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Diastereoselective synthesis of the polyol-containing side chain of the *ent*-bengamides

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Abstract—The synthesis of the non-natural antipode of the bengamide polyol-containing side chain has been achieved utilizing a diastereoselective oxygenated-enolate aldol reaction as the key step. A substrate-controlled reduction was used to complete the stereochemical array.

1. Introduction

The bengamides are a caprolactam-containing family of natural products isolated from *Jaspis* sponges, of which there are currently twenty-four known members.[1] The various bengamides differ in the constitution of the caprolactam terminus, but share a common *syn–syn–anti* polyol-containing side chain (Fig. 1). Some of the bengamides have shown potentially useful antiproliferative activity (<100 nM) as well as striking differential cytotoxicity.[2] Their interesting biological profile, coupled with the restricted supply of material from natural sources, has made these molecules popular targets for total synthesis.[3] In this communication, we disclose a new approach to the synthesis of the bengamide side chain utilizing the diastereoselective oxygenated-enolate aldol reaction discovered by Carda and Marco[4] as the critical step.

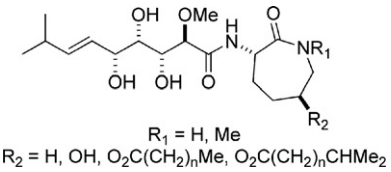

Figure 1. The bengamide family.

2. Discussion

We chose to focus our efforts on the synthesis of the unnatural antipode of the side chain due to the accessibility of starting materials.[5] The synthesis began with a diastereoselective aldol reaction of ketone **1** with cinnamaldehyde using the conditions described by Carda and Marco (Scheme 1).[4] The reaction, which presumably proceeds via an *E*-boron enolate, provided the desired *syn–anti* aldol adduct **2** with good yield and diastereoselectivity.[6] Treatment of the aldol adduct with Meerwein's salt and proton sponge provided the methyl ether **3**.[7] All that remained to construct the fully elaborated stereochemical array of the bengamide side chain was to perform a diastereoselective *syn*-reduction of the ketone. Gratifyingly, treatment of the ketone with sodium borohydride at low temperature successfully reduced the ketone with a high level of diastereocontrol to provide the protected *syn–syn–anti* pentaols **4** and **5** as a mixture of silyl migration isomers. During the reaction, a small amount of the benzoyl migration product **6** was also formed, and when the reaction was performed on large scale significant quantities of this side product could be isolated. Fortuitously, this side product was crystalline and X-ray crystallographic analysis of **6** verified the stereochemical assignment. To confirm that **6** was not formed from a minor isomer in either the aldol or the reduction steps, **4** and **6** were both converted to the identical *tris*-benzoyl ester **7** by benzoylation.

A series of protecting group interconversion steps provided *tris*-TBS ether **8** which was now differentially functionalized at the two termini for completion of the

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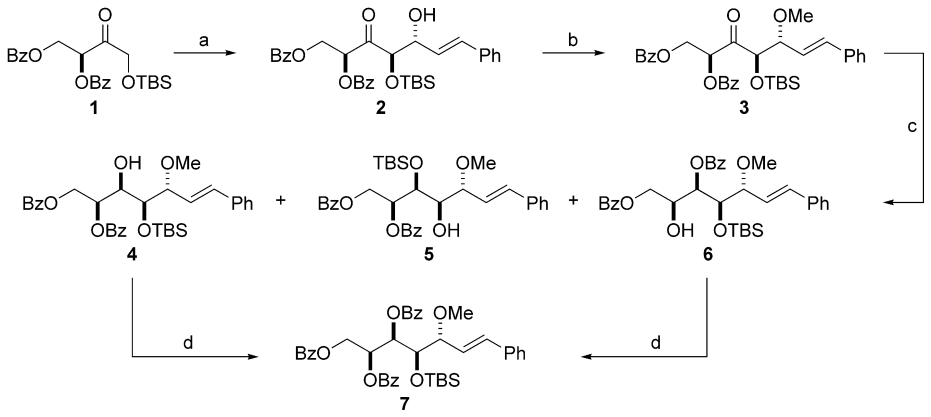
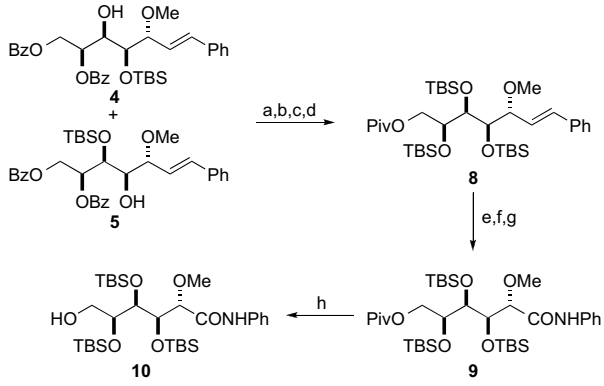
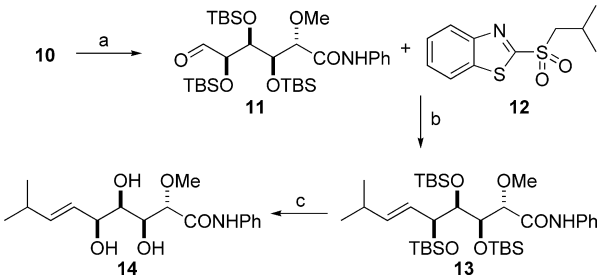


Scheme 1. Reagents and conditions: (a) Cy_2BCl, Et_3N, PhCH=CHCHO, Et_2O, 0 °C, 9:1 dr, 93%; (b) $Me_3O{\cdot}BF_4$, proton sponge, 60%; $NaBH_4$MeOH, −78 °C, >95:5 dr, 73% (combined), 2.5:1 **4**:**5** + traces of **6**; (d) BzCl, pyr, DMAP.



Scheme 2. Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 74%; (b) Dibal-H, CH_2Cl_2, −78 °C, 49%; (c) PivCl, pyr, CH_2Cl_2, 0 °C, 65%; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 80%; (e) O_3, pyr, MeOH/CH_2Cl_2, −78 °C then DMS, −78 °C to rt; 80% (f) $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, Me_2C=CHMe, H_2O/^{t}BuOH; (g) $(COCl)_2$ DMF, CH_2Cl_2 then aniline, pyr/CH_2Cl_2, 79% (two steps); (h) MeLi, Et_2O, 0 °C, 44% (82% brsm).



Scheme 3. Reagents and conditions: (a) SO_3·pyr, ^{i}Pr$_2$NEt, DMSO, CH_2Cl_2, −30 °C 95%; (b) LiHMDS, DME, −78 °C to rt, >20:1 *E*:*Z*; (c) TBAF, THF, 41% (two steps).

synthesis (Scheme 2).[8] The styryl moiety was converted to carboxamide **9** by sequential ozonolysis of the double bond, oxidation of the resulting aldehyde, and amide formation via an intermediate acid chloride.[9] Removal of the pivaloyl protecting group, however, proved somewhat troublesome. Use of nucleophilic hydride sources (e.g., Dibal) resulted in competitive reduction of the amide functionality. An acceptable solution, however, was found when **9** was treated with methyllithium.[10] In this case, the reaction had to be quenched at incomplete (~50–60%) conversion; at higher levels of conversion, alcohol **10** was isolated as a mixture of α-epimers along with a significant quantity of α,β-unsaturated amide (formed by elimination of the β-siloxy group). It is likely that as the reaction slows at high levels of conversion, the formed alkoxide competitively acts as a base leading to α-epimerization and elimination.[11] Nonetheless, when the reaction is arrested at incomplete conversion, alcohol **10** can be isolated in acceptable yield as a single epimer and the overall mass recovery allows this to be a viable process.

The synthesis was completed using the Julia olefination conditions developed by Banwell.[3i] Following Parikh–Doering oxidation[12] of alcohol **10**, the resulting aldehyde was treated with the lithium anion of sulfone **12**[3i] (3 equiv) to provide olefin **13** with exceptional control of the alkene geometry. Removal of the silyl groups using TBAF completed the synthesis of triol **14** (see Scheme 3).

In summary, a diastereoselective synthesis of the polyol-containing side chain of the bengamides has been accomplished utilizing the substrate-controlled oxygenated-enolate aldol reaction developed by Carda and Marco. The synthesis is also highlighted by a substrate-controlled borohydride reduction to complete the stereochemical array.

Acknowledgements

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