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Assembly of the Isoindolinone Core of Muironolide A by Asymmetric Intramolecular Diels-Alder Cycloaddition

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Abstract

The hexahydro-1*H*-isoindolin-1-one core of muironolide A was prepared by asymmetric intramolecular Diels Alder cycloaddition using a variant of the MacMillan organocatalyst which sets the C4,C5 and C11 stereocenters.

Marine invertebrates show an astounding repertoire of capabilities in biosynthesis of biologically active macrolides, a capacity likely owed to their associations with stable consortia of marine bacteria that augment biosynthetic expression and sequestration of natural products. Sponge-derived macrolides, like peloruside,^{1a} and halichondrin B,^{1b} have undergone preclinical or clinical trials as antitumor agents. Muironolide A (**1**)² is an uncommon isoindolinone polyketide macrolide isolated from the same specimen of marine sponge, *Phorbas* sp., that earlier afforded phorboxazoles A and B (**2a,b**),³ and phorbasides A–E,⁴ F,⁵ and G–I.⁶

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The nitrogenous polyketide **1** is rare in three ways: it is the singular representative of a natural product with an esterified trichloromethylcarbinol, embodying three ketide segments – two esters and an amide within a macrolide ring– and a rarely-encountered hexahydro-1*H*-isoindolin-1-one heterocycle (hereafter, referred to as an 'isoindolinone'). Muironolide A (**1**) is also scarce: the total yield from the only available specimen of *Phorbas* sp. was 90 µg. Although **1** shows activity against the pernicious fungal pathogen *Cryptococcus neoformans*, the remaining amount of sample precludes further biological evaluation. Recollection of the sponge is not tenable (*Phorbas* sp. has not been encountered again by us or others⁷ since the original isolation of **2a** and **2b**), and total synthesis is the only feasible method to secure additional **1**. We describe here the assembly of the stereo-complex hetero-bicyclic core **3** of muironolide A with control of all three stereocenters in the isoindolinone core of **1**, through asymmetric catalysis.

Inspection of the molecular structure of **1** reveals a potential biosynthesis based on assembly of three ketide units and formation of the isoindolinone core through an intramolecular Diels Alder (IMDA) reaction. The latter inspired a biomimetic approach which is outlined in Scheme 1, proceeding through the isoindolinone enoate ester **3** and the key cyclohexene carboxaldehyde **4**, assembled from IMDA of **5**.

Compound **5**, in turn, is elaborated from the open-ring allylic acetate ester **6**, through intermediates **8–10**, and pentadienoic acid (**7a**) or sorbic acid (**7b**). Asymmetry would be introduced by catalytic IMDA of **5** using MacMillan's imidazolidinones (Figure 1, **11a–c**) which have been proven to promote [4+2] cycloadditions with high enantioselectivity.⁸

We anticipated the role of the *N*-protecting group P¹ (viz. **5**, Scheme 1) would be critical for two reasons: ease of removal near completion of **1**, but primarily to provide steric bias to populate the *s*-cis rotamer of tertiary amide, necessary to achieve the DA transition state. Control of the three stereocenters C4, C5 and C11 in the isoindolinone rings of **1** would follow from the consequences of the *endo* rule and base-promoted epimerization at C4⁹ (c.f. **4**, Scheme 1).

These three objectives were realized through the completion of two pilot syntheses of model isoindolinones – racemic (±)-**12a** and optically enriched (5*R*)-**4** – as described below.

The dienophile precursor, **8** (Scheme 2), for the IMDA reaction was prepared from allylic bromide **10**¹⁰ by S_N2 displacement with *p*-methoxybenzylamine under conditions¹¹ (Cs₂CO₃, DMF) that select for the monoalkylated product (95%). Diene components – pentadienoic acid (**7a**)¹² and commercially available sorbic acid (**7b**) – were separately coupled with **8** and **9** to give tertiary amides **6a,b** in good yields (73% and 80%, respectively). Thermal IMDA of **6a** (toluene, 110 °C) gave only sluggish conversion to the

racemic cycloaddition product ($\pm$)-**6a**. In contrast, microwave-promoted reaction of **12a** (200 °C, chlorobenzene, 30 min), in the presence of a radical inhibitor, gave smooth conversion to ($\pm$)-**12a** in very good yield (86%) but with poor diastereoselectivity (1:2 trans to *cis*). When the product was redissolved in ethanol and subjected to microwave conditions (120 °C), product **12a** (*dr* ~1:2) equilibrated completely to *cis*-**12a** (*dr* > 30:1). Formation of the predominantly *cis*-product suggested α -epimerization of **12a**, similar to that observed during IMDA of allylic sorbates to bicyclic γ -butyrolactones.¹³ The stage was set to explore optimized conditions for asymmetric IMDA.

The precursor asymmetric IMDA was prepared in two steps by methanolysis (K₂CO₃, MeOH) of the acetate ester **6a** to the corresponding allylic alcohol which was oxidized (MnO₂, CH₂Cl₂) to aldehyde **5a**¹⁴ in good overall yield (53% over two steps). Exposure of **5a** to either catalyst **11a** or **11b** (Scheme 2) gave slow [4+2] cycloaddition, a disappointing yield of cycloadduct **4a** (~4%) and poor recovery of starting material, probably due to the tendency of the diene to polymerize.¹⁵ Reasoning that a terminally-substituted diene may fare better in the IMDA, aldehyde **5b** was prepared using the same sequence of reactions and replacement of pentadienoic acid with sorbic acid **11b**. In the presence of catalyst **11b**, aldehyde **5b** underwent clean asymmetric IMDA in good yield (Table 1, Entry 2, 84%), exclusively in *endo* mode, to give mostly (+)-(4*S*,5*R*,8*R*)-**4b**¹⁶ with a lesser amount of (4*R*,5*R*,8*R*)-**4b** (*dr* >20:1), albeit in modest enantiomeric excess (42% ee). The relative configurations of the separated pure isomers (HPLC) were determined from extensive 1D-NOE experiments (Figure 2 and Supporting Information).

Optimization of the asymmetric IMDA (Table 1) was undertaken and, similar to observations by MacMillan,⁸ it was found that the catalyst structure, counterion, and temperature all played important roles in affecting the yield, diastereoselectivity and enantioselectivity. Catalyst **11a** (HCl salt) gave poorer yields of **4b** (Entry 1, 5%), even after 72 h. A slight gain in enantioselectivity in formation of the major epimer 4*S*-**4b** (Entry 3, 50% ee) was seen with catalyst **11b** (HClO₄ salt) when the temperature was lowered from 23 °C to 10 °C, however, at the expense of lower yield, diastereoselectivity (60%, *dr* 6:1) and reaction time (57 h instead of 4.5 h).

Gratifyingly, *N*-(2-hydroxy-1-ethyl)-imidazolidone **11c**, a MacMillan-type catalyst reported by Kristensen and coworkers¹⁷ as an intermediate in the preparation of copolymer-supported catalysts, gave the best outcomes.¹⁸ Under conditions similar to those used with **11b** (Entry 2), IMDA of **5b** in the presence of **11c** (20 mol %, 23 °C, Entry 5) gave (+)-**4b** with almost double the enantioselectivity (72% ee), albeit with lower diastereoselectivity (73%, *dr* = 3.8:1). Optimal conditions for IMDA of **5b** (Entry 9, 20 mol% **11c**, 0 °C, 73 h) gave **4b** (84% yield, *dr* = 6:1, 88% ee).¹⁹ Base treatment of **4b** (DBU, C₆D₆, 23 °C, 13 h, Scheme 3) epimerized C4 and inverted the 4*R*:4*S* ratio to >20:1 in favor of the configuration required for **1**.²⁰ Thus, pure (+)-(4*R*,5*R*,8*S*,11*S*)-**4b** was obtained in 70% yield over two steps after preparative HPLC.

The steric bulk of the *N*-protecting group influences the outcome of the IMDA reaction through torsional strain that also populates the required *s-cis* conformation of the tertiary amide. Replacement of the *N*-PMB protecting group with a 2,4-dimethoxybenzyl group (*N*-

DMB) was investigated to determine the effect on yield, enantio- and stereo-selectivity. Compound **5c**, prepared from **9** using a similar sequence for **5b**, was treated with **11c** (20 mol%, 3 °C, 54 h) to afford **4c** in 67% yield, with slightly lower enantioselectivity (84% ee) but with high 4*S*:4*R* diastereoselectivity (*dr* >20:1).²¹

The kinetics of base-equilibration of purified (4*S*,8*R*)-**4b** (DBU, C₆D₆, 23 °C, Scheme 3 and Supporting Information) were briefly investigated. ¹H NMR revealed rapid conversion of the (4*S*,8*R*)-**4b** to the more stable isomer (4*R*,8*R*)-**4b**,²² and finally, slower conversion of the latter to a third isomer, (4*R*,8*S*)-**4b**.

At equilibrium in C₆D₆ (12 h), (4*S*,8*R*)-**4b** was absent and the relative concentration of (4*R*,8*R*)-**4b** to (4*R*,8*S*)-**4b** was 2:1. Interestingly, very rapid epimerization of C4 was observed with NaH (DMF, 23 °C, 15 min) with complete conversion of (4*S*,8*R*)-**4b** to a mixture of (4*R*,8*R*)-**4b** and (4*R*,8*S*)-**4b** (*dr* = 4:1). Deuterium incorporation studies (NaOCD₃, CD₃OD) confirmed that H4 was rapidly exchanged for D followed by slower replacement of H8, consistent with the higher p*K*_a of the H8 in the β,γ-unsaturated lactam.

No conjugated double bond isomers of **4b** were detected under any of the isomerization conditions tried (NaOMe-MeOH, DBU-benzene, NaH-DMF). Attempted kinetic trapping of the dienolate generated from **4b** with strong base (KHMDs, -78 °C; 1 equiv CH₃COOH) returned only starting materials as a mixture of C4 and C8 epimers.^{23,24} From these results, we deduced that enolization of the IMDA product occurred by deprotonation-reprotonation at C8, but the β,γ-double bond isomer is more stable than the conjugated isomer.²⁵

Finally, aldehyde **4b** was chain-extended (Scheme 4) by Horner-Wadsworth-Emmons reaction under Roush-Masamune conditions²⁶ to give exclusively *E*-**3** in 86% yield.

In summary, a simple stereocontrolled route to **3**, embodying the isoindolinone core of muironolide A (**1**), was achieved by asymmetric intramolecular Diels-Alder cycloaddition of an acyclic trienal precursor catalyzed by **11c**.

Efforts towards extending the IMDA approach to completion of **1** are underway in our laboratories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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14. Contained ~5–10% of the Z-isomer.
15. Inclusion of a radical inhibitor **C** (Scheme 1) did not suppress formation of polymer; therefore, the mechanism of polymerization is likely ionic in nature.
16. The absolute configuration follows from the expected sense of asymmetric induction demonstrated by MacMillan and coworkers. Ref 8.
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18. Catalyst **11c** is more conveniently prepared from L-phenylalanine methyl ester and inexpensive ethanolamine than **11a,b** which requires the more expensive, 'controlled substance', MeNH₂.
19. The hydroxyethyl side chain in **11c** may play an important role in stabilizing either the transition state by hydrogen bonding, or through intramolecular nucleophilic capture of the incipient iminium ion.
20. The relative configurations of (4*S*,8*R*)-**4b** and (4*R*,8*R*)-**4b** were assigned by 1D NOESY studies.
21. See Supporting Information, Table S1 for optimization of conditions for IMDA of **5c** to give **4c**.
22. The cyclohexene ring conformation changed to a pseudo-boat.
23. Clearly, the biosynthesis of **1** favors the α,β -unsaturated lactam. Models show that the macrolide ring adopts a 'ring flipped' cyclohexene half-chair compared to models of **4b** in which the C4 and C5 substituents are held in the pseudo-equatorial orientation, which may favor the conjugated lactam.
24. Alternative methods can be used to move the C=C double bond into conjugation with the lactam C=O as required for **1** (e.g. hydrogenation α -selenation, followed by H₂O₂ oxidation-selenoxide elimination).

25. Molecular modeling and semi-empirical calculations (PM3) of enthalpies of formation of models of **4** (the *N*-protecting group was removed for simplicity) show that the non-conjugated isomers are *disfavored* over the α,β -conjugated isomers by $\sim 1 \text{ kcal.mol}^{-1}$.
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Figure 1.

MacMillan organocatalysts **11a,b** (Ref 8) and Kristensen's derivative **11c** (Ref 17).

Figure 2.

1D-NOE of (4*S*)- and (4*R*)- isomers of **4b** (mixing time, t_m = 400 mS). Numbering follows that of **1** (see Ref 2).

$R^2 = \text{H, alkenyl, Me}$; $P^1\text{--}P^4 = \text{protecting groups}$ **7a** $R^2 = \text{H}$; **7b** $R^2 = \text{Me}$

Scheme 1.
Biomimetic approach to **1**: retrosynthetic analysis.

Scheme 2.

Synthesis of isoindolinones ($\pm$)-**12a** and **4a–c** by intramolecular Diels-Alder cycloaddition (IMDA).^aprepared from the acid chloride of **7b**. ^byield over two steps.

Scheme 3. Base-promoted isomerization of (4*S*,8*R*)-**4b**.

Scheme 4.
Chain extension of aldehyde (*4R,8R,11S*)-**4b**.

Table 1

Optimization of asymmetric IMDA of **5b** using MacMillan type catalysts (see Figure 1 and Scheme 2).

entry	catalyst	11-HX ^a	temp, °C	time, h	yield, % ^b	dr ^c 4S-4b:4R-4b % ee ^d
1	11a	HCl	23	72	5	1.6:1 14
2	11b	HClO ₄	23	4.5	84	>20:1 42
3	11b	HClO ₄	10	57	60	6:1 50
4	11c	HCl	23	36	38	1.1:1 10
5	11c	HClO ₄	23	40	73	3.8:1 72
6	11c	CF ₃ COOH	23	39	25	2.6:1 78
7	11c	HClO ₄	23	6	48	10:1 52
8	11c	CF ₃ COOH	23	18	86	3.4:1 36
9	11c	HClO ₄	0	84	73	6:1 88
10	11c	HClO ₄	10	48	69	4:1 71
11	none	–	80	90	83 ^e	3.2:1 ^f

^a 20 mol% catalyst, CH₃CN, 2% H₂O, [**5b**] = 0.5 M.

^b Combined isolated yield of 4S- and 4R-isomers.

^c From ¹H NMR integrations.

^d % ee of major isomer, determined by chiral HPLC (Chiracel OD, 3:7 *i*-PrOH-hexane).

^e carried out in toluene.

^f racemic product.