Communication

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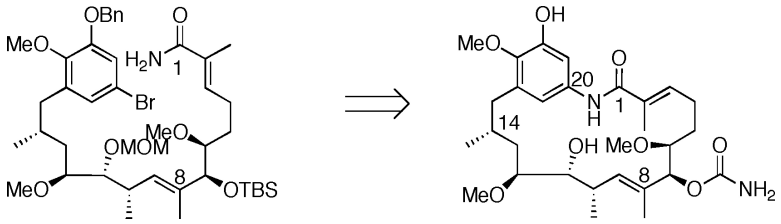

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Total Synthesis of Reblastatin

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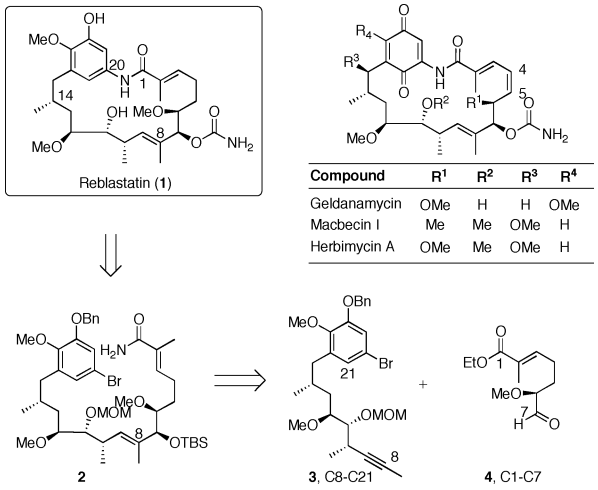
During screening experiments intended to identify novel compounds that inhibit phosphorylation of the retinoblastoma protein (Rb), Takatsu and co-workers isolated in 2000 a benzenoid ansamycin-like cell cycle inhibitor, reblastatin (**1**).[1] This material was originally isolated from the culture of *Streptomyces hygroscopicus* subsp. hygroscopicus SANK 61995, which also produces the Hsp90 disrupter geldanamycin. Reblastatin has been shown to exhibit antitumor activity against human histiocytic lymphoma U-937 with an IC_{50} value of 0.43 μg/mL.[1] Reblastatin was also reported to exhibit potent inhibitory activity in the cell-based oncostatin M signaling assay with an IC_{50} value of 0.16 μM.[2] Structurally related natural products, such as geldanamycin,[3] macbecin I,[4] and herbimycin A,[5] have a common benzoquinone ring and a C2−C5 dieneoate embedded within the ansa chain (Scheme 1). By comparison, reblastatin contains an aromatic phenol ring, and the C2−C5 segment is saturated at C4−C5. The promising antitumor activity and unique structure of reblastatin make it an important target for chemical synthesis. Herein we describe the first enantioselective synthesis of reblastatin (**1**).

Our strategy for the synthesis of reblastatin (**1**) is shown in Scheme 1. We envisioned the 19-membered macrocycle to be formed from the acylic framework **2** through an intramolecular copper(I)-mediated amidation reaction.[6] Although Buchwald has demonstrated the ability of Cu(I) systems to generate five-membered heterocycles,[6,7] its use in the construction of macrocyclic lactams had not yet been demonstrated. To assemble the acyclic skeleton **2**, we envisaged that the C7 alcohol could be obtained from addition of an *E*-vinyl zirconium species, derived from alkyne **3** to aldehyde **4**.[8]

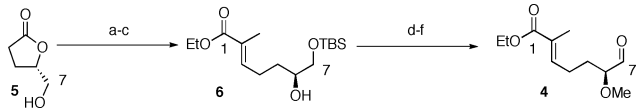
The synthesis of C1−C7 fragment **4** started with the readily available lactone **5** (Scheme 2). Making use of an analogous strategy employed by Forsyth for preparation of the C ring of thyrsiferol,[9] we converted lactone **5**[10] to the (*E*)-α,*β*-unsaturated ester **6** via a three-step sequence. Protection of the primary hydroxy group of **5** as a TBS ether, followed by reduction of the lactone with Dibal-H and treatment of the resulting lactol with (carbethoxyethylidene)triphenyl phosphorane, provided ester **6**. Methylation of the secondary alcohol followed by TBS deprotection with dilute HCl and subsequent Swern oxidation of the resulting primary alcohol gave the desired C1−C7 fragment **4**.

The synthesis of the C8−C21 fragment **3** (Scheme 3) started from aromatic aldehyde **7**, which was easily obtained in three steps from commercially available 2,3-dihydroxybenzaldehyde (57%).[11] Crotylation[12] of this aldehyde **7** with (*R*,*R*)-crotylsilane **8** provided the desired syn homoallylic alcohol **9** in 64% yield and with high diastereoselectivity (dr >20:1). Removal of the unnecessary alcohol by ionic deoxygenation (60%) was followed by hydroboration of the *β*,*γ*-unsaturated ester with BH_3·SMe_2 (dr 8:1), which proceeded with concomitant reduction of the methyl ester to afford the 1,3-diol **10**.[12] Selective protection of the primary alcohol as a TBS ether and subsequent methylation of the secondary alcohol with Meerwein's reagent gave the protected triol. Removal of the primary TBS ether with HCl in methanol, followed by selective deprotection of the benzyl ether with BCl_3·Me_2S,[13] afforded the 1,2-diol. This material was subjected to oxidative cleavage using sodium periodate to furnish aldehyde **11**.

Scheme 1. Structure and Retrosynthetic Analysis of Reblastatin



Scheme 2. Synthesis of C1−C7 Fragment[a]



[a] Reagents and conditions: (a) TBSCl, imidazole, DMF; (b) Dibal-H, toluene, −78 °C; (c) $CH_3C(=PPh_3)CO_2Et$, benzene, 73%; (d) Me_3OBF_4, proton sponge, 4 Å MS, DCM; (e) MeOH, HCl; (f) $(COCl)_2$, DMSO, NEt_3, DCM, −78 °C, 93%.

A matched crotylation[14] between aldehyde **11** and (*S*,*S*)-crotylboronate **12**[15] gave the desired syn homoallylic alcohol **13** in 80% yield, with a diastereoselectivity of 20:1. The resulting alcohol was protected as a MOM ether and further converted to the methyl alkyne **3** using a four-step sequence. Dihydroxylation of the terminal alkene, followed by oxidative cleavage of the diol, provided the chiral α-methyl aldehyde. Finally, exposure to Gilbert−Seyferth[16] reagent provided the terminal alkyne, which was further methylated using LiHMDS and MeI.

To achieve the crucial fragment coupling of advanced intermediates **3** and **4**, we explored the utility of a hydrozirconation−transmetalation addition sequence to aldehyde **4** originally developed by Wipf (Scheme 4).[8] Although most reports utilize 1-alkynes, there have been limited examples of internal alkynes participating in these reactions.[8,17] Our initial experiments indicated that elevated temperature and use of 2 equiv of Cp_2ZrHCl led to excellent levels of regioselectivity (>20:1) and conversion with 2-alkyne **3**.[18] Accordingly, hydrozirconation of **3**, followed by transmetalation and addition to aldehyde **4**, gave the desired allylic alcohol **14** in

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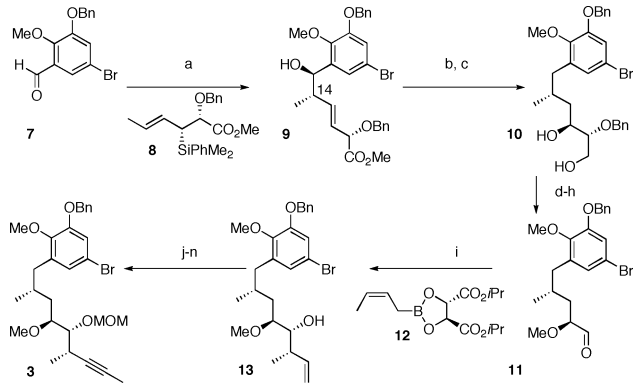
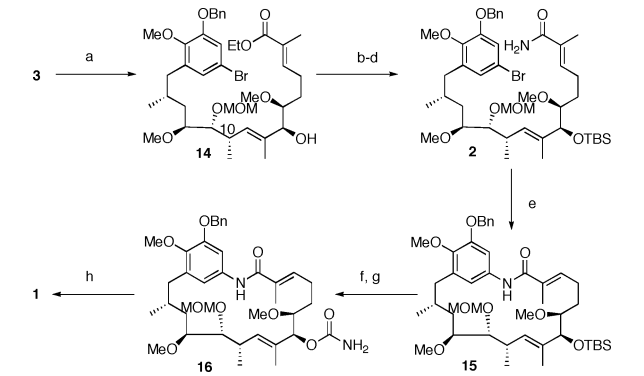
Scheme 3. Synthesis of Aromatic C8−C21 Fragment[a]



[a] Reagents and conditions: (a) TMSOTf, **8**, DCM, −50 °C, 64%, 20:1 dr; (b) Et_3SiH, $BF_3{\cdot}OEt_2$, DCM, 60%; (c) (i) $BH_3{\cdot}Me_2S$, THF, 0 °C to room temperature, (ii) NaOH, H_2O_2 62%; (d) TBSCl, imidazole, DMF, Et_2O; (e) Me_3OBF_4, DCM; (f) HCl, MeOH, 95%; (g) $BCl_3{\cdot}Me_2S$, DCM, −78 to 0 °C, 90%; (h) $NaIO_4$, $NaHCO_3$, acetone/H_2O, 99%; (i) **12**, 4 Å MS, toluene, −78 °C, 80%, 20:1 dr; (j) MOMCl, DMAP, DIPEA, DCM, 89%; (k) OsO_4, NMO, acetone/H_2O; (l) $Pb(OAc)_4$, K_2CO_3, benzene; (m) $(MeO)_2P(O)CHN_2$, *t*-BuOK, THF, −78 °C; (n) LiHMDS, MeI, −78 °C, 74%.

Scheme 4. Fragment Coupling, Intramolecular Amidation, and Completion of the Synthesis[a]



[a] Reagents and conditions: (a) (i) Cp_2ZrHCl, toluene, 50 °C, (ii) $ZnMe_2$, toluene, −65 °C, (iii) **4**, 0 °C, 55%, 20:1 dr; (b) TBSOTf, 2,6-lutidine, DCM, 0 °C, 92%; (c) LiOH, THF:MeOH:H_2O, 92%; (d) (i) $(CH_3)_2CHCH_2$-OCOCl, NEt_3, DCM, −20 °C, (ii) $NH_3(g)$, 59% (92% based on recovered starting material); (e) CuI, *N*,*N*′-dimethylethylenediamine, K_2CO_3, toluene, 100 °C, 83%; (f) HF·Pyr, Pyr, THF, 88%; (g) $Cl_3CCONCO$, MeOH, K_2CO_3, 80%; (h) BCl_3, −78 °C, DCM, 52%.

55% yield.[19] Analysis of the crude reaction mixtures showed partial epimerization at C10; fortunately, the two diastereomers could be readily separated by chromatography.[20,21]

After coupling of fragments **3** and **4**, several chemical manipulations were necessary before macrocyclization. To that end, the secondary alcohol **14** was protected as a TBS ether, the ethyl ester was hydrolyzed, and the resulting acid was converted to the amide **2** via a mixed anhydride in good overall yield. Having the required bromoamide **2** in hand, we proceeded to explore the crucial macrocyclization step. Subjection of the acyclic skeleton **2** to Buchwald's amidation conditions smoothly provided the desired macrolactam **15** in 83% yield. Deprotection of the TBS ether was achieved using HF/pyridine in pyridine to obtain the secondary alcohol in 88% yield. Subjection of the secondary alcohol to reaction conditions reported by Kocovsky provided the desired carbamate **16**.[22] Finally, deprotection of the MOM and benzyl ethers was accomplished using BCl_3 to reveal reblastatin (**1**) in 53% yield. The synthetic reblastatin exhibited physical, spectroscopic and spectrometric characteristics (^1H, ^{13}C NMR, IR, $[\alpha]_D$, and HRMS) identical to those reported for the natural product.[1]

In summary, the first total synthesis of reblastatin has been achieved in 25 steps (longest linear sequence). Notable features of our synthetic approach include a highly regio- and diastereoselective hydrometalation addition reaction to install the C7 stereocenter. This effort also documents the first example of an intramolecular copper-mediated amidation to close the 19-membered macrolactam, thereby further expanding the scope of this useful reaction. This convergent synthesis allows for construction of stereochemical analogues of reblastatin for further biological testing, which will be reported at the appropriate time.

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

References

(1) Takatsu, T.; Ohtsuki, M.; Muramatsu, A.; Enokita, R.; Kurakata, S. I. *J. Antibiot.* **2000**, *53*, 1310.
(2) Stead, P.; Latif, S.; Blackaby, A. P.; Sidebottom, P. J.; Deakin, A.; Taylor, N. L.; Life, P.; Spaull, J.; Burrel, F.; Jones, R.; Lewis, J.; Davidson, I.; Mander, T. *J. Antibiot.* **2000**, *53*, 657.
(3) DeBoer, C.; Meulman, P. A.; Wnuk, R. J.; Peterson, D. H. *J. Antibiot.* **1970**, *23*, 442.
(4) Tanida, S.; Hasegawa, T.; Higashide, E. *J. Antibiot.* **1980**, *33*, 199.
(5) Omura, S.; Iwai, Y.; Takahashi, Y.; Sadakane, N.; Nakagawa, A.; Oiwa, H.; Hasegawa, Y.; Ikai, T. *J. Antibiot.* **1979**, *32*, 255.
(6) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.
(7) The synthesis of five- to seven-membered rings using Cu(I) has also been reported: (a) Yamada, K.; Kubo, T.; Tokuyama, H.; Fukuyama, T. *Synlett* **2002**, *2*, 231. (b) Lebedev, A. Y.; Khartulyari, A. S.; Voskoboynikov, A. Z. *J. Org. Chem.* **2005**, *70*, 596.
(8) (a) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197. (b) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853. (c) Wipf, P.; Xu, W.; Takahashi, H.; Jahn, H.; Coish, P. D. G. *Pure Appl. Chem.* **1997**, *69*, 639. (d) Wipf, P.; Kendall, C. *Chem.—Eur. J.* **2002**, *8*, 1778.
(9) González, I. C.; Forsyth, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 9099.
(10) Herdeis, C. *Synthesis* **1986**, 232.
(11) For experimental details, see Supporting Information.
(12) Panek, J. S.; Xu, F.; Rondón, A. C. *J. Am. Chem. Soc.* **1998**, *120*, 4113.
(13) Congreve, M. S.; Davison, E. C.; Fuhry, M. A. M.; Holmes, A. B.; Payne, A. N.; Robinson, R. A.; Ward, S. E. *Synlett* **1993**, 663.
(14) (a) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348. (b) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Park, J. C. *J. Org. Chem.* **1990**, *55*, 4109.
(15) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339.
(16) (a) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982**, *47*, 1837. (b) Brown, D. G.; Velthuisen, E. J.; Commerford, J. R.; Brisbois, R. G.; Hoye, T. R. *J. Org. Chem.* **1996**, *61*, 2540.
(17) Hu, T.; Panek, J. S. *J. Am. Chem. Soc.* **2002**, *124*, 11368.
(18) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4912.
(19) The absolute configuration of C7 alcohol was confirmed by Mosher ester analysis. See Supporting Information for details.
(20) Approximately 5−10% epimerized product was determined by crude ^1H NMR. Recovery of starting material as the 2*Z*-alkene showed a similar ratio of C10 diastereomers.
(21) We rationalize that reversible addition of a second equivalent of Cp_2-ZrHCl, followed by elimination at C10−C11, may lead to partial epimerization. For precedent of this mechanism, see: (a) Schwartz, J.; Labinger, J. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333. (b) Wailes, P. C.; Weigold, H.; Bell, A. P. *J. Organomet. Chem.* **1971**, *27*, 373.
(22) Kocovsky, P. *Tetrahedron Lett.* **1986**, *27*, 5521.

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