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

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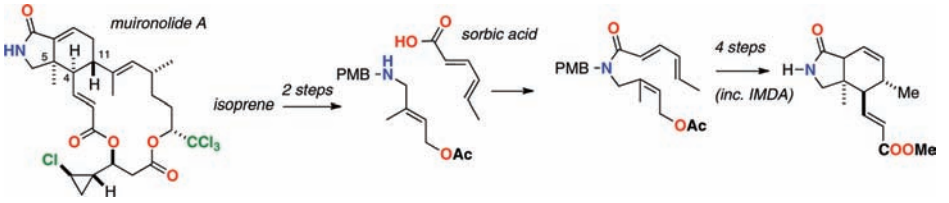
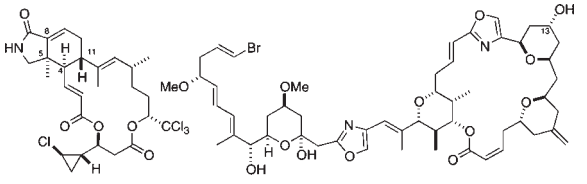
ABSTRACT



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]



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

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(1) (a) West, L. M.; Northcote, P. T.; Battershill, C. N. *J. Org. Chem.* **2000**, *65*, 445. (b) Bai, R. L.; Paull, K. D.; Herald, C. L.; Malspeis, L.; Pettit, G. R.; Hamel, E. *J. Biol. Chem.* **1991**, *266*, 15882.

(2) Dalisay, D. S.; Morinaka, B. I.; Skepper, C. K.; Molinski, T. F. *J. Am. Chem. Soc.* **2009**, *31*, 7552.

(3) (a) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126. (b) Searle, P. A.; Molinski, T. F.; Brzezinski, L. J.; Leahy, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 9422. (c) Molinski, T. F. *Tetrahedron Lett.* **1996**, *37*, 7879.

(4) (a) MacMillan, J. B.; Xiong-Zhou, G.; Skepper, C. K.; Molinski, T. F. *J. Org. Chem.* **2008**, *73*, 3699. (b) Skepper, C. K.; MacMillan, J. B.; Zhou, G. X.; Masuno, M. N.; Molinski, T. F. *J. Am. Chem. Soc.* **2007**, *129*, 4150. (c) MacMillan, J. B.; Xiong-Zhou, G.; Molinski, T. F. *J. Org. Chem.* **2008**, *73*, 3699.

(5) Dalisay, D. S; Molinski, T. F. *J. Nat. Prod.* **2009**, *72*, 739.

(6) Dalisay, D. S; Molinski, T. F. *J. Nat. Prod.* **2010**, *73*, 679.

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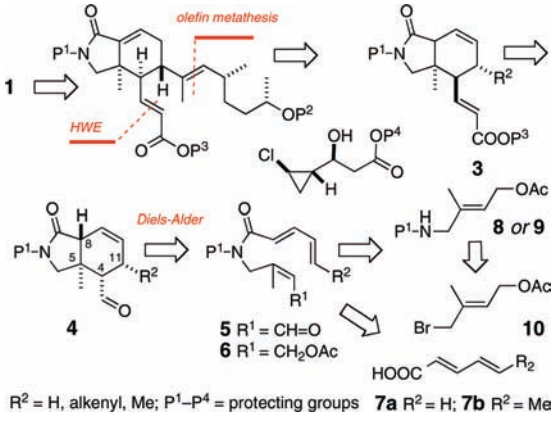
been encountered again by us or others[7] since the original isolation of **2a** and **2b**), and total synthesis is the only feasible method to secure additional **1**. We describe here the assembly of the stereocomplex heterobicyclic core **3** of muironolide A with control of all three stereocenters in the isoindolinone core of **1**, through asymmetric catalysis.

Scheme 1. Biomimetic Approach to **1**: Retrosynthetic Analysis



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**.

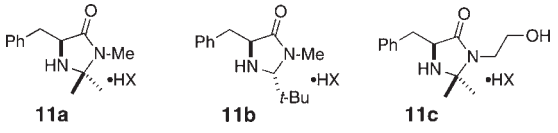


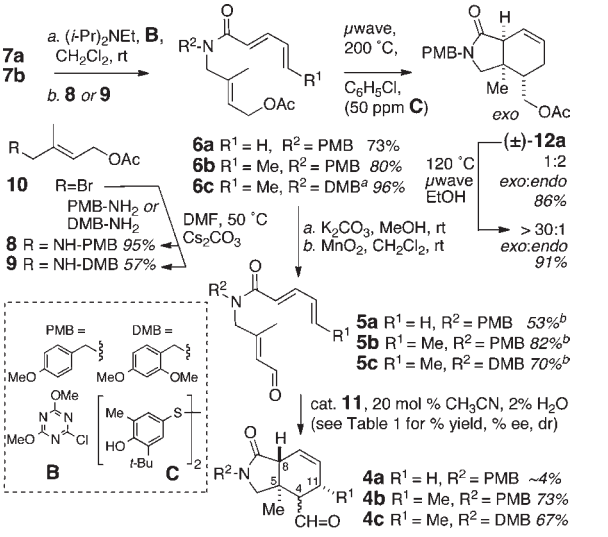
Figure 1. MacMillan organocatalysts **11a**,**b** (ref 8) and Kristensen's derivative **11c** (ref 18).

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 P^1 (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 C4[9] (*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.

Scheme 2. Synthesis of Isoindolinones (±)-**12a** and **4a**–**c** by Intramolecular Diels–Alder Cycloaddition (IMDA)[a,b]



[a] Prepared from the acid chloride of **7b**. [b] Yield over two steps.

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 conditions[11] (Cs_2CO_3, 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

(7) Capon, R. J.; Skene, C.; Liu, E. H.; Lacey, E.; Gill, J. H.; Heiland, K.; Friedel, T. *Nat. Prod. Res* **2004**, *18*, 305. This report of occurrence of **2a**,**b** in a sponge identified as *Raspailia* sp. from the Indian Ocean some 1200 km south of the site of collection of *Phorbas* sp. provokes the intriguing speculation that the two sponges are one and the same and that *Raspailia* sp. may contain **1**.

(8) (a) Wilson, R. M.; Jen, W. S.; MacMillan, D. *J. Am. Chem. Soc.* **2005**, *127*, 11616. (b) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

(9) IMDA of α,β-unsaturated aldehydes with MacMillan organocatalysts does not always conserve the α,β-relative configuration of the starting trienal.

(10) Prepared by 1,4-addition of the elements of Br and OAc to isoprene (NBS, AcOH). Babler, J. H.; Buttner, W. J. *Tetrahedron Lett.* **1976**, *17*, 239.

(11) (a) Salvatore, R. N.; Nagle, A. S.; Schmidt, S. E.; Jung, K. W. *Org. Lett.* **1999**, *1*, 1893. (b) Salvatore, R. N.; Nagle, A. S.; Schmidt, S. E.; Shin, S. I.; Nagle, A. S.; Worrell, J. H.; Jung, K. W. *Tetrahedron Lett.* **2000**, *41*, 9705. (c) Salvatore, R. N.; Nagle, A. S.; Jung, K. W. *J. Org. Chem.* **2002**, *67*, 674.

(12) (a) Idoux, J. P.; Ghane, H. *J. Chem. Eng. Data* **1979**, *24*, 157. (b) Jessup, P. J.; Petty, C. B.; Roos, J.; Overman, L. E. *Org. Synth.* **1988**, *6*, 95.

racemic cycloaddition product (±)-**12a**. In contrast, microwave-promoted reaction of **6a** (200 °C, chlorobenzene, 30 min), in the presence of a radical inhibitor, gave smooth conversion to (±)-**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 optimzed conditions for asymmetric IMDA.

The precursor asymmetric IMDA was prepared in two steps by methanolysis (K_2CO_3, MeOH) of the acetate ester **6a** to the corresponding allylic alcohol which was oxidized (MnO_2, CH_2Cl_2) 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** ($HClO_4$ 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 co-workers[17] 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, C_6D_6, 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.

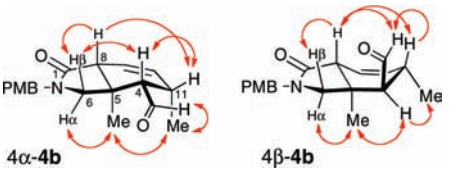
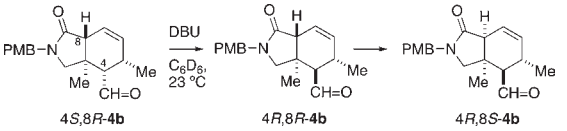


Figure 2. 1D-NOE of (4*S*)- and (4*R*)- isomers of **4b** (mixing time, t_m = 400 mS). Numbering follows that of **1** (see ref).

Scheme 3. Base-Promoted Isomerization of (4*S*,8*R*)-**4b**



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 determined the effect on yield, enantio- and stereoselectivity. 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, C_6D_6, 23 °C, Scheme 3 and Supporting Information) were briefly investigated. ^{1}H 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**.

(13) (a) Wu, J.; Yu, H.; Wang, Y.; Xing, X.; Dai, W.-M. *Tetrahedron Lett*. **2007**, *48*, 6543. (b) Guy, A.; Lemaire, M.; Guiette, M. *Tetrahedron Lett*. **1985**, *26*, 3575. (c) Boeckman, R. K., Jr.; Demko, D. M. *J. Org. Chem*. **1982**, *47*, 1789. (d) Martin, S. F.; Williamson, S. A.; Gist, R. P.; Smith, K. M. *J. Org. Chem*. **1983**, *48*, 5170.

(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 McMillan and co-workers.

(17) Kristensen, T. E.; Vestli, K.; Jakobsen, M. G.; Hansen, F. K.; Hansen, T. *J. Org. Chem*. **2010**, *75*, 1620–1629.

(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" $MeNH_2$.

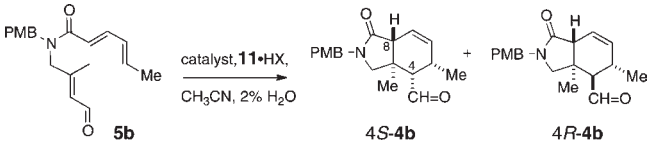
(19) The hydroxyethyl side chain in **11c** may play an important role in stabilizing either the transition state by hydrogen bonding or through intramolecular nucleophilic capture of the incipient iminium ion.

(20) The relative configurations of (4*S*,8*R*)-**4b** and (4*R*,8*R*)-**4b** were assigned by 1D NOESY studies.

(21) See Table S1, Supporting Information, for optimization of conditions for IMDA of **5c** to give **4c**.

(22) The cyclohexene ring conformation changed to a pseudoboat.

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] 4*S*-**4b**/4*R*-**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_3COOH	23	39	25	2.6:1	78
7	**11c**	$HClO_4$	23	6	48	10:1	52
8	**11c**	CF_3COOH	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]

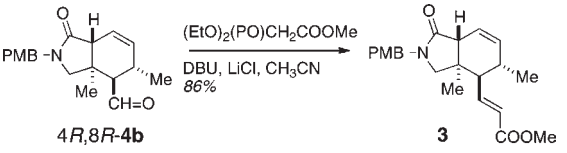
[a] 20 mol % catalyst, CH_3CN, 2% H_2O, [**5b**] = 0.5 M. [b] Combined isolated yield of 4*S*- and 4*R*-isomers. [c] From ^1H NMR integrations. [d] % ee of major isomer, determined by chiral HPLC (Chiracel OD, 3:7 *i*-PrOH−hexane). [e] Carried out in toluene. [f] Racemic product.

At equilibrium in C_6D_6 (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 ($NaOCD_3$, CD_3OD) confirmed that H4 was rapidly exchanged for D followed by slower replacement of H8, consistent with the higher pK_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 CH_3COOH) 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 conditions[26] to give exclusively *E*-**3** in 86% yield.

Scheme 4. Chain Extension of Aldehyde (4*R*,5*R*,8*R*,11*S*)-**4b**



In summary, a simple stereocontrolled asymmetric 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 toward extending the IMDA approach to completion of **1** are underway in our laboratories.

Acknowledgment. We thank B. Morinaka for assistance with NMR measurements, J. Pigza for helpful discussions, J. Haeckl and B. Ruby for preparation of some catalysts and intermediates, Y. Su for HRMS measurements (all UCSD), and R. New (UC Riverside) for additional MS data. This work was supported by the NIH (AI-039987, CA-122256).

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.

(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 pseudoequatorial 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 H_2O_2 oxidation−selenoxide elimination).

(25) Molecular modeling and semiempirical calculations (PM3) of enthalpies of formation of models of **4** (the *N*-protecting group was removed for simplicity) show that the nonconjugated isomers are *disfavored* over the α,β-conjugated isomers by ~1 kcal·mol^{-1}.

(26) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett*. **1984**, *25*, 2183.