH₂Cl₂, 90%. CSA = camphorsulfonic acid, DIBAL-H = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, DMF = *N,N*-dimethylformamide, DMSO = dimethyl sulfoxide, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride, HMPA = hexamethylphosphoramide, NaHMDS = sodium hexamethyldisilazide, py = pyridine, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

Benzyl protection of the newly formed hydroxy group at C6 was unexpectedly difficult. The etherification with BnBr in the presence of NaH resulted in unwanted side products in pure DMSO or DMF. Fortunately, this problem was later satisfactorily solved by using a 5:1 mixture of THF/DMF as the solvent and performing the alkylation at –10°C.

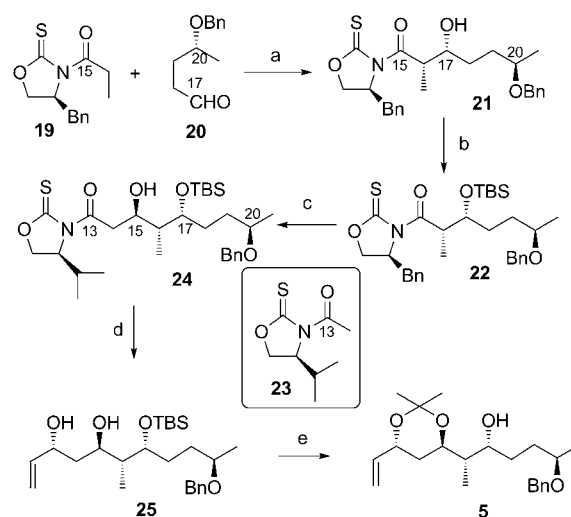
Furthermore, the incorporation of the C1/C2 unit was planned by an Evans aldol reaction. Thus, the C3 atom had to be transformed into an aldehyde first. To this end, the TBS protecting group at the primary OH group (C3) was selectively cleaved with MeOH in the presence of a catalytic amount of CSA, while the TBS group on the secondary OH group (C10) remained intact. The resulting alcohol **14** was then treated with SO₃·py in CH₂Cl₂ to deliver the expected terminal aldehyde **15**, thus setting the stage for the incorporation of the first two carbon atoms in the C1 to C11 fragment (**4**).

The aldol reaction was achieved (Scheme 4) under the conditions described by Crimmins et al.^[8] including TiCl₄/sparteine/NMP. The enantiomerically pure **17** was then treated with PIFA^[9] to deprotect the thioketal protecting group. Finally, removal of the TBS group with HF afforded alkene **4**, which is needed for the later catenation with **5**.

The synthesis of fragment **5** was started with the installation of the C16/C17 stereogenic centers (Scheme 5). The aldol reaction of **19** with **20** gave **21** in 99% yield. TBS protection of the hydroxy group with TBSOTf/2,6-lutidine followed by cleavage of the oxazolidinethione auxiliary with DIBAL-H gave the intermediate aldehyde.



Scheme 4. Conversion of **15** into **4**. Reagents and conditions: a) **16**, TiCl₄, (+)-sparteine, NMP, CH₂Cl₂, 0°C, 90%; b) PIFA, MeOH/H₂O, 78%; c) 40% HF, MeCN, 96%. NMP = *N*-methyl-2-pyrrolidinone, PIFA = phenyliodine(III) bis(trifluoroacetate).



Scheme 5. Synthesis of **5**. Reagents and conditions: a) TiCl₄, (+)-sparteine, NMP, CH₂Cl₂, 0°C, 99%; b) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0°C, 95%; c) 1) DIBAL-H, CH₂Cl₂, –78°C, 88%; 2) **23**, TiCl₄, *i*Pr₂NEt, CH₂Cl₂, –78°C, 77%; d) 1) MeNH(OMe)·HCl, Me₃Al, CH₂Cl₂; 2) (CH₂=CH)₄Sn, MeLi, THF; 3) Me₄NBH(OAc)₃, AcOH, MeCN, –15°C, 71% from **24**; e) 1) Me₂C(OMe)₂, acetone, *p*-TsOH; 2) *n*Bu₄NF, THF, 93% from **25**. Ts = toluenesulfonyl.

To extend the chain by two carbon units and install a new stereogenic center at C15, an asymmetric acetate aldol reaction that was induced by an oxazolidinethione auxiliary was performed next. Generally speaking, the diastereoselectivity for such reactions is less satisfactory than that for the corresponding propionate aldol condensations under similar conditions. Several elegant protocols^[10] for dealing with these types of problems have been reported. However, the advantages of using these protocols appear to be somewhat counterbalanced by, for instance, the extra efforts required for gaining access to the special auxiliaries (with sterically more hindered substituents at the stereogenic centers). In hope to find an alternative that is more suitable to us, we

one step was then achieved with 2,6-lutidine under heating. Gratifyingly, **2** was obtained in 60% overall yield (from **29**).

Coupling of **2** with **31** (prepared from **2** by protection with a TES group and removal of the chiral auxiliary) under the Yamaguchi conditions provided **33**, which on removal of the TES group and the chiral auxiliary gave **34**. Lactonization of **34** afforded product **1**, the ^1H and ^{13}C NMR spectra and the specific rotation ($[\alpha]_{\text{D}}^{27} = +36.33$ ($c = 0.20$, MeOH), lit.^[14] $[\alpha]_{\text{D}}^{17} = +40.2$ ($c = 1.0$, MeOH)) of which were consistent with those of the natural product **1**.

Only the relative configuration of natural product **1** was ever experimentally determined, although the absolute configuration that was arbitrarily depicted in the report of the structure^[1b] happened to be correct. In retrospect, the first synthesis^[3a,b] of **1** by Lee and co-workers would have allowed to establish the absolute configuration. But unfortunately, the Lee group measured the rotation of **1** in CHCl_3 rather than MeOH,^[15] the absolute configuration of natural product **1** thus remained unelucidated to date.

In summary, an efficient synthesis of IKD-8344 has been achieved with a novel “three rings in one step” transformation as the key step. Apart from the formation of multiple THF rings in an unprecedented difficult and complex situation, the efficient chain assembly and the tricky saturation of the $\text{C}=\text{C}$ bond in a highly sensitive substrate are also interesting. The absolute configuration of natural product **1**, which was arbitrarily depicted in the original report of the configuration^[1b] and mistaken as proven without being noticed to date, is also verified for the first time; the corresponding hidden and potential confusions in the literature and the major online data bases are thus cleared.

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- [15] Comparison of rotations measured in different solvents cannot provide any reliable clues to the absolute configuration. For instance, pamamycin 621A, also a THF-containing natural product, gave opposite rotations in CHCl_3 and CH_2Cl_2 (Ref. [5a,b]). The rotation for **1** in CHCl_3 from this work is $[\alpha]_{\text{D}}^{27} = +20.2$ ($c = 0.38$, CHCl_3), and thus remarkably different from that in Ref. [3a,b] ($[\alpha]_{\text{D}}^{15} = +39.7$ ($c = 0.25$, CHCl_3), the only complete rotation data for **1** (erroneously registered with a never proven absolute configuration) that can be found in leading online databases such as SciFinder and Reaxys to date).