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Stereocontrolled Total Synthesis of (−)-Ebelactone A

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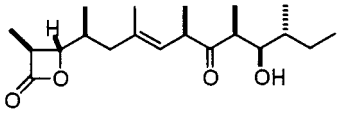
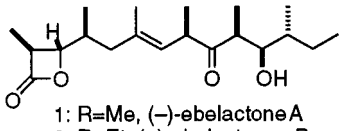
ABSTRACT



The highly stereocontrolled hydroboration of an alkene, a subsequent Suzuki−Miyaura cross-coupling reaction, a silylcupration on a nonterminal acetylene, and an iododesilylation were the key steps in a convergent total synthesis of (−)-ebelactone A.

The ebelactones are a small group of β-lactone enzyme inhibitors, isolated by the Umezawa group in 1980 from a cultured strain of soil actinomycetes (MG7-G1 related to *Streptomyces aburaviensis*).[1] The structure of ebelactone A **1** was determined by X-ray crystallography, and that of ebelactone B **2** was based on spectroscopic comparisons with ebelactone A. The ebelactones show structural characteristics common to macrolide antibiotics,[2] and biosynthetic studies using [1-^{13}C]-labeled acetate, propionate, and butyrate precursors indicate that they are likewise of polyketide origin.[3]



1: R=Me, (−)-ebelactone A
2: R=Et, (−)-ebelactone B

The natural products containing a β-lactone ring display a wide range of biological properties,[4] which have stimulated considerable interest in their chemistry and synthesis.[5] The ebelactones are inhibitors of esterases, lipases, and *N*-formylmethionine aminopeptidases located on the cellular membrane of various kinds of cells. Furthermore, they possess an enolizable ketone and a sensitive β-lactone ring. Paterson and Hulme reported the only total synthesis so far of (−)-ebelactone A, relying on aldol condensations and a Claisen rearrangement strategy.[6] Their overall yield was 4% in 12 linear steps. However, there were a few drawbacks such as its linear nature, the poor diastereoselectivity for the *anti*-aldol reaction used to set up the C2−C3 stereochemistry (52:44:4), and the hydrogenation used to install the C12 stereochemistry (61:39). Here a second synthesis of (−)-ebelactone A in 20% overall yield is reported. It is convergent, more highly stereocontrolled, and uses 20 steps in the longest linear sequence.

The retrosynthetic analysis is based on a stereoselective hydroboration to create component **3** for a Suzuki−Miyaura coupling with vinyl iodide fragment **C** as the key step, with most of the carbon skeleton of the latter set up in the reaction of aldehyde fragment **B** with a crotylstannane (Scheme 1).

The synthesis of fragment **A** begins with Evans' *syn* aldol reaction between *N*-propionyl oxazolidinone **4** and α-benzyloxyacetaldehyde to afford the *syn* aldol product **5** in 95% yield as a single diastereoisomer (Scheme 2).[7]

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(1) (a) Umezawa, H.; Takaaki, A.; Uotani, K.; Hamada, M.; Takeuchi, T.; Takahashi, S. *J. Antibiot.* **1980**, *33*, 1594. (b) Uotani, K.; Naganawa, H.; Kondo, S.; Aoyagi, T.; Umezaba, H. *J. Antibiot.* **1982**, *35*, 1495. (c) Uotani, K. Ph.D. Thesis, Institute of Microbial Chemistry, Tokyo, Japan.

(2) For a review of macrolide antibiotics, see: *Macrolide Antibiotics: Chemistry, Biology and Practice*; Omura, S., Ed.; Academic Press: New York, 1984.

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(5) (a) Paterson, I.; Hulme, A. N. *Tetrahedron Lett.* **1990**, *31*, 7513. (b) For a synthetic approach to ebelactone A using organosilicon chemistry, see: Fleming, I. *Pure Appl. Chem.* **1990**, *62*, 1879.

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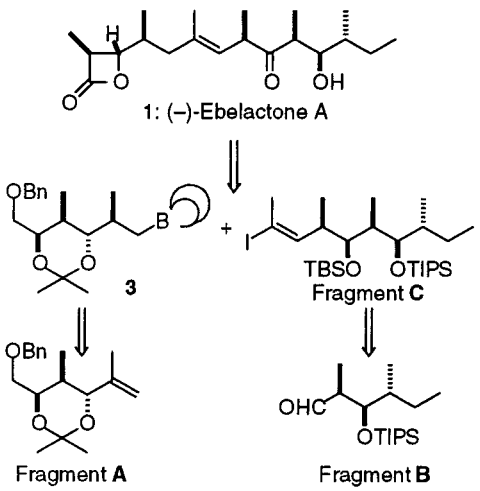
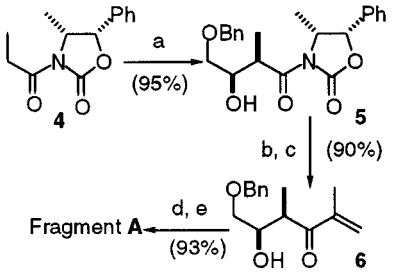
Scheme 1



Transformation of this imide to the Weinreb amide was achieved by treatment with $AlMe_3$ and Me(OMe)NH·HCl. Addition of 2.5 equiv of 2-propenylmagnesium bromide at

Scheme 2[a]



[a] (a) Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C, 45 min; $BnOCH_2CHO$, −78 °C, 3 h, H_2O_2; (b) Me_3Al, Me(MeO)NH·HCl, THF, 0 °C, 3 h; (c) 2-propenylmagnesium bromide, −78 °C, 1 h, −30 °C, 2 h; (d) $Me_4NBH(OAc)_3$, MeCN/AcOH (1:1, v/v), −20 °C, 48 h; (e) 2,2-dimethoxypropane, PPTS, rt, 2 h.

−30 °C proceeded smoothly to furnish the enone **6** in 90% yield over two steps. Evans 1,3-*anti* reduction[8] with $Me_4NBH(OAc)_3$ gave the *anti* diol, which was converted to the acetonide fragment A using $Me_2C(OMe)_2$/PPTS.

The synthesis of Fragment **C** employs Roush's matched double asymmetric reaction between the known aldehyde **7** and the (*S*,*S*)-diisopropyl tartrate derived (*E*)-crotylboronate to give the homoallylic alcohol **8** in 85% yield with 97:3 diastereoselectivity (Scheme 3).[9]

The homoallylic alcohol **8** was protected as its TIPS ether, and hydrogenation gave the disilyl ether **9** in 98% yield over

(7) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.
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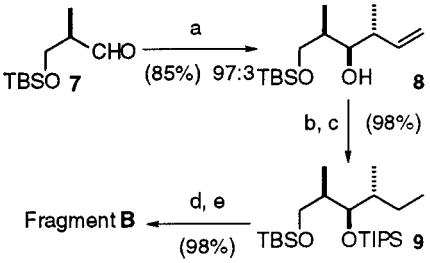
Scheme 3[a]

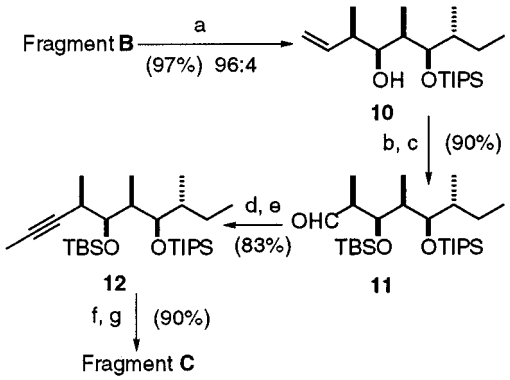


[a] (a) (*S*,*S*)-Diisopropyltartrate modified (*E*)-crotylboronate, 4 Å molecular sieves, − 78 °C, 3 h, then −20 °C, 10 h, aq NaOH; (b) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 6−12 h; (c) 5% Pd/C, H_2, rt, 12 h; (d) PPTS, EtOH, 55 °C, 16 h; (e) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 30 min, Et_3N, −78 to −20 °C, 30 min.

two steps. Reversing the sequence of the last two reactions led to epimerization at C12.[10] Selective cleavage of the primary TBS group with catalytic PPTS in EtOH and Swern oxidation of the primary alcohol gave the aldehyde Fragment **B**.

Fragment **B** was elaborated to homoallylic alcohol **10** via BF_3·OEt_2-mediated crotylstannane addition in 97% yield with 96:4 diastereomeric ratio. Keck has shown that silyl protection at the hydroxyl group β to the aldehyde functionality is necessary for the high *syn-syn* diastereoselectivity seen in this type of reaction.[11] TBS protection of the homoallylic alcohol, followed by ozonolysis and treatment with dimethyl sulfide, gave the aldehyde **11**, which was further elaborated to the acetylene **12** using the method of Corey and Fuchs.[12] Silylcupration[13] of the acetylene **12** gave a vinylsilane, which was converted with retention of configuration into the vinyl iodide fragment **C** with NIS[14] in 90% yield over the two steps (Scheme 4).

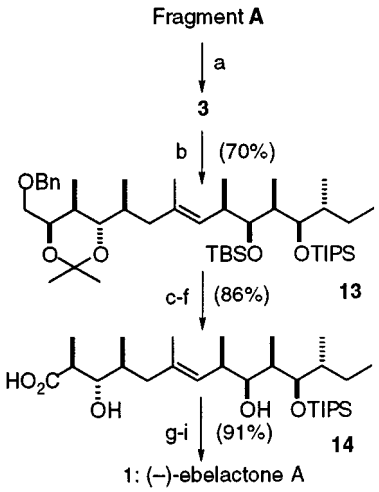
Scheme 4[a]



[a] (a) (*E*)-Crotyl tributylstannane, BF_3·OEt_2, −98 °C to rt 8 h; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 16 h; (c) O_3, CH_2Cl_2/MeOH (1:1, v/v), −78 °C, then Me_2S, −78 °C to rt, 3 h; (d) CBr_4, Ph_3P, 0 °C, 30 min, **11**, 0 °C, 4 h; (e) ^{n}BuLi, −78 to 0 °C, 2 h, MeI, 0 °C to rt, 12 h; (f) $PhMe_2SiLi$, CuCN, 0 °C, 40 min, **12**, 0 °C, 1 h; (g) *N*-iodosuccinimide, MeCN/THF (4:1, v/v) rt, 16 h.

Stereoselective hydroboration of the acetonide fragment **A** with 9-BBN gave the borane **3**. This step installed C4

Scheme 5[a]



[a] (a) Fragment **A**, 9-BBN, THF, rt, 24 h; (b) fragment **C**, Pd(dppf)Cl_2, **3**, aq NaOH, rt, 2 h; (c) CSA, MeOH/CH_2Cl_2 (3:1, v/v), rt, 8 h; (d) lithium naphthalenide, THF, −78 °C, 1 h; (e) $NaIO_4$, MeOH/H_2O (4:1, v/v), rt, 30 min; (f) $NaClO_2$, NaH_2PO_4, ^{t}BuOH/H_2O (4:1, v/v), 2-methyl-2-butene, rt, 10 h; (g) $PhSO_2Cl$, py, −20 °C, 40 h; (h) Dess−Martin periodinane, CH_2Cl_2, rt, 30 min; (i) 48% HF, MeCN, rt, 2 h.

with the correct stereochemistry based on Still's hydroboration of allylic alcohols.[15] Suzuki−Miyaura cross-coupling[16] was achieved between the borane **3** and the vinyl iodide fragment **C** using catalytic Pd(dppf)Cl_2 to furnish the desired cross-coupled product **13** in 70% yield as a single diastereoisomer based on its 500 MHz ^{1}H NMR spectrum analysis. Selective cleavage of the acetonide and the TBS ether took place using CSA in MeOH/CH_2Cl_2, which was followed by benzyl ether cleavage employing lithium naphthalenide. Sodium periodate cleaved the 1,2-diol, and the aldehyde was oxidized to the dihydroxy carboxylic acid **14** using Pinnick's conditions.[17] Adam's β-lactonization[18] gave the β-lactone. There was no trace of the possible 10-membered lactone. Dess−Martin periodinane oxidation of the free hydroxyl functionality at C9 in the β-lactone gave the ketone in good yield, and cleavage of the TIPS ether using 48% hydrofluoric acid in acetonitrile gave (−)-ebelactone A **1** in 100% yield (Scheme 5).

The spectra [^{1}H NMR ($CDCl_3$, 500 and 800 MHz), ^{13}C NMR ($CDCl_3$, 500 MHz), IR, MS] and specific rotation were recorded and were identical to those of natural (−)-ebelactone A and to Paterson and Hulme's synthetic sample. The melting point was also in agreement with the literature data.

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Supporting Information Available: Experimental procedure and spectral data for compound **13**, and high-resolution mass, 800 MHz ^{1}H and 500 MHz ^{13}C NMR spectra of (−)-ebelactone A along with the ^{1}H correlation and ^{13}C correlation tables. This material is available free of charge via the Internet at http://pubs.acs.org.

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