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Supplementary Material Available: Experimental procedures and full characterization for all compounds reported in this communication (12 pages). Ordering information is given on any current masthead page.

A Convergent, Enantiospecific Total Synthesis of the Novel Cyclodepsipeptide (+)-Jasplakinolide (Jaspamide)

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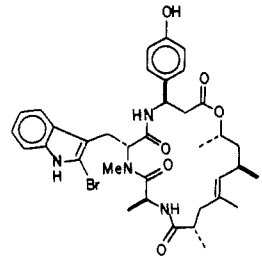
Jasplakinolide (**1**),[2] a novel cyclodepsipeptide isolated from a soft-bodied sponge, *Jaspis* sp., contains a new amino acid, 2-



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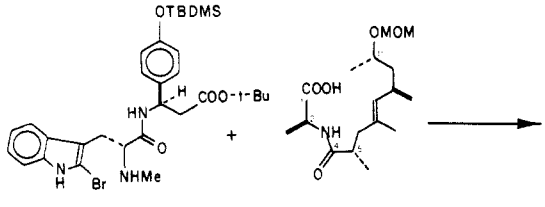
bromoabrine, possessing the unnatural D configuration and the rare amino acid (*R*)-β-tyrosine.[3] The potent insecticidal, antifungal, and anthelminthic properties[2] of jasplakinolide have been responsible for considerable synthetic activity in both industrial and academic laboratories. We wish to record the first total synthesis of (+)-jasplakinolide. The approach detailed below is both highly convergent and enantiospecific.

Our strategy for elaboration of jasplakinolide centered around the coupling of dipeptide **2** with the L-alanine derived acyclic fragment **3**. Construction of dipeptide **2** necessitated prior development of synthetic routes to the unnatural amino acids, (*R*)-β-tyrosine and D-bromoabrine.



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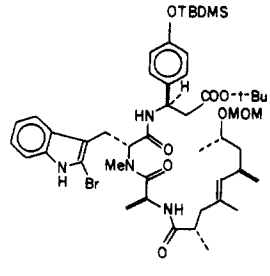

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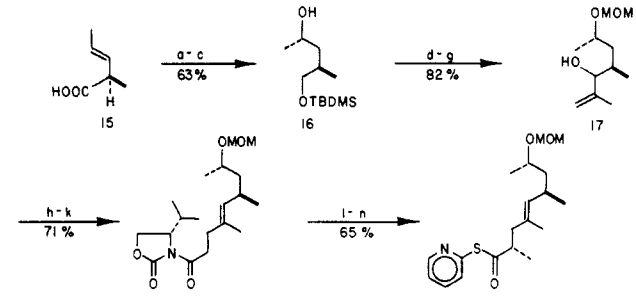
(1) Berlex Predoctoral Fellow, 1987-1988.

(2) (a) Crews, P.; Manes, L. V.; Boehler, M. *Tetrahedron Lett.* **1986**, *27*, 2797. (b) Zabriskie, T. M.; Klocke, J. A.; Ireland, C. M.; Marcus, A. H.; Molinski, T. F.; Faulkner, D. J.; Xu, C.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 3123.

(3) Natural (*S*)-β-tyrosine was first found in two peptide antibiotics, edeine A and edeine B, obtained from cultures of *Bacillus brevis* Vm 4.[4]

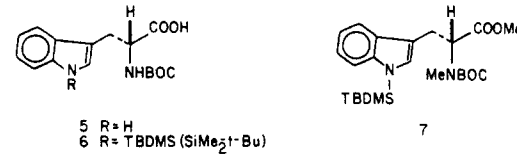
Scheme I. Synthesis of the C(4)-C(11) Fragment **19**[a]



18 19

[a] (a) $NaHCO_3$, I_2, H_2O, MeOH; (b) $LiAlH_4$, Et_2O, 0 °C; (c) *t*-$BuMe_2SiCl$, DMAP, Et_3N, CH_2Cl_2; (d) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C → room temeprature; (e) Bu_4NF, THF; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; (g) isopropenylmagnesium bromide, THF, -78 °C; (h) $CH_3C(OEt)_3$, propionic acid (catalyst), 120 °C, 3 h; (i) KOH, MeOH, H_2O; (j) *t*-BuCOCl, Et_3N, Et_2O; (k) lithio-(*S*)-4-isopropyl-2-oxazolidinone, THF, -78 °C; (l) $NaN(TMS)_2$, THF, -78 °C, MeI; (m) KOH, MeOH, H_2O; (n) $(PyS)_2$, Ph_3P, CH_2Cl_2.

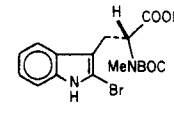
Our initial efforts were focused on the preparation of N^{α}-*t*-BOC-D-bromoabrine (**9**). Sequential treatment of a 0.2 M solution of commercially available N^{α}-*t*-BOC-D-tryptophan (**5**) in tetra-



5 R = H
6 R = TBDMS ($SiMe_2$-t-Bu)

7

hydrofuran at -78 °C with 3.0 equiv of sodium hexamethyldisilazide and 1.0 equiv of *tert*-butyldimethylchlorosilane provided in near quantitative yield N^{α}-*t*-BOC-N^{i}-*tert*-butyldimethylsilyl-D-tryptophan (**6**), $[\alpha]_D$ -21.2 ° (*c* 1.70, $CHCl_3$). Simultaneous N- and O-methylation (NaH, xsMeI, THF-DMF, 10:1, 60 °C) of **6** gave rise in ca. 80% yield to **7**, $[\alpha]_D$ +39.0° (*c* 1.27, $CHCl_3$), which upon exposure (0 °C → 25 °C, 3 h) to 2.0 equiv of pyridinium bromide perbromide in ether-chloroform, 1:1, afforded directly 2'-bromo-$N\alpha$-*t*-BOC-D-abrine methyl ester (**8**), $[\alpha]_D$ +69.4° (*c* 1.14, $CHCl_3$), in 50% yield. Saponification (1 N



8 R = Me
9 R = H

NaOH, H_2O-THF, 1:1) of **8** gives rise to a 96% yield of 2'-bromo-N^{α}-*t*-BOC-D-abrine (**9**), $[\alpha]_D$ +83.4° (*c* 1.28, MeOH). The formation of **9** proceeds without any racemization as evidenced by the proton NMR of 2'-bromo-D-abrine methyl ester in the presence of tris[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato]europium(III).

Preparation of the (*R*)-β-tyrosine derivative **13** commenced with commercially available L-4-hydroxyphenylglycine. *tert*-Butyloxycarbonylation (BOC-ON, Et_3N, H_2O-dioxane, 1:1)[5] of L-4-hydroxyphenylglycine followed by silylation [(a) *t*-$Bu(Me)_2SiCl$, imidazole, DMF; (b) K_2CO_3, MeOH, H_2O] provided **10**, $[\alpha]_D$ +81.0° (*c* 1.34, $CHCl_3$) in 98% overall yield. *N*-*t*-BOC amino acid **10** was converted (ClCOOEt, Et_3N, Et_2O) into a mixed anhydride which upon treatment with ethereal diazomethane generated diazoketone **11** in 81% yield. Wolff rearrangement of **11** proceeded smoothly in the presence of silver benzoate and triethylamine in *tert*-butyl alcohol giving rise to **12**, $[\alpha]_D$ +22.6°

(4) Wojciechowska, H.; Ciaskowski, J.; Chmara, H.; Borowski, E. *Experientia* **1972**, *28*, 1423.

(5) Itoh, M.; Hagiwara, D.; Kamiya, T. *Tetrahedron Lett.* **1975**, 4393.

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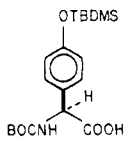

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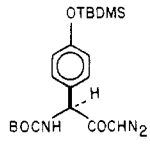

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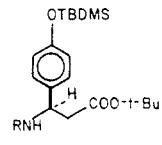
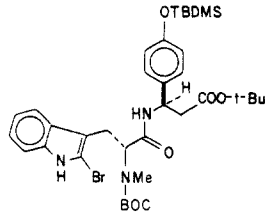


12 R = BOC
13 R = H

(c 1.14, $CHCl_3$), in 61% yield. Selective cleavage of the *N-t*-BOC group in **12** in the presence of the *tert*-butyl ester was realized in ca. 70% overall yield employing *tert*-butyldimethylsilyl triflate (TBDMSOTf) in methylene chloride containing 2,6-lutidine followed by cleavage of the resultant *N-tert*-butyldimethylsilyloxycarbonyl group with potassium carbonate in aqueous methanol–THF(1:1:2).[6]

Coupling (DCC, HBT, THF) of the (*R*)-β-tyrosine derivative **13** with amino acid **9** provided the fully protected dipeptide **14**,



14

$[\alpha]_D$ +27.9° (c 1.88, $CHCl_3$), in 91% yield. Selective cleavage [(a) TBDMSOTf, CH_2Cl_2, 2,6-lutidine; (b) K_2CO_3, H_2O–MeOH–THF, 1:1:2][6] of the *N-t*-BOC group in **14** afforded in 55% yield dipeptide **2**, $[\alpha]_D$ +41.6° (c 2.29, $CHCl_3$).

Construction of the C(1)–C(11) fragment **3** originated with enantiomerically pure (*R*)-(−)-15,[7] $[\alpha]_D$ −60.1° (c 1.38, ether), readily available by resolution of the racemic acid with (−)-α-methylbenzylamine in ether. The absolute configuration of **15** was unambiguously established by single-crystal X-ray analysis of the crystalline ammonium salt.

Iodolactonization of (*R*)-(−)-**15** (Scheme I) followed by reduction and protection of the primary hydroxyl provided **16** in 63% overall yield. Conversion of the secondary hydroxyl into a methoxy methyl ether followed by desilylation and oxidation afforded the corresponding aldehyde which was directly treated with 2-propenylmagnesium bromide. Application of an ortho ester Claisen rearrangement to allylic alcohol **17** generated a rearranged ester which was hydrolyzed and transformed into the *N*-acyloxazolidine **18**, $[\alpha]_D$ +45.3° (c 1.08, $CHCl_3$). Alkylation[8] of the sodium enolate ($NaN(TMS)_2$, THF, −78 °C) of **18** with methyl iodide afforded the desired diastereomer in 71% yield. Removal of the chiral auxiliary employing 3.0 equiv of 2.1 N aqueous potassium hydroxide in methanol gave way to the corresponding carboxylic acid which was converted in a straightforward manner into the pyridinethiol ester **19**, $[\alpha]_D$ +25.6° (c 1.64, $CHCl_3$). Condensation[9] of activated ester **19** with 1.2 equiv of *N*-TMS-Ala-OTMS[10] in tetrahydrofuran (15 h) provided in 91% yield amide **3**, $[\alpha]_D$ −24.5° (c 1.10, $CHCl_3$), thus completing construction of the C(1)–C(11) fragment of jasplakinolide.

Completion of the total synthesis of jasplakinolide required coupling of dipeptide **2** with the C(1)–C(11) segment **3**, which was accomplished with 1.05 equiv of DCC and 1.0 equiv of HBT[11] in tetrahydrofuran. The coupled product **4**, $[\alpha]_D$ +24.4° (c 1.09, $CHCl_3$), was obtained in ca. 50% yield. Conversion of **4** into **1** was realized by the following sequence: (1) cleavage (82%) of the *tert*-butyl ester employing TBDMSOTf (3.0 equiv)/2,6-lutidine (4.0 equiv) in methylene chloride followed by treatment with potassium carbonate (H_2O–MeOH–THF, 1:1:2),[6] (2) deprotection (51%) of the secondary hydroxyl at C(11) with boron trifluoride etherate/ethanedithiol in methylene chloride at 0 °C, (3) macrolactonization (79%) using DCC/DMAP·TFA/DMPA in refluxing chloroform,[12] and (4) desilylation (Bu_4NF, THF, 95%). The synthetic (+)-jasplakinolide, $[\alpha]_D$ +65.6° (c 0.98, CH_2Cl_2), thus obtained was identical ($[\alpha]_D$, TLC, 300 MHz ^1H NMR, CMR, IR, and MS) with an authentic sample of natural material kindly provided by Professor Phillip Crews.

Acknowledgment. Generous support for this work from the National Cancer Institute, National Institutes of Health (Grant CA 28865) and Rohm and Haas Company is gratefully acknowledged. We are grateful to Peter Ramberg for working out the details for the resolution of unsaturated acid **15**, to Drs. Colin Swithenbank and Zev Lidert (Rohm and Haas) for bringing this important problem to our attention, and to Professor Phillip Crews (University of California, Santa Cruz) for a generous sample of natural jasplakinolide.

Supplementary Material Available: Spectral and analytical data for key intermediates **4**, **9**, and **14** and the acid precursor to **19** (1 page). Ordering information is given on any current masthead page.

(6) Cf. Ohfune, Y.; Sakaitani, M. *Tetrahedron Lett.* **1985**, *26*, 5543.
(7) Cf. Corey, E. J.; Hase, T. *Tetrahedron Lett.* **1979**, 335.
(8) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
(9) Mukaiyama, T.; Matsueda, R.; Suzuki, M. *Tetrahedron Lett.* **1970**, *1901*.
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(11) König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788.
(12) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.

Bis(trimethylstannyl)benzopinacolate-Mediated Intermolecular Free-Radical Carbon–Carbon Bond-Forming Reactions: A New One-Carbon Homologation

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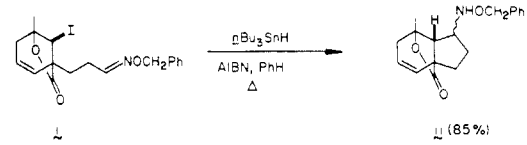
During the course of a total synthesis underway in our laboratories, a need arose for a synthetic method in which a carbon-centered free radical would couple with a one-carbon addend.[1] A survey of the literature suggested that few such methods existed, the most promising being an interesting nitrile synthesis recently developed by Stork.[2] On the basis of the knowledge that free radicals add intramolecularly to oxime ethers,[3,4] we decided to examine an intermolecular variant of this reaction by using *O*-benzylformaldoxime as an addend. The preliminary results of this study are outlined herein.

We began by examining the reactions shown below. Thus, treatment of 1 equiv of iodocyclohexane with tri-*n*-butyltin hydride

† Alfred P. Sloan Fellow, 1983–1987.

(1) For an overview of intermolecular free-radical addition reactions in organic synthesis, see: Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Baldwin, J. E., Ed.; Pergamon Press: New York, 1986.
(2) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1983**, *105*, 6765. Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303.
(3) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, 2821.
(4) (a) Prior to the onset of this study, we demonstrated that **i** could be converted to a 1:1 mixture of diastereomeric perhydroindans **ii** (unpublished results with Dr. Balan Chenera). (b) Also, see: Barlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, following paper in this issue.



i ii (85%)