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Enantioselective Synthesis of the Bromopyrrole Alkaloids Manzacidin A and C by Stereospecific C−H Bond Oxidation

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Bromopyrrole alkaloids comprise a large and varied class of marine natural products possessing interesting and potentially useful pharmacological activities as α-adrenoreceptor blockers, seretonin antagonists, and actomyosin ATPase activators.[1] The manzacidins, A, B, and C (**1a**−**c**), represent one small family of such compounds isolated as bioactive constituents of the Okinawan sponge, *Hymeniacidon* sp (Figure 1).[2,3] Subsequent evaluation of these metabolites as possible therapeutic leads has been precluded by the lack of available material from natural sources, thus motivating efforts to prepare such structures through total synthesis.[4] Our own interest in formulating a route to the manzacidins is stimulated further by the unusual chemical structures of these targets, which consist of a uniquely substituted tetrahydropyrimidine core.[5] Recently, we have described a new method for saturated C−H bond functionalization that makes possible the stereospecific installation of tetrasubstituted carbinolamines.[6] By employing this chemistry, a rapid, enantioselective, and high throughput synthesis of both manzacidins A and C has been achieved. In all, the demonstrated work highlights the distinct power of C−H amination methodology for simplifying problems in alkaloid synthesis.

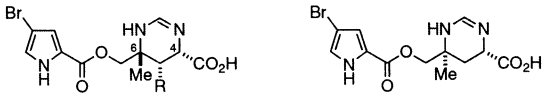


Figure 1. Bromopyrrole alkaloids from *Hymeniacidon* sp.

Oxidative C−H insertion of sulfamate esters under Rh catalysis occurs efficiently and with absolute retention of configuration at stereodefined tertiary centers (Figure 2).[6a] The product oxathiazinane heterocycles **4** can be activated for facile nucleophilic ring opening to give myriad 1,3-difunctionalized amine products.[6a,7] Application of this reaction sequence toward the synthesis of manzacidin A thus leads to the identification of sulfamate ester **3** as a viable precursor to the natural product. In principle, sulfamate **3** and its C6 epimer (manzacidin numbering) could be fashioned from a common synthetic intermediate, thereby facilitating a synthesis of both manzacidins A and C through this stereospecific C−H insertion strategy. Accordingly, homoallyl alcohol **2** was considered an optimal starting material for our synthesis, as selective hydrogenation of the prochiral alkene could afford either of the desired C6-methyl diastereomers.[8]

Homoallyl alcohol **5** is readily available from ethyl glyoxylate on a preparative scale (20 g) and in >90% ee through application of an extremely efficient Evans' asymmetric ene reaction.[9] With access to this compound, directed olefin hydrogenation was first

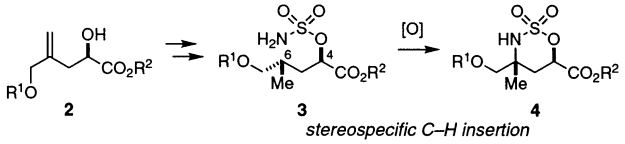
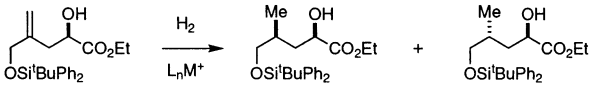


Figure 2. Sulfamate ester insertion to install the tetrasubstituted C6 stereocenter.

Table 1. Selected Hydrogenation Reactions of Alcohol **5**



entry	catalyst[a]	ligand	**6a/6c**[b]
1	5% Pt-C	none	50:50
2	$(Ph_3P)_3RhCl$	none	50:50
3	$Ir[(cod)(pyr)(PCy_3)]PF_6$	none	65:35
4	**$Rh(cod)_2OTf$**	**(*R*)-PHANEPHOS**[c]	**75:25**
5	$Rh(nbd)_2BF_4$	dppb	40:60
6	$Rh(nbd)_2BF_4$	(*R*)-BINAP	20:80
7	**Rh[(*S*,*S*)-Et-DUPHOS)(cod)]OTf**	none	**>5:95**

[a] With the exception of entry 1, which was performed in C_6H_6 at 1 atm H_2, all other reactions were conducted in CH_2Cl_2 at ca. 1000 psi H_2 (yields are essentially quantitative). [b] Product ratio determined by ^1H NMR integration of the unpurified reaction mixture. [c] PHANEPHOS = 4,12-bis(diphenylphosphino)-[2.2]-paracyclophane.

explored using catalytic $(Ph_3P)_3RhCl$ at varying H_2 pressures (Table 1).[8b] All conditions tested, however, afforded a stereorandom mixture of **6a** and **6c**.[10] Fortunately, the application of chiral phosphine ligands in combination with cationic Rh(I) sources and **5** provided a favorable solution to this problem.[8a,10] As highlighted in Table 1, either epimeric product may be prepared with good selectivity depending on the choice of chiral catalyst.[11] Following sulfamoylation of the hydrogenated products **6a**/**6c** (see Scheme 1), the individual diastereomers can be isolated as stereopure materials.[12] As observed first with sulfamate **7a**, oxidative cyclization proceeds smoothly and stereospecifically with 2 mol % $Rh_2(OAc)_4$ and 1.1 equiv of $PhI(OAc)_2$ to generate the crystalline oxathiazinane product **8a** in 85% yield. The combined four-step process to **8a** commencing from ethyl glyoxylate enables synthesis of >5 g of the oxathiazinane in a single throughput.

Reaction of oxathiazinane **8a** with Boc_2O and pyridine is performed as a first step toward completion of the manzacidin A synthesis (Scheme 1). The unpurified carbamate **9a** is treated directly with NaN_3 (DMF, 25 °C) to give the ring-opened product (92%, two steps). Sequential reduction of the azido moiety in **10a** and acylation of the resulting amine occur in one operation and generate formamide **11a** quantitatively.[13] A significant obstacle was encountered, however, with the subsequent cyclodehydration of the

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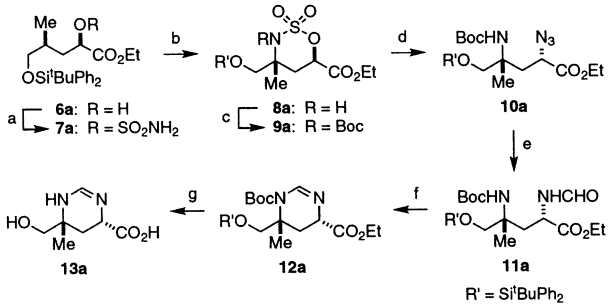
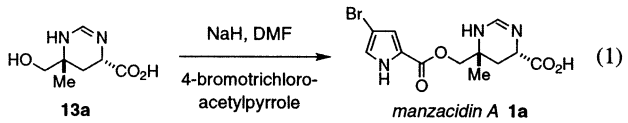
Scheme 1[a]



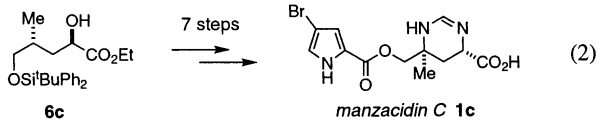
[a] Conditions: (a) $ClSO_2NCO$, HCO_2H, 87% (3:1 mixture of C6 epimers); (b) 2 mol % $Rh_2(OAc)_4$, $PhI(OAc)_2$, MgO, CH_2Cl_2, 85%; (c) Boc_2O, C_5H_5N; (d) NaN_3, DMF, 92%, two steps; (e) H_2, Pd−C, then *N*-formylbenzotriazole; (f) $POCl_3$, 2,6-^{t}Bu$_2$-4-MeC_5H_2N, 73%, two steps; (g) 8 M HCl, DME, 60 °C, $NaHCO_3$, 60 °C, 99%.

C6 Boc-amine onto the C4 formyl unit. This problem was exacerbated by the fact that little precedent exists for the assembly of stereochemically complex tetrahydropyrimidine ring systems and by our desire to formulate a protocol that would leave in place the Boc-protecting group so as to facilitate purification of the highly polar heterocycle.[14] A screen of several dehydrating agents revealed neat $POCl_3$ with 0.75 equiv of 2,6-di-*tert*-butyl-4-methylpyridine as an optimal solution.[15] Under these conditions, the tetrahydropyrimidine **12a** is produced with the Boc group intact and without attendant epimerization at C4 (73% from **10a**). This compound may be easily purified by chromatography on silica gel prior to performing the final deprotection and bromopyrrole acylation steps.



(1)

Cleavage of the Boc, silyl ether, and ester groups in **12a** is most easily accomplished with 8 M HCl (DME, 60 °C). These conditions, although somewhat forcing, provide the core structure of **1a** in near quantitative yield. Following the precedent of Ohfune, the resultant acid-alcohol **13a** reacts with excess NaH and 4-bromotrichloroacetylpyrrole to afford manzacidin A as a white solid (90% from **12a**, eq 1), a compound identical in all respects to the natural product (^{1}H and ^{13}C NMR, IR, HRMS, $[\alpha]_D$).[4,16] Altogether, the synthetic route to **1a** comprises 10 linear steps from ethyl glyoxylate with an overall yield of 28% and has enabled the preparation of >350 mg of the desired target in a single pass. Through an identical strategy beginning with sulfamate **6c**, an equivalent amount of manzacidin C has been prepared (32% overall, eq 2).[17]



(2)

The synthesis of manzacidins A and C demonstrates for the first time the efficacy of Rh-catalyzed sulfamate ester insertion reactions in the context of complex natural product synthesis. Problems encountered with the generation of optically pure tetrasubstituted carbinolamines are conveniently addressed through the application of stereospecific C−H amination methods developed by our lab, and, as such, synthetic analysis of the manzacidins is greatly simplified. In addition to highlighting this unique oxidation chemistry, the path to these natural products showcases the application of modern asymmetric methods for carbonyl-ene and directed hydrogenation reactions, and the delineation of a novel experimental protocol for tetrahydropyrimidine synthesis. The facile preparation of hundreds of milligrams of these scarce natural products offers testament to the power of these combined methodologies.

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Supporting Information Available: Experimental details and analytical data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Synthetic **1a**: $[\alpha]^{27}_D = -26.5°$ ($c = 0.65$, MeOH). Natural **1a**: $[\alpha]^{27}_D = -28°$ ($c = 0.67$, MeOH).
(17) In agreement with Ohfune's findings (ref 4), the optical rotation of **1c** ($[\alpha]^{27}_D = +98°$ ($c = 0.76$, MeOH)) differs substantially from the value reported for the isolated natural product ($[\alpha]^{27}_D = +37°$ ($c = 0.23$, MeOH)). This discrepancy may be attributed to impurities in natural **1c**.

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