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Simple Enantiospecific Syntheses of the C(2)-Diastereomers of Omuralide and 3-Methylomuralide

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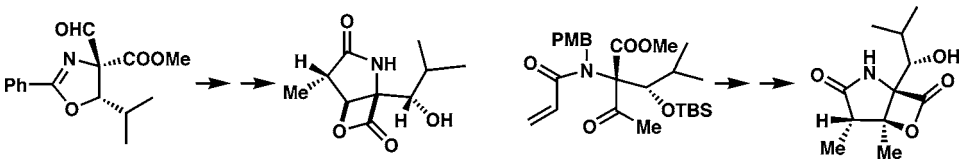
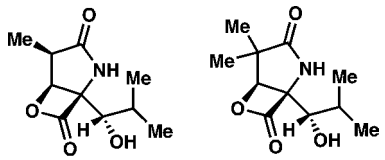
ABSTRACT



Syntheses of two novel omuralide derivatives are described.

Omuralide (**1**) is a highly selective and potent covalent inhibitor of the proteasome, the cylindrical multiprotein assembly that degrades polyubiquitinated proteins.[1,2] The proteasome functions to remove damaged or misfolded proteins and to play a major role in maintaining optimum levels of individual proteins in cells and tissues. This role is especially important for regulatory proteins such as those involved in signaling, cell-cycle control, DNA repair, transcription, and apoptosis.[2] As a result of previous synthetic work in these laboratories, we were able to develop a clear structure−activity correlation for a considerable number of omuralide analogues.[1a] One interesting finding was that 2-methylomuralide[3,4] (**2**) retained most of the potency of **1**.[1a] This fact prompted us to develop a synthesis of 2-epi-omuralide (**3**) for evaluation of its activity in proteasome inhibition, especially because of the availability in our laboratory of advanced intermediates for the synthesis, specifically the ester−aldehyde **4** (see Scheme 1). This chiral ester aldehyde can be prepared in quantity from methyl 4-methyl-2-pentenoate by the use of catalytic enantioselective methodology.[4]



1 **2**

Reaction of **4** with 2 equiv of the *E*-*tert*-butyldimethylsilyl enol ether of methyl propionate in THF (from LDA and methyl propionate in THF at −78 °C) and 1.1 equiv of powdered $LiClO_4$ (moisture-containing, but not dry) in CH_2Cl_2 at −78 °C for 20 h gave as major product the *syn* aldol adduct **5**. Acid-catalyzed methanolysis of crude **5** with refluxing methanolic HCl and concomitant lactamization provided the pure γ-lactam benzoate **6** (63% overall from **4**) after flash chromatography on silica gel. Saponification of the benzoate-methyl ester **6** provided the dihydroxy acid

(1) (a) Reviewed in: Corey, E. J.; Li, W.-D. Z. *Chem. Pharm. Bull.* **1999**, *47*, 1−10. (b) Corey, E. J.; Reichard, G. A.; Kania, R. *Tetrahedron Lett.* **1993**, *34*, 6977−6980. (c) Corey, E. J.; Reichard, G. A. *J. Am. Chem. Soc.* **1992,** *114*, 10677−10678. (d) Fenteany, G.; Standaert, R. F.; Reichard. G. A.; Corey, E. J.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 3358−3362.

(2) (a) Hershko, A. *Le Prix Nobel*; Nobel Foundation: Stockholm, 2005. (b) http://nobelprize.org/chemistry/laureates/2004/public.html. (c) De Martino, G. N.; Slaughter, C. A. *J. Biol. Chem.* **1999**, *274*, 22123−22126. (d) Glickman, M. H.; Liechanover, A. *Physiol. Rev.* **2001**, *82*, 373−428. (e) Tansey, N. P. *New Engl. J. Med.* **2004**, *351*, 393−394. (f) Ehlers, M. D. *Nature Neurosci.* **2003**, *6*, 231−242. (g) Adams, J. *Proteasome Inhibitors in Cancer Therapy*; Humana Press: New York, 2004.

(3) Corey, E. J.; Li, W.-D. Z. *Tetrahedron Lett.* **1998**, *39*, 7475−7478.

(4) Saravanan, P.; Corey, E. J. *J. Org. Chem.* **2003**, *68*, 2760−2764.

10.1021/ol050874w CCC: $30.25
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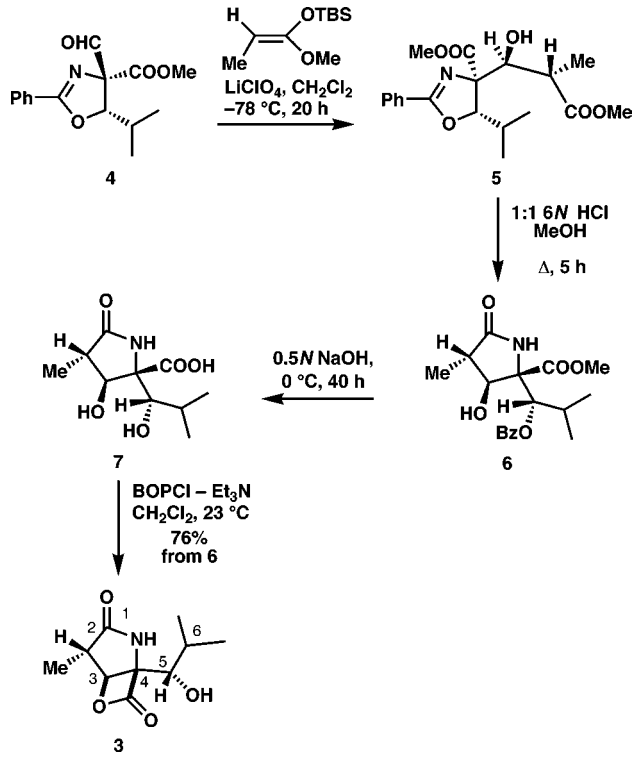
Scheme 1



7. Reaction of **7** with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl) and Et_3N in CH_2Cl_2 at 23 °C for 1 h gave, after extractive isolation (EtOAc) and flash chromatography on silica gel, the desired β-lactone **3**, mp 170−172 °C.[5] The structure of **3** was confirmed by single-crystal X-ray diffraction analysis (Figure 1).

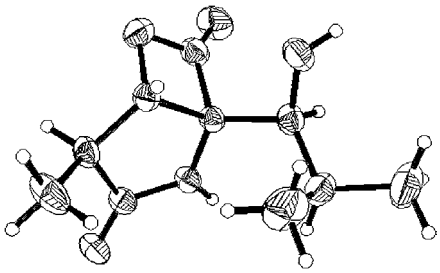
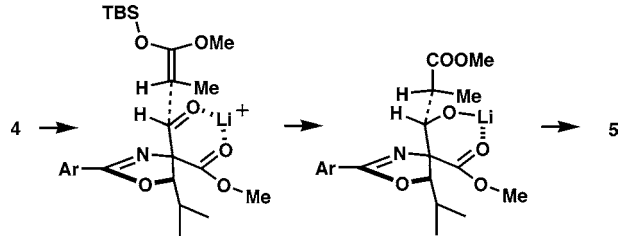


Figure 1. ORTEP presentation of **3**.

A key step in the synthesis of **3** that is outlined in Scheme 1 is the doubly diastereoselective Mukaiyama aldol coupling **4** → **5**. The preparation of the very sensitive aldehyde **4** was accomplished by addition of a −78 °C solution of the Swern reagent formed from DMSO and ClCOCOCl in CH_2Cl_2 to the primary alcohol precursor and Et_3N at −78 °C,[4] addition of pentane to the reaction product, filtration, and evaporation in vacuo (95% yield). It was crucial to use a nonaqueous workup since **4** rapidly undergoes retroaldol cleavage under aqueous conditions. Pure **4** could be stored unchanged at −78 °C for at least 1 day. The optimum catalyst for the transformation **4** → **5** was found to be $LiClO_4$ (not rigorously dried and containing a small amount (>2%) of moisture). One straightforward explanation for the observed syn aldol diastereoselectivity is outlined in Scheme 2. In this sequence, the formyl and COOMe carbonyl oxygens of **4** coordinate with $LiClO_4$ to form a chelated intermediate which then couples with the enol silyl ether as shown in Scheme 2 to generate the *syn* aldol adducts. This pathway to the *syn* product **5** appears to be favored over alternative pre-transition-state assemblies because it involves a minimum of steric repulsion.

Scheme 2



We have also taken advantage of the availability of an advanced intermediate (**10**) for the synthesis of other omuralide derivatives[6] to prepare 3-methyl-2-*epi*-omuralide (**8**), a hybrid of **3**, and salinosporamide A (**9**) (Scheme 3), for which we have described three different routes.[6,7,8] The keto acrylamide **10**[6,7] was added to the Kulinkovich reagent[9] (3.5 equiv) formed by treatment of 4 equiv of Ti(*i*-PrO)$_4$ with 7 equiv of cyclopentylmagnesium chloride in *t*-BuOMe at −40 °C for 30 min and then allowed to react at −40 °C for another 1 h and at −20 °C for 20 h. The cyclized titanium-containing intermediate thus formed (see below) was then quenched with excess 1 *N* hydrochloric acid. Extractive isolation afforded a single diastereomeric γ-lactam, **11**, which was isolated in 95% yield after flash chromatography on silica gel.[10,11] The TBS ether protecting group of **11** was cleaved using 1:1 48% aq HF in acetonitrile to form the

(5) Physical data for **3**: R_f 0.50 (neat EtOAc); $[\alpha]^{23}_D$ −70.1 (*c* 1.0, MeCN); FTIR (film) ν_{max} 3456, 2948, 1835, 1719, 1648, 1510, 1250, cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.0 (1H, br s, −*NH*), 4.86 (1H, s), 3.75 (1H, dd, J = 13.2, 6.0 Hz), 3.58 (1H, d, J = 7.2 Hz), 2.70 (1H, q, J = 7.8 Hz), 1.78 (1H, m), 1.24 (3H, d, J = 8.4 Hz), 0.99 (3H, d, J = 6.9 Hz), 0.90 (3H, d, J = 6.8 Hz).

(6) Reddy, L. R.; Fournier, J.-F.; Subba Reddy, B. V.; Corey, E. J. *J. Am. Chem. Soc.*, published online June 2, 2005 http://dx.doi.org/10.1021/ja052376o.

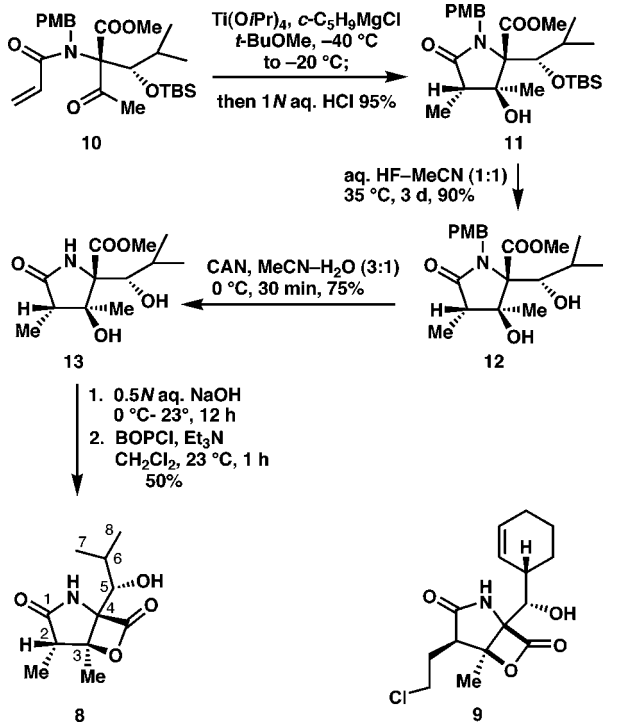
(7) Reddy, L. R.; Fournier, J.-F.; Subba Reddy, B. V.; Corey, E. J. *Org. Lett.* **2005**, *7*, 2699−2702.

(8) Reddy, L. R.; Saravanan, P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230−6231.

(9) For reviews on the application of titanacyclopropane reagents, see: (a) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597−2632. (b) Sato, F.; Okamoto, S. *Adv. Synth. Catal.* **2001**, *343*, 759−784.

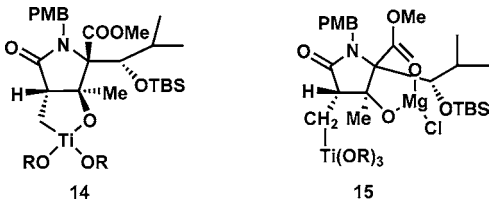
(10) For the closest precedent to this cyclization involving δ,ϵ-enones, see: (a) Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 3182−3191. (b) Mandal, S. K.; Amin, S. R.; Crowe, W. E. *J. Am. Chem. Soc.* **2001**, *123*, 6457−6458. (c) Crowe, W. E.; Vu, A. T. *J. Am. Chem. Soc.* **1996**, *118*, 1557−1558. (d) Quan, L. G.; Cha, J. K. *Tetrahedron Lett.* **2001**, *42*, 8567−8569.

Scheme 3



dihydroxy ester **12**,[12] further transformed into **13** by oxidative cleavage of the *N*-*p*-methoxybenzyl protecting group.[13] Saponification of methyl ester **13** followed by lactonization of the resulting dihydroxy acid yielded 3-methyl-2-*epi*-omuralide **8** as a colorless solid[14] that was distinctly different from a sample of 3-methylomuralide.[7]

The relative stereochemistry of the titanacyclopentene-mediated cyclization **10** → **11** about carbons 3 and 4 follows unambiguously from the formation of the β-lactone ring. Since the absolute configurations at carbons 4 and 5 have been established unambiguously by previous work[6,7] and since the absolute configuration at carbon 2 is now also clear, there is no doubt about the overall correctness of the transformation **10** → **11**. The *trans* relationship of the methyl substituent at C(2) and the hydroxyl group at C(3) of **11** contrasts with previous work on the Ti-mediated cyclization of δ,ϵ-unsaturated ketones[10] and is thus surprising. This observed *trans* arrangement of substituents at C(2) and C(3) indicates that the cyclization occurs not through a bicyclic organotitanium intermediate such as **14**, but via a monocyclic structure such as **15**. The formation of intermediate **15** may



occur by a pathway such as the following: (1) transfer of $(RO)_2Ti$ from the Kulinkovich complex with cyclopentene to the acrylamide α,β-double bond of **10** and (2) radical addition of that intermediate to a chelate of $MgCl^+$ with the COOMe and CH_3CO carbonyl oxygens of the complex from **10** to effect cyclization to **15**. Proteolysis of **15** obviously leads to the observed product **11**. Regardless of the mechanistic pathway for the formation of **11** from **10**, it seems likely that Kulinkovich complex induced cyclizations have even greater synthetic potential than previously realized.

In summary, the omuralide analogues **3** and **8** are now available by efficient and practical stereocontrolled routes.

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Supporting Information Available: Complete data for the X-ray crystal structure of **3** are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Characterization data for **11**: R_f 0.40 (hexanes−EtOAc 50:50); mp 43−44 °C; $[\alpha]^{23}_D$ +10.4 (*c* 2.5, $CHCl_3$); FTIR (film) ν_{max} 3386, 2954, 2935, 1748, 1683, 1515, 1245, 1177, 1055, 835 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.09 (2H, d, J = 8.8 Hz), 6.81 (2H, d, J = 8.8 Hz), 4.88 (1H, d, J = 15.5 Hz), 4.54 (1H, d, J = 16 Hz), 4.13 (1H, d, J = 0.8 Hz), 4.04 (1H, s), 3.76 (3H, s), 3.49 (3H, s), 2.59 (1H, m), 2.41 (1H, q, J = 7.6 Hz), 1.41 (3H, s), 1.17 (3H, d, J = 7.6 Hz), 1.09 (3H, d, J = 7.2 Hz), 0.94 (9H, s), 0.90 (3H, d, J = 6.4 Hz), 0.17 (3H, s), −0.05 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.62, 173.18, 158.31, 130.95, 127.58, 113.98, 80.77, 79.78, 77.58, 55.44, 52.47, 48.40, 47.28, 28.80, 26.62, 24.34, 20.05, 19.11, 16.01, 10.37, −1.51, −4.08; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{44}NO_6Si$ [M + H$^+$] 494. 2938, found 494.2932.

(12) Characterization data for **12**: colorless solid; R_f 0.60 (EtOAc); mp 126−128 °C $[\alpha]^{23}_D$ +22.0 (*c* 0.3, $CHCl_3$); FTIR (film) ν_{max} 3392, 2952, 2912, 1752, 1673, 1515, 1246, 1177, 1036, 835 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.32 (2H, d, J = 8.4 Hz), 6.85 (2H, d, J = 9.0 Hz), 4.75 (2H, d, J = 6.6 Hz), 3.80 (3H, s), 3.70 (3H, s), 3.65 (1H, d, J = 5.5 Hz), 2.63 (1H, q, J = 7.2 Hz), 2.15 (1H, m), 1.32 (3H, s), 1.24 (3H, d, J = 7.2 Hz), 0.92 (3H, d, J = 7.2 Hz), 0.87 (3H, d, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.36, 172.44, 158.62, 131.24, 128.87, 113.90, 80.33, 77.54, 55.45, 52.48, 48.85, 46.27, 30.40, 21.48, 18.86, 17.86, 10.15; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{30}NO_6$ [M + H$^+$] 380.2028, found 380.2024.

(13) Characterization data for **13**: colorless solid; R_f = 0.2 (EtOAc); mp ~180 °C dec; $[\alpha]^{23}_D$ −2.6 (*c* 1.5, MeOH); FTIR (film) ν_{max} 3325, 2956, 2925, 1725, 1683, 1252, 1167, 1096, 1021, 835 cm^{-1}; ^{1}H NMR (CD_3OD, 600 MHz) δ 5.49 (1H, s, NH), 3.80 (1H, d, J = 4.8 Hz), 3.73 (3H, s), 2.35 (1H, q, J = 7.8 Hz), 1.63 (1H, m), 1.49 (3H, s), 1.26 (3H, d, J = 7.8 Hz), 0.94 (3H, d, J = 7.2 Hz), 0.90 (3H, d, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.41, 171.33, 80.48, 78.96, 74.60, 51.23, 50.97, 31.33, 20.28, 18.51, 16.98, 11.53; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{22}NO_5$ [M + H$^+$] 260.1498, found 260.1495.

(14) Characterization data for **8**: R_f = 0.53 (EtOAc); mp 145−147 °C; $[\alpha]^{23}_D$ −12.2 (*c* 0.6, $CHCl_3$); FTIR (film) ν_{max} 3355, 2966, 2927, 1825, 1704, 1345, 1048, 850 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.63 (1H, br), 3.75 (1H, d, J = 7.0 Hz), 2.79 (1H, q, J = 8.0 Hz), 1.92 (1H, m) 1.69 (3H, s), 1.24 (3H, d, J = 6.0 Hz), 1.12 (3H, d, J = 7.5 Hz), 1.08 (1H, d, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.03, 169.91, 87.00, 79.59, 71.51, 44.36, 31.48, 19.87, 18.69, 16.84, 13.09; HRMS (CSI) calcd for $C_{11}H_{21}IN_2O_4$ [M + NH$_4$]$^+$ 245.1501, found 245.1491.