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## $\alpha,\beta$ -Unsaturated $\beta$ -Silyl Imide Substrates for Catalytic, Enantioselective Conjugate Additions: A Total Synthesis of (+)-Lactacystin and the Discovery of a New Proteasome Inhibitor

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Enantioenriched  $\beta$ -silyl carboxylic acid derivatives are versatile building blocks for organic synthesis,<sup>1</sup> allowing subsequent diastereoselective transformations<sup>2</sup> and the possibility of stereospecific Si-C bond oxidation.<sup>3</sup> To date, enantioselective routes to these compounds have relied mainly on auxiliary-based methods.<sup>4</sup> Asymmetric, catalytic conjugate addition of C-centered nucleophiles to  $\beta$ -silyl- $\alpha$ , $\beta$ -unsaturated acid derivatives represents a most attractive, but relatively undeveloped, alternative.<sup>5,6</sup> We describe here the application of a new  $\beta$ -silyl unsaturated imide in highly enantioselective, catalytic Michael additions. This methodology serves as the basis for a concise total synthesis of the natural product (+)-lactacystin and of a new, synthetic 26S proteasome inhibitor with comparable activity to omuralide.

Aluminum salen complexes, such as  $\mu$ -oxo dimer **1**, have proven effective for a variety of asymmetric catalytic conjugate additions,<sup>7</sup> including Michael reactions of electron-deficient nitrile nucleophiles with  $\alpha,\beta$ -unsaturated imides.<sup>8</sup> Addition of aminocyanoacetate derivatives can result in direct formation of  $\gamma$ -lactam derivatives with high enantio- and diastereoselectivity. We recognized the potential applicability of this methodology to the preparation of important  $\gamma$ -lactam-containing natural products, such as the proteasome inhibitor lactacystin (2).9 Over the last 14 years since Corey first accomplished the total synthesis of  $2^{10}$ , there have been numerous approaches to lactacystin reported, including several elegant asymmetric catalytic routes.<sup>11,12</sup> One of the key challenges in any lactacystin synthesis is the efficient, stereoselective construction of the functionalized  $\gamma$ -lactam. In evaluating this target, we considered methods by which asymmetric catalysis could allow quick access to a core lactam structure amenable to further elaboration. In particular, use of a  $\beta$ -silyl imide substrate in an asymmetric 1.4-addition (Figure 1) could provide an appropriately functionalized intermediate for the synthesis of 2 and related structures, and might further allow general access to a variety of useful  $\beta$ -silyl carboxylic acid derivatives in enantioenriched form.

Initial screening of (N-p-methoxybenzylamino) cyanoacetate addition to various  $\alpha,\beta$ -unsaturated  $\beta$ -silvl imides in the presence of 10 mol % of (R,R)  $\mu$ -oxo dimer 1 led to the identification of allyldimethylsilyl imide  $4^{13}$  as a promising substrate (95% ee, 5:1 dr, 28% yield).14 Increasing the amount of tert-butyl alcohol (from 1.2 to 2.0 equiv relative to imide) and lowering reaction concentration (from 0.5 to 0.1 M) led to substantially improved product yields while maintaining high enantioselectivity (Table 1, entry 1). The synthesis of lactam 5a was performed on either milligram or multigram scale with similar results. Gratifyingly, a variety of other nitrile-bearing nucleophiles also underwent reaction with 4 with high enantioselectivity under the optimized conditions (entries 2-8). Both unsubstituted and aryl-substituted cyanoacetate derivatives are useful substrates, in the latter case affording enantioenriched products bearing quaternary stereocenters with good diastereoselectivity (entries 5-7).



Figure 1. Retrosynthesis of (+)-lactacystin.

Table 1. Enantioselective Conjugate Additions to Silyl Imide 4

Si Me M	N Ph + 4 (0.1 M)	NC E [(saler R (1, 10 R f-BuOH nucleophile cyclohex	(S,S)-(salen) (S,S)-(salen) mol%) ► 5a-g (2.0 equiv) aane, 23 °C t-Bu		
entry	nucleophile	time/catalyst	product	yield (%) <sup>a</sup>	ee(%) <sup>b</sup> /dr <sup>c</sup>
1	NHPMB NC <sup>C</sup> CO <sub>2</sub> Et (1.0 equiv)	5 d ( <i>S</i> , <i>S</i> )-1	N-PMB N-PMB NCO2Et Me <sup>St</sup> CN 5a	87 <sup>d</sup>	98°/9:1 [94°/8:1] <sup>r</sup>
2	NHBoc NC CO <sub>2</sub> Et (1.2 equiv)	5 d ( <i>R</i> , <i>R</i> )-1		818	99/15:1
3	NC <sup>C</sup> N (1.0 equiv)	2 d ( <i>R</i> , <i>R</i> )-1	Me Si Me NC NC CN 5c Sc H Ph	81	97*
4 <sup><i>i</i></sup>	NC <sup>CO2</sup> Me (1.2 equiv)	5 d ( <i>R</i> , <i>R</i> )-1	Me Si <sup>Me</sup> O NC CO <sub>2</sub> Me 5d	88	>99/1.2:1
5	Ph NC ⊂CO₂Me (1.5 equiv)	5 d ( <i>S</i> , <i>S</i> )-1	Me Si Me Ph H MeO <sub>2</sub> C CN 5e	73	92/4:1
6	$Ar$ $NC CO_2Me$ $Ar = p-MeOC_6H_4$ (1.2 equiv)	5 d ( <i>S</i> , <i>S</i> )-1	Me Si Me Ar MeO <sub>2</sub> C CN MeO <sub>2</sub> C CN	70	95/9:1
7	Ar NC $CO_2Me$ Ar = $m$ -BrC <sub>6</sub> H <sub>4</sub> (1.2 equiv)	5 d ( <i>R</i> , <i>R</i> )-1	Me Sí Me Ar NC CO <sub>2</sub> Me 5g	71	94/8:1

<sup>*a*</sup> Isolated yield, after chromatography, of diastereomerically pure material unless noted otherwise (0.2 mmol scale). <sup>*b*</sup> Determined by HPLC using commercial chiral columns unless noted otherwise. <sup>*c*</sup> Determined by <sup>1</sup>H NMR. <sup>*d*</sup> Inseparable from unreacted nucleophile and minor diastereomer; yield determined by <sup>1</sup>H NMR. <sup>*e*</sup> Determined by SFC after reduction of the ester with NaBH<sub>4</sub>. <sup>*f*</sup> 25 mmol scale. <sup>*s*</sup> Inseparable from unreacted nucleophile, yield calculated by <sup>1</sup>H NMR analysis. <sup>*h*</sup> Determined by SFC. <sup>*i*</sup> 5.0 mol % of catalyst was used.

With lactam **5a** in hand, we undertook the total synthesis of lactacystin (Scheme 1). Separation of the diastereomers of **5a** proved





<sup>*a*</sup> Reagents and conditions: (a) LHMDS, THF, -78 °C, 30 min, then MeI, -78 to 0 °C over 4 h, 9:1 dr; (b) NaBH<sub>4</sub>, MeOH, 0 °C, 6 h; 60% from **4** (3 steps); (c) Dess-Martin periodinane, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1.5 h; (d) isopropenyl MgBr, THF, -78 °C, 4 h; 73% (2 steps), >95:5 dr (addition to major isomer); (e) Red-Al, toluene, -78 to 0 °C over 2 h, then 1.0 M tartaric acid; (f) NaClO<sub>2</sub>, NaH<sub>2</sub>PO<sub>4</sub>, 2-methyl-2-butene, *t*-BuOH, H<sub>2</sub>O, rt, 35 min; (g) H<sub>2</sub>O<sub>2</sub>, KF, KHCO<sub>3</sub>, DMF, H<sub>2</sub>O, rt, 11 h; 49% (3 steps) of a single diastereomer; (h) H<sub>2</sub>, 10% Pd/C, AcOH, MeOH, rt, 2 h; 94%; (i) Tf<sub>2</sub>O, DMAP, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 11 h; (j) NaNO<sub>2</sub>, DMF, rt, 1.5 h; 80% (2 steps); (k) CAN, MeCN, H<sub>2</sub>O, 0 °C, 10 h; (l) *N*-acetyl-L-cysteine, Me<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, rt, 4 h; 68% (2 steps).

difficult, so the enriched mixture was employed through the early steps.  $\alpha$ -Methylation proceeded with complete diastereoselectivity, and two-step transformation of the ethyl ester to the corresponding aldehyde afforded **6** in 60% overall yield from  $\beta$ -silyl imide **4**. Treatment of **6** with isopropenylmagnesium bromide at -78 °C provided alcohol **7** with excellent diastereoselectivity (>95:5). Similarly selective addition reactions have been noted in closely related systems.<sup>11a,b</sup> X-ray structural analysis of **7** allowed confirmation of both the configuration at C-9 and the relative stereochemical outcomes of the conjugate addition and methylation steps.

Formal hydrolysis of nitrile **7** was envisaged using a mild twostep reduction/oxidation sequence. Unexpectedly, reduction of **7** with Red-Al was accompanied by intramolecular allyl group displacement by the alkoxide intermediate and formation of cyclic silyl ether **8**,<sup>15</sup> thereby imparting the beneficial effect of activating the C-6–Si bond for subsequent oxidation. Furthermore, the diastereomeric impurity that had been advanced from the original conjugate addition step failed to undergo analogous cyclization. Unpurified aldehyde **8** was subjected to oxidation to the corresponding acid, and Si–C bond cleavage was accomplished under standard Tamao oxidative conditions to provide diol **9** as a single diastereomer after aqueous workup.<sup>16</sup> With this protocol, the unactivated diastereomeric impurity failed to undergo oxidation and was removed simply by selective extraction from the reaction mixture.

At this point, completion of the synthesis required resolution of two key issues: inversion of the C-6 stereocenter and activation



Figure 2. Inhibition of the proteasome by omuralide (3).

of the carboxylic acid toward eventual displacement by *N*-acetyl cysteine. In attempts to activate the C-6 hydroxyl toward displacement, it was discovered that treatment of **9** with various sulfonyl chloride and anhydride derivatives led instead to facile spiro  $\beta$ -lactone formation.<sup>17,18</sup> With prior hydrogenation of **9** to the corresponding isopropyl derivative, sulfonylation with a large excess of Tf<sub>2</sub>O resulted in  $\beta$ -lactone construction and triflate formation in one pot to provide **10**. All of the electrophilic functionality needed for the final steps of the synthesis was thereby established in an efficient manner.

Invertive triflate displacement was accomplished cleanly in the presence of the  $\beta$ -lactone by treating **10** with NaNO<sub>2</sub> in DMF.<sup>19</sup> Removal of the *N*-PMB group provided a mixture of lactam **11** and *p*-anisaldehyde. The stability of the spiro  $\beta$ -lactone during these steps was particularly notable, with no decomposition of the strained bicyclic framework detected at any stage. Reaction of **11** with *N*-acetyl-L-cysteine in the presence of dimethylethylamine afforded (+)-lactacystin (**2**).

Interest in lactacystin is tied to its important biological activity: it is a potent, yet selective inhibitor of the 26S proteasome, the protein complex involved in ubiquitin-mediated protein degradation.<sup>20</sup> This complex has emerged as an important clinical target, especially in the context of cancer treatment.<sup>21</sup> Studies by Corey and Schreiber led to identification of the proteasome as the target of lactacystin and implicated *clasto*-lactacystin  $\beta$ -lactone (omuralide, **3**, Figure 1) as the active agent in the inhibition mechanism.<sup>9,22</sup> Omuralide, generated by intramolecular attack of the C-6 hydroxyl on the adjacent thioester, is cell-permeable and serves as an acylating agent toward the catalytic N-terminal threonine residue of the proteasome's chymotrypsin-like site (Figure 2).<sup>23</sup> The resulting acyl enzyme complex has been characterized by X-ray crystallography.<sup>24</sup>

SAR studies carried out by the Corey group were key in identifying the structural features responsible for the activity of lactacystin.<sup>9a,25</sup> Most relevant to our own synthetic efforts, analogues that were epimeric at C-6 or lacked the C-6 hydroxyl displayed either significant or complete loss of activity. Corey ascribed these observations to the inability of such compounds to form the requisite  $\beta$ -lactone.

Our results show that C-6 epimeric intermediates readily form spiro  $\beta$ -lactones, which undergo ring opening with thiol nucleophiles in a manner similar to that of omuralide. This reactivity pattern observed with **11** led us to consider whether it might extend to interaction with the proteasome. Though a spiro  $\beta$ -lactone intermediate has been postulated to explain the weak activity of 6-epilactacystin,<sup>9a</sup> to our knowledge, such compounds have not been examined in the context of proteasome inhibition.

Spiro lactacystin  $\beta$ -lactone **11** along with omuralide (**3**) and 6-epispiro-lactacystin  $\beta$ -lactone **12**<sup>26</sup> were assayed for inhibition of rabbit muscle 26S proteasome using fluorogenic peptide substrates (Table 2).<sup>27</sup> Analogue **12** was accessed from intermediate **9** by a route analogous to that used in the lactacystin synthesis, omitting triflate formation and invertive substitution by a hydroxyl equivalent. Interestingly, spiro  $\beta$ -lactone **11** was found to inhibit all three

 Table 2.
 Effect of Inhibitors on Peptidase Activities of Rabbit

 Muscle 26S Proteasome<sup>a</sup>
 1

substrate	<b>3</b> (10 μM) <sup>b</sup>	<b>11</b> (10 μM) <sup>b</sup>	<b>12</b> (200 μM)
% inhibition of chymotrypsin-like site	87.4 ± 3.7	$83.1 \pm 3.2$	19.1
% inhibition of caspase-like site	$15.5\pm3.9$	$20.5\pm5.0$	no inhibition
% inhibition of trypsin-like site	$35.6\pm0.2$	$24.6\pm2.8$	no inhibition

<sup>*a*</sup> Purified 26S proteasome was used at a concentration of 1  $\mu$ g/mL. Peptidase activity was measured using fluorogenic substrates specific for each site, in the presence of inhibitors or 1% DMSO as a control. <sup>*b*</sup> The results shown represent the mean  $\pm$  the range of two experiments, each run in duplicate.

proteolytic subunits at similar levels as omuralide (3) under identical conditions. In contrast, the epimeric spiro  $\beta$ -lactone 12 was inactive at concentrations below 200  $\mu$ M. Though the possibility that spiro  $\beta$ -lactone 11 could undergo isomerization into omuralide under the assay conditions must also be considered, this appears unlikely given the observed stability of 11.28 Rather, these data indicate that the position of the  $\beta$ -lactone is not important for activity, and that the configuration at C-6 is critical for reasons other than  $\beta$ -lactone formation. Recent work has demonstrated the importance of a hydrogen bond between the C-6 hydroxyl and the N-terminal amino group of the proteasome subunit in stabilizing the omuralideproteasome complex (Figure 2); the presence of the C-6 hydroxyl prevents the binding of the water molecule necessary for hydrolysis.<sup>29</sup> An analogous hydrogen bond is revealed in the crystal structure of the proteasome bound to the dipeptide boronic acid inhibitor bortezomib.<sup>30</sup> These results with 11 and 12 lend additional support to the importance of this H-bond interaction as a guiding principle in the design of new proteasome inhibitors.

The total synthesis of lactacystin was accomplished in 13 steps and 11.0% overall yield from silyl imide **4**. The route is efficient, requiring a single protecting group and only five chromatographic purifications. The pursuit of lactacystin as a target inspired the design of a new imide substrate for aluminum salen-catalyzed conjugate additions. Moreover, an unusual spiro  $\beta$ -lactone was employed for the first time as an intermediate in total synthesis, allowing for a novel lactacystin end-game strategy. Spiro  $\beta$ -lactone **11** has proven interesting in a completely different context, as well, as an inhibitor of the 26S proteasome with similar potency to the known inhibitor omuralide.

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**Supporting Information Available:** Experimental procedures, ee analyses, characterization data for all new compounds, details of proteasome assay experiments, and X-ray coordinates for **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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