Inostamycin A

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# The Total Synthesis of Inostamycin A

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***Abstract:*** *The first total synthesis of inostamycin A is described. With efficient and stereoselective synthetic routes to aldehyde* ***3*** *and ketone* ***4*** *developed through asymmetric aldol reactions, addition reactions and reduction, and with chiral building blocks, the two large fragments were coupled with remarkable anti stereoselectivity and efficiency by aldol condensation. The coupling reaction provided the complete carbon skeleton with all the requisite functional groups and stereogenic centers for inostamycin A. The two quaternary carbons at C20 and C16 of ketone* ***4*** *were elaborated in a highly stereocontrolled manner by addition reactions of the transmetallated* ***5*** *to ethyl ketone* ***6*** *and the transmetallated* ***7*** *to methyl ketone* ***8****, respectively, in which the use of* $LaCl_3$ *for transmetallation was critical for high coupling efficiency.*

Inostamycin A was isolated from the fermentation broth of *Streptomyces* sp. MH816-AF15 in 1990.[1] Its structure was first assigned by NMR spectroscopy and later confirmed by X-ray analysis of its sodium salt to manifest the relative stereochemistry. The crystal structure of the sodium salt showed an ionophoric pseudo cyclic molecular shape, in which the sodium cation coordinates to the two carboxylate oxygens, the two hydroxyl oxygens at C9 and C17, the carbonyl oxygen, and the inner tetrahydrofuranyl oxygen.[1] Scrutiny of the reported crystal structure allowed us to identify a mistakenly translated stereochemistry of the ethyl group at the C2 position. Accordingly, the relative stereochemistry of inostamycin A should be revised from **1** to **2** (Figure 1). The related compounds, inostamycins B and C, were separated from the same microorganism a few years later, and the structures were differentiated by a C2 methyl substituent and a missing carboxylic acid group, respectively.[2] It is likely that the C2 stereochemistry of inostamycin B should also be corrected. Inostamycins are known to display antimicrobial and cytocidal activities, with inostamycin A showing the highest potency.[2] Only inostamycin A exhibits inhibitory activity against cytidine-5′- diphosphate 1,2-diacyl-*sn*-glycerol (CDP-DG):inositol transferase to reduce phosphatidylinositol turnover, and restrain cell proliferation and transformation.[3a] Other prospective physiological properties of inostamycin A include restoration of paclitaxel cytotoxicity to augment apoptosis,[5] and cytostatic suppression of tumor recurrence.[3b] The structural complexity, anticancer agents from multidrug resistance,[4] and potentiation of and pharmacological potential of inostamycin A attracted us to attempt its synthesis. Herein, we describe the first total synthesis of inostamycin A **2**.[6]

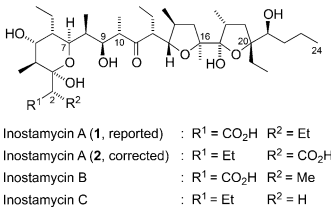
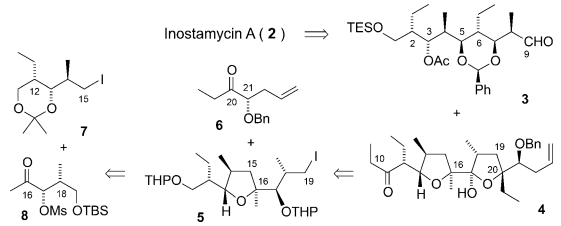



***Figure 1.*** Structures of inostamycins.

Our retrosynthetic blueprint was framed by severing the C9–C10 bond of **2** to engender the aldehyde part **3** and the ethyl ketone part **4** (Scheme 1). For synthesis of **3**, we planned




***Scheme 1.*** Retrosynthetic analysis.

to cleave the C2–C3 and C5–C6 bonds, which would be restored with the four stereogenic centers by aldol condensations. The remaining asymmetric centers were to be supplied by two enantiomeric chiral building blocks for the methyl groups and by hydroxyl-induced 1,3-reduction of the C7 carbonyl group. To elaborate **4**, its C19–C20 bond was disconnected to iodide **5** and ethyl ketone **6**. Their combination was chosen to set up the C20 quaternary stereocenter based on the dual effects of Felkin model behavior and dipole–dipole repulsion. While **6** was expected to be readily prepared from a known compound, assembly of **5** was designed by addition of lithiated **7** to methyl ketone **8**, in which the C16 stereochemistry was envisioned to be undesirable as a result of the aforementioned dual effect. Subsequently, its required inversion was planned through epoxide formation followed by cyclization. Other asymmetric centers would be built by aldol condensations and a chiral building block.

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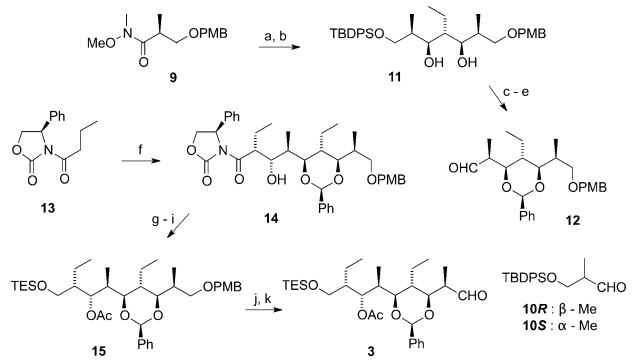
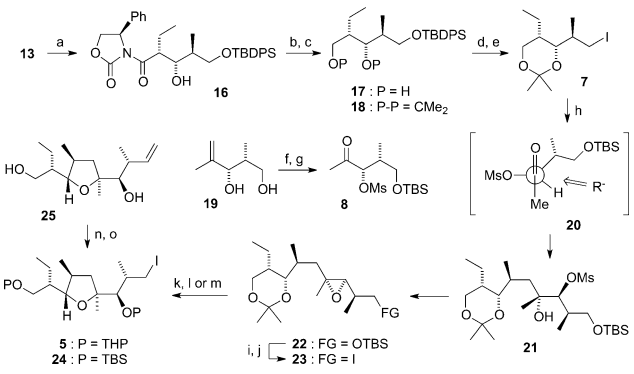
The synthesis was initiated with the known Weinreb amide **9**[7] by Grignard addition to form propyl ketone in 94% yield (Scheme 2). The ketone was subjected to *anti*-aldol condensation using boron chloride with aldehyde **10*R***. The generated aldolate was reduced in situ stereoselectively through boron-chelated aldolate[8] to afford *syn*-1,3-diol **11** in 91% yield with a few percent of diastereomer(s). After chromatographic purification, **11** was protected as benzylidene and desilylated to the primary alcohol in 93% overall yield. After oxidation of the alcohol,[9] the prepared aldehyde **12** was reacted with (*Z*)-boron enolate derived from the oxazolidinone **13**[10] to furnish *syn*-adduct **14** in 93% yield without appreciable diastereomer. Reduction of **14**[11] followed by silylation and acetylation delivered PMB ether **15** in 83% overall yield. The PMB group of **15** was removed[12] and the resulting primary alcohol was oxidized[13] to secure the aldehyde **3**, one of the coupling partners for the natural product.



***Scheme 2.*** Reagents and conditions. a) *n*PrMgCl, THF, −20 °C, 94%; b) *c*Hx$_2$BCl, Et$_3$N, Et$_2$O, −78 to 0 °C, then **10*R***, −78 to −20 °C, then LiBH$_4$, −78 °C, then MeOH, aq NaOH, H$_2$O$_2$, −78 to 25 °C, 91%; c) PPTS, PhCH(OMe)$_2$, PhH, 110 °C, Dean–Stark trap, 95%; d) TBAF, THF, 0 to 25 °C, 98%; e) (COCl)$_2$, DMSO, CH$_2$Cl$_2$, −78 °C, then Et$_3$N, −78 to 0 °C; f) *n*Bu$_2$BOTf, Et$_3$N, CH$_2$Cl$_2$, 0 °C, then **12**, −78 to −20 °C, 93%; g) LiBH$_4$, H$_2$O, Et$_2$O, 0 °C, 95%; h) TESCl, Et$_3$N, CH$_2$Cl$_2$, −78 °C, 96%; i) Ac$_2$O, DMAP, Et$_3$N, CH$_2$Cl$_2$, 0 to 25 °C, 91%; j) DDQ, pH 7 phosphate buffer, CH$_2$Cl$_2$, 0 °C, 95%; k) TPAP, NMO, molecular sieves 4 Å, CH$_2$Cl$_2$, 25 °C. PMB = *p*-methoxybenzyl, TBDPS = *tert*-butyldiphenylsilyl, PPTS = pyridinium *p*-toluenesulfonate, TES = triethylsilyl, Ac = acetyl, DMAP = 4-(dimethylamino)-pyridine, DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, TPAP = tetrapropylammonium perruthenate, NMO = 4-methylmorpholine *N*-oxide.

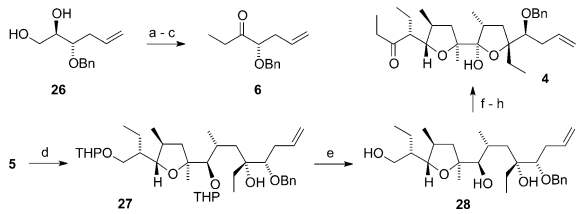
Synthesis of the other coupling moiety **4** began with aldol condensation of **13** with aldehyde **10*S*** to give *syn*-aldol product **16** in 91% yield without diastereomeric detection (Scheme 3). Subsequently, **16** was reduced to alcohol **17**, protected as acetonide **18**, and desilylated and substituted to iodide **7** in 88% overall yield. To prepare the ketone **8** as the addition counterpart of **7**, the known diol **19**[14] was chemoselectively silylated, oxidatively cleaved, and mesylated to **8** in 79% yield. Their coupling was achieved by transmetalation of **7** followed by sequential addition of $LaCl_3$[15] and **8** to provide a near 1:1 mixture of the adduct (hydroxy mesylate) **21** and the cyclized epoxide **22**. The generated mixture was treated with base in situ to furnish the epoxide **22** in 88%



***Scheme 3.*** Reagents and conditions. a) *n*Bu$_2$BOTf, Et$_3$N, CH$_2$Cl$_2$, 0 °C, then **10*S***, −78 to −20 °C, 91%; b) LiBH$_4$, H$_2$O, Et$_2$O, 0 °C, 94%; c) PPTS, Me$_2$C(OMe)$_2$, PhH, 110 °C, Dean–Stark trap, 96%; d) TBAF, CH$_2$Cl$_2$, 25 °C; e) I$_2$, Ph$_3$P, imidazole, CH$_2$Cl$_2$, 0 to 25 °C, 98% (over 2 steps); f) TBSCl, DMAP, Et$_3$N, CH$_2$Cl$_2$, 0 °C, 92%; g) O$_3$, CH$_2$Cl$_2$, −78 °C, then Et$_3$N, −78 to 0 °C, then MsCl, DMAP, 0 °C, 86%; h) *t*BuLi, THF, −78 °C, then LaCl$_3$·2 LiCl in THF, −78 °C, then **8** in THF, −78 °C, then 0.3 M KOH, Et$_3$NBnCl, −78 to 25 °C, 88%; i) TBAF, THF, 0 to 25 °C, 98%; j) I$_2$, Ph$_3$P, imidazole, THF, 0 to 25 °C, 97%; k) TsOH·H$_2$O, MeOH, −10 °C, 82%; l) PPTS, DHP, CH$_2$Cl$_2$, 0 to 25 °C, 92%; m) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, 0 to 25 °C, 85%; n) O$_3$, MeOH, −78 °C, then NaBH$_4$, −78 °C, 91%; o) I$_2$, Ph$_3$P, imidazole, THF, 0 to 25 °C, 92%. Ms = methanesulfonyl, Bn = benzyl, TsOH = *p*-toluenesulfonic acid, DHP = 3,4-dihydro-2*H*-pyran, THP = tetrahydropyranyl.

yield without detection of its diastereomeric product. It was noted that **22** was obtained less than 20% yield with similar stereoselectivity in the absence of $LaCl_3$ on transmetalation. The observed stereochemistry of the adduct can be rationalized by the model of approach for **20** based on the aforementioned Felkin model and dipolar repulsion. Compound **22** was converted into iodide **23** in 95% yield by a sequential desilylation and substitution. Acidic hydrolysis of the acetonide group of **23** induced cyclization of the generated γ-hydroxy epoxide to the corresponding tetrahydrofuran, the two hydroxy groups of which were protected as THP ethers to produce diastereomeric **5** in 75% overall yield. The tertiary hydroxy stereochemistry of **21** was identified by converting **21** and the reported **25**[6a] into the identical compound **24**, respectively.

For another addition reaction with **5**, substrate **6** was derived from known diol **26**[16] in 71% yield by a sequence of oxidative cleavage, Grignard reaction, and oxidation[17] (Scheme 4). As described for **7**, the iodides **5** were transmetalated and the resulting lanthanium alkylides were reacted with **6** to give a diastereomeric mixture of adducts **27**. The mixture was hydrolyzed to the desired triol **28** in 79% yield from **5** along with 3% of its diastereomeric tertiary alcohol, which was readily separated. It was observed that transmetalation of TBS-protected **24** instead of **5** resulted in an extensive 1,3-silyl migration from the secondary silyloxy group to the terminal carbon. Given that **28** was recently reported,[6a] the tertiary hydroxy stereochemistry of **27** was unambiguously determined, although it also can be predicted by a similar model of approach proposed for **20** in Scheme 3. Subsequently, **28** was converted into the bicyclic ethyl ketone **4** as a single stereoisomer in 81% yield through chemo-

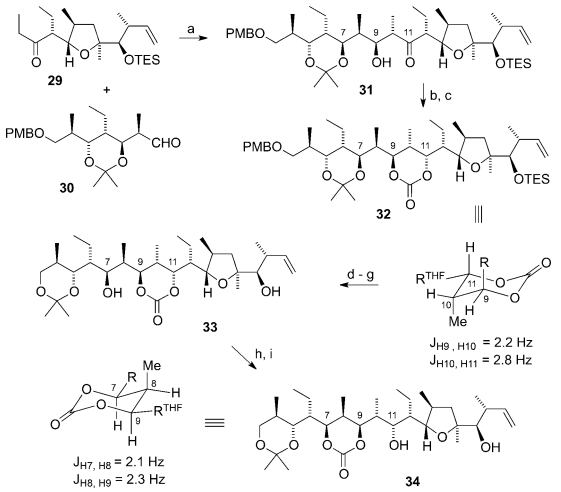


***Scheme 4.*** Reagents and conditions. a) $NaIO_4$, $H_2O$, THF, 0 °C; b) EtMgBr, THF, −78 °C; c) DMP, $CH_2Cl_2$, 25 °C, 71 % (over 3 steps); d) *t*BuLi, THF, −78 °C, then $LaCl_3{\cdot}2\,LiCl$ in THF, −78 °C, then **6** in THF, −78 °C; e) PPTS, EtOH, 40 °C, 79 % (over 2 steps); f) TEMPO, PhI(OAc)$_2$, $CH_2Cl_2$, 0 to 25 °C; g) EtMgBr, THF, −78 °C; h) AZADO, PhI(OAc)$_2$, $CH_2Cl_2$, 0 to 25 °C, 81 % (over 3 steps). DMP = Dess–Martin periodinane, TEMPO = 2,2,6,6-tetramethylpiperidine 1-oxyl, AZADO = 2-azaadamantane *N*-oxyl.

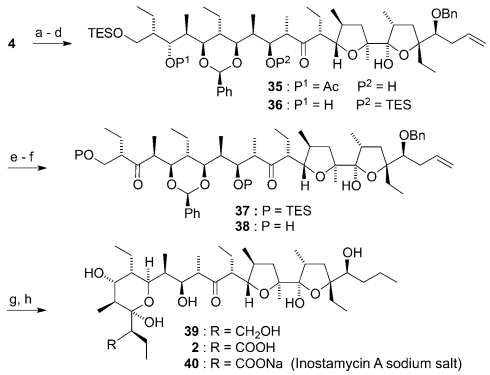
selective TEMPO oxidation,[18] Grignard addition, and AZADO double oxidation[19] conducted in sequence.

Having achieved efficient synthetic routes to **3** and **4**, their coupling was planned by aldol condensation. To screen effective aldol conditions, model studies were conducted by choosing two models **29**[6a,20] and **30**,[20] which are structurally simpler but similar to **4** and **3** (Scheme 5). Because it was necessary to generate (*E*)-enolate from **29** for the required stereochemistry, **27** was treated with *c*Hx$_2$BCl[21] and $Et_3N$ at various temperatures, and then **30** to recover only the starting materials. Alternatively, **29** was deprotonated with LiTMP/LiBr[22] in THF and the generated lithium (*E*)-enolate was reacted with *c*Hx$_2$BCl followed by **30** at −78 °C to give a 20:1 mixture of two diastereomers in 62 % yield. The identical condensation in $Et_2O$ instead of THF proceeded at −20 °C more slowly (18 vs. 3 h) with a similar diastereoselectivity and 50 % yield. When the condensation was implemented in the absence of *c*Hx$_2$BCl, the two diastereomeric aldol products were formed in 92 % yield as a 20:1 mixture in THF but in 71 % yield as a 1:1 mixture in $Et_2O$. After chromatographic removal of the minor component, the major product, which was predicted as **31**, was reduced in a 1,3-*anti* fashion[23] and carbonated to carbonate **32** for its stereochemical assignment. The following functional group adjustment produced another carbonate **34**. The stereocenters C9, C10, and C11 were newly generated, and the relative stereochemistry between C9 and C11 should be *anti*. From the $^1$H NMR spectra of **32**, the coupling constants $J_{H9,H10}$ and $J_{H10,H11}$ were 2.2 and 2.8 Hz, respectively, and NOE enhancements were measured between $H_9$ and $H_{10}$, $H_{10}$ and $H_{11}$, and $H_9$ and $Me_{10}$. The observation indicates that $H_{10}$ occupies an equatorial position, and the relative spatial relationships between $H_9$ and $H_{10}$ and between $H_{10}$ and $H_{11}$ are *anti* and *syn*, respectively. To determine their absolute configurations, **34** was prepared. Its $^1$H NMR spectra showed $J_{H7,H8}$ and $J_{H8,H9}$ coupling constants of 2.1 and 2.3 Hz, respectively, and NOE enhancement between $H_7$ and $H_9$. The experimental data suggest that $H_7$ and $H_9$ are located axially, and $H_8$ equatorially. Therefore, the stereochemical relationship is *syn* between $H_7$ and $H_9$. It is concluded that the aldol product between **29** and **30** has the stereochemistry of 9*S* and 10*S* as drawn in structure **31**.

With the effective aldol condensation conditions identified from the model studies, they were applied to the aldol reaction between aldehyde **3** and ketone **4** to produce the desired *anti*-aldol adduct 35 in 92 % yield along with 4 % of its diastereomer (Scheme 6). With **35** comprising the required whole carbon skeleton and functional groups, adjustment of the oxidation states of some functional groups was required to complete the target molecule synthesis. After TES protection of **35**, the resulting disilyl acetate was subjected to deacetylation. However, the reaction was very slow and the prolonged reaction time induced desilylation of the primary silyloxy group. As an alternative, the disilyl acetate was desilylated at the primary silyloxy group and deacetylated in one pot, and resilylated at the primary hydroxy group to



***Scheme 5.*** Reagents and conditions. a) TMP·HBr, *n*BuLi, THF, −78 °C, then **30** in THF, −78 °C, 90 %; b) $Me_4NBH(OAc)_3$, AcOH, MeCN, 0 to 25 °C, 80 %; c) triphosgene, Py, $CH_2Cl_2$, −78 to 0 °C, 90 %; d) $Et_3N{\cdot}3HF$, MeCN, 40 °C, 95 %; e) DDQ, pH 7 phosphate buffer, $CH_2Cl_2$, 0 °C, 88 %; f) 1 M aq HCl, THF, 25 °C, 94 %; g) PPTS, $Me_2C(OMe)_2$, $CH_2Cl_2$, 0 °C, 93 %; h) $K_2CO_3$, MeOH, 25 °C, 92 %; i) triphosgene, Py, $CH_2Cl_2$, −78 to 0 °C, 89 %, TMP = 2,2,6,6-tetramethylpiperidine.



***Scheme 6.*** Reagents and conditions. a) TMP·HBr, *n*BuLi, THF, −78 °C, then **3** in THF, −78 °C, 92 %; b) TESOTf, 2,6-lutidine, $CH_2Cl_2$, −78 °C, 94 %; c) PPTS, EtOH, −20 °C, then $K_2CO_3$, −20 to 25 °C; d) TESCl, $Et_3N$, $CH_2Cl_2$, −78 °C, 94 % (over 2 steps); e) AZADO, PhI(OAc)$_2$, $CH_2Cl_2$, Py, 0 to 25 °C, 92 %; f) $Et_3N{\cdot}3HF$, MeCN, 25 °C, 92 %; g) $H_2$, 10 % Pd/C, Amberlite IRA-67, EtOH, 25 °C, 94 %; h) TEMPO, $NaO_2Cl$, NaOCl, pH 6.7 phosphate buffer, $H_2O$, MeCN, 25 °C, then aq $Na_2S_2O_3$, aq $NaHCO_3$, 84 %.

furnish alcohol **36** in 88% overall yield. Compound **36** was oxidized and desilylated to dihydroxy ketone **38** in 85% overall yield. Compound **38** was subjected to hydrogenolysis/hydrogenation conditions using 10% Pd/C or 20% $Pd(OH)_2$/C in EtOH or EtOAc to yield desired lactol **39** together with a less polar compound. The molecular weight of the byproduct corresponded to that of the dehydrated **39**, conceivably being the bicyclic ketal (2,7-dioxabicyclo[2.2.1]heptane) derived from the five-membered lactol alcohol moiety at the right end (Scheme 6). The reaction did not proceed at all in the presence of $NaHCO_3$. When the reaction was performed in the presence of weakly basic Amberlite IRA-67[24] and stopped as soon as the byproduct was detected by TLC, **39** was formed cleanly in 70% yield along with incomplete conversion of intermediate(s). This was resubjected to identical hydrogenolysis/hydrogenation conditions to produce an additional 24% yield of **39**, corresponding to 94% total yield by two cycles. Chemoselective TEMPO oxidation[25] of **39** provided the target natural product inostamycin A **2**, which was isolated as its sodium salt **40** in 84% yield. The $^1$H NMR spectra were identical to those for the natural sample provided by Prof. Imoto at Keio, and the $^{13}$C NMR chemical shift data matched those previously reported.[1] The optical rotation of synthetic **40** was $[\alpha]_D^{22} = +2.5$ ($c = 0.5$, $CHCl_3$), which is comparable with the reported value, $[\alpha]_D^{25} = +2.4$ ($c = 0.5$, $CHCl_3$).[1]

In summary, we have completed the first total synthesis of inostamycin A sodium salt **40** with the longest linear synthetic sequence being 24 steps from butyryl oxazolidinone **13** with a 17.6% overall yield. The synthesis culminated in a highly stereoselective and productive aldol condensation of the large aldehyde **3** with lithium (*E*)-enolate generated from another large ketone **4**. Fragment **3** was assembled through a sequence of *anti*-aldol, in situ 1,3-*syn* reduction and *syn*-aldol reactions starting from the known chiral building block **9**. Fragment **4** was constructed through two remarkably diastereoselective addition reactions between the transmetalated **7** and methyl ketone **8**, and the transmetalated **5** and ethyl ketone **6**. The addition components **5**–**8** were prepared from the readily available chiral substrates **13**, **19**, and **26** through a *syn*-aldol reaction and appropriate derivatization of the functional groups. For example, our synthesis shows the structure of inostamycin A and its absolute configuration.

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**Keywords:** aldol reactions · inostamycin A · quaternary stereocenters · retrosynthesis · total synthesis

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