ORGANIC LETTERS

2010
Vol. 12, No. 18
4074−4077

Two Concise Total Syntheses of (−)-Bitungolide F

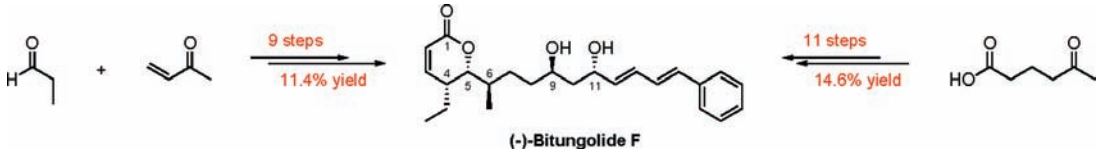
Abdelatif ElMarrouni, Shyamsunder R. Joolakanti, Aude Colon, Montserrat Heras,[†] Stellios Arseniyadis,* and Janine Cossy*

Laboratoire de Chimie Organique, ESPCI ParisTech, CNRS, 10 rue Vauquelin, 75231 Paris Cedex 05, France

stellios.arseniyadis@espci.fr; janine.cossy@espci.fr

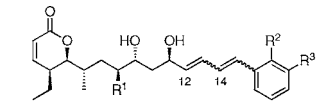
Received July 17, 2010

ABSTRACT



The enantioselective total synthesis of the dual-specificity phosphatase inhibitor (−)-bitungolide F has been achieved using two convergent routes. Both strategies feature an asymmetric boron-mediated pentenylation, a stereoselective aldol, and a hydroxyl-directed 1,3-*anti*-reduction in order to control the stereogenic centers at C4, C5, C9, and C11. Whereas the first total synthesis was achieved in 11 steps and 14.6% overall yield using an Evans-type asymmetric alkylation, the second was completed in 9 steps and 11.4% overall yield using a highly enantioselective organocatalytic Michael addition as a key step and a protecting group free strategy.

Natural products that incorporate a γ-ethyl substituted α,β-unsaturated δ-lactone moiety such as the leustroducsins,[1] the phoslactomycins,[2] and pironetin[3] have attracted considerable attention over the past two decades due to their promising pharmacological properties. More recently, Tanaka et al.[4] isolated a new family of structurally related polyketides from the Indonesian sponge *Theonella cf. swinhoei*, bitungolides A−F, which incorporate, in addition to the 5,6-dihydropyran-2-one motif, an *anti*-1,3-diol unit and a diene attached to a substituted arene (Figure 1).[5] These compounds exhibited cytotoxic effects against 3Y1 rat normal fibroblast cells and inhibition toward VH1-related (VHR) dual-specificity phosphatase, thus becoming attractive targets for both synthetic and medicinal chemists.



(+)-Bitungolide A : 12*Z*,14*Z*, R^1 = Me, R^2 = Cl, R^3 = OH
(+)-Bitungolide B : 12*E*,14*E*, R^1 = Me, R^2 = Cl, R^3 = OH
(+)-Bitungolide C : 12*Z*,14*E*, R^1 = Me, R^2 = Cl, R^3 = OH
(+)-Bitungolide D : 12*E*,14*Z*, R^1 = Me, R^2 = Cl, R^3 = OH
(+)-Bitungolide E : 12*E*,14*E*, R^1 = Me, R^2 = R^3 = OH
(+)-Bitungolide F : 12*E*,14*E*, R^1 = R^2 = R^3 = H

Figure 1. Structures of natural bitungolides.

As part of our ongoing efforts in developing synthetically useful methods[6−8] and applying them to the synthesis of structurally intriguing molecules, we became particularly interested in using a stereoselective boron-mediated pente-

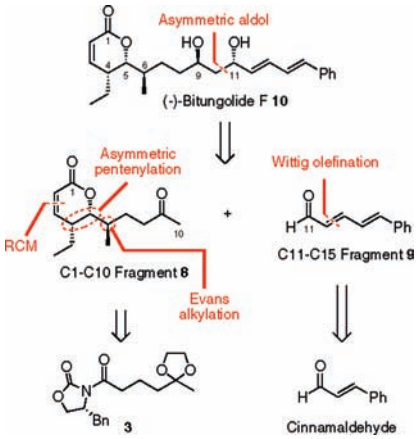
[†] Department of Chemistry, Faculty of Sciences, University of Girona, Campus de Montilivi, E-17071 Girona, Spain.

(1) (a) Kohama, T.; Enokita, R.; Okazaki, T.; Miyaoka, H.; Torikata, A.; Inukai, M.; Kaneko, I.; Kagasaki, T.; Sakaida, Y.; Satoh, A.; Shiraishi, A. *J. Antibiot.* **1993**, *46*, 1503–1511. (b) Kohama, T.; Nakamura, T.; Kinoshita, T.; Kaneko, I.; Shiraishi, A. *J. Antibiot.* **1993**, *46*, 1512–1519. (c) Matsuhashi, H.; Shimada, K. *Tetrahedron* **2002**, *58*, 5619–5626.

(2) (a) Fushimi, S.; Nishikawa, S.; Shimazu, A.; Seto, H. *J. Antibiot.* **1989**, *42*, 1019–1025. (b) Fushimi, S.; Furihata, K.; Seto, H. *J. Antibiot.* **1989**, *42*, 1026–1036. (c) Ozasa, T.; Suzuki, K.; Sasamata, M.; Tanaka, K.; Kobori, M.; Kadota, S.; Nagai, K.; Saito, T.; Watanabe, S.; Iwanami, M. *J. Antibiot.* **1989**, *42*, 1331–1338. (d) Ozasa, T.; Tanaka, K.; Sasamata, M.; Kaniwa, H.; Shimizu, M.; Matsumoto, H.; Iwanami, M. *J. Antibiot.* **1989**, *42*, 1339–1343. (e) Shibata, T.; Kurihara, S.; Yoda, K.; Haruyama, H. *Tetrahedron* **1995**, *51*, 11999–12012. (f) Sekiyama, Y.; Palaniappan, N.; Reynolds, K. A.; Osada, H. *Tetrahedron* **2003**, *59*, 7465−7471. (g) Choudhuri, S. D.; Ayers, S.; Soine, W. H.; Reynolds, K. A. *J. Antibiot.* **2005**, *58*, 573–582. (h) Mizuhara, N.; Usuki, Y.; Ogita, M.; Fujita, K.; Kuroda, M.; Doe, M.; Lio, H.; Tanaka, T. *J. Antibiot.* **2007**, *60*, 762–765.

10.1021/ol101659y
Published on Web 08/20/2010

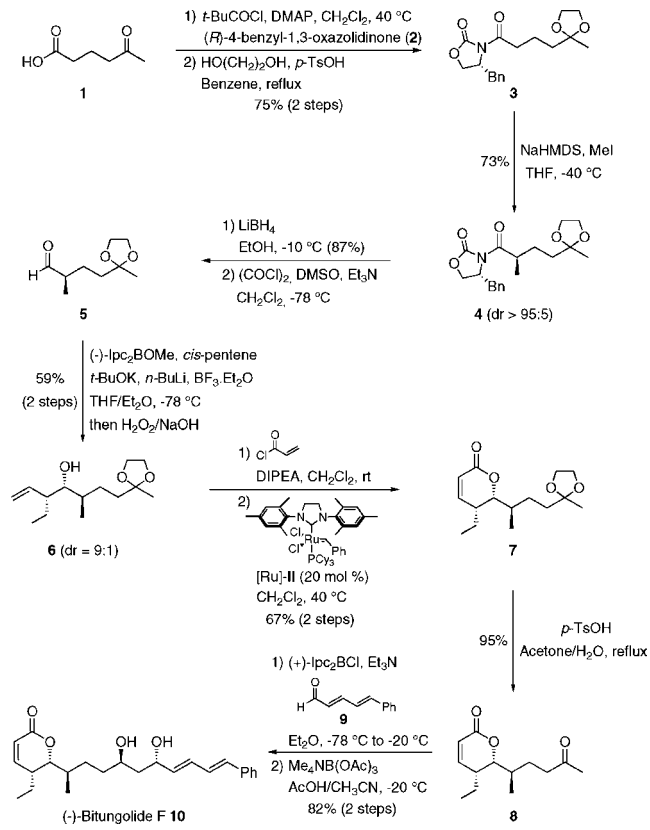
Scheme 1. First Strategy for the Synthesis of (−)-Bitungolide F



nylation[6,9] as a key step in the synthesis of (−)-bitungolide F. We therefore embarked in this project with the aim of developing a highly straightforward and flexible route that would allow an easy access to the natural product as well as to various analogues thereof. We report here the results of our endeavor.

In order to guarantee high efficacy as well as potential late-stage diversification, our initial strategy relied on four key reactions: a chiral boron-mediated aldolization to generate the C10−C11 bond and concomitantly set the C11 stereogenic center, a stereoselective pentenylation to introduce the ethyl side chain at C4, an asymmetric Evans alkylation to install the C6 stereogenic center, and a ring-closing metathesis (RCM) to build the lactone ring (Scheme 1). Two

Scheme 2. Synthesis of (−)-Bitungolide F *via* an Asymmetric Evans Alkylation



key fragments, **8** and **9**, were therefore identified. The synthesis of the C1−C10 fragment **8** began by converting levulinic acid **1** to the corresponding chiral *N*-acyloxazolidinone [*t*-BuCOCl, DMAP, 40 °C, followed by (*R*)-4-benzyl-1,3-oxazolidinone (**2**)] and protecting the ketone [HO-$(CH_2)_2$OH, *p*TsOH, benzene, reflux] as a ketal (Scheme 2). The resulting chiral *N*-acyloxazolidinone was then subjected to a highly diastereoselective Evans alkylation[10] (NaHMDS, MeI, THF, −40 °C) to afford the corresponding methylated product **4** in 73% yield (dr >95:5).[11] Removal of the chiral auxiliary[12] using $LiBH_4$ (87%) followed by the oxidation of the resulting allylic alcohol under standard Swern conditions

(3) (a) Yoshida, T.; Koizumi, K.; Kawamura, Y.; Matsumoto, K.; Itazaki, H. Japan Patent Kokai 5-310726, 1993. (b) Yoshida, T.; Koizumi, K.; Kawamura, Y.; Matsumoto, K.; Itazaki, H. European Patent 560389 A1, 1993. (c) Yasui, K.; Tamura, Y.; Nakatani, T.; Kawada, K.; Ohtani, M. *J. Org. Chem.* **1995**, *60*, 7567–7574. (d) Kobayashi, S.; Tsuchiya, K.; Harada, T.; Nishide, M.; Kurokawa, T.; Nakagawa, T.; Shimada, N.; Kobayashi, K. *J. Antibiot.* **1994**, *47*, 697–702. (e) Kobayashi, S.; Tsuchiya, K.; Harada, T.; Nishide, M.; Kurokawa, T.; Nakagawa, T.; Shimada, N.; Iitaka, T. *J. Antibiot.* **1994**, *47*, 703–707.

(4) Sirirath, S.; Tanaka, J.; Ohtani, I. I.; Ichiba, T.; Rachmat, R.; Ueda, K.; Usui, T.; Osada, H.; Higa, T. *J. Nat. Prod.* **2002**, *65*, 1820–1823.

(5) While the structure of these new *Theonella* metabolites was elucidated by X-ray diffraction, the absolute stereochemistry was secured by total synthesis, first by Ghosh et al. and then by She et al.; see: (a) Ghosh, S.; Kumar, S. U.; Shashidhar, J. *J. Org. Chem.* **2008**, *73*, 1582–1585. (b) Xu, Y.; Huo, X.; Li, X.; Zheng, H.; She, X.; Pan, X. *Synlett* **2008**, 1665–1668. (c) Su, Y.; Xu, Y.; Han, J.; Zheng, J.; Qi, J.; Jiang, T.; Pan, X.; She, X. *J. Org. Chem.* **2009**, *74*, 2743–2749.

(6) For the development of an asymmetric Brown-type pentenylation, see: (a) Sonawane, R. P.; Joolakanti, S. R.; Arseniyadis, S.; Cossy, J. *Synlett* **2009**, 213–216. For applications in natural product synthesis, see: Bressy, C.; Vors, J.-P.; Hillebrand, S.; Arseniyadis, S.; Cossy, J. *Angew. Chem, Int. Ed.* **2008**, *47*, 10137–10140. (b) Moïse, J.; Sonawane, R. P.; Corsi, C.; Wendeborn, S. V.; Arseniyadis, S.; Cossy, J. *Synlett* **2008**, 2617–2620.

(7) For the development of a cross-metathesis involving vinyl-functionalized azoles, see: (a) Dash, J.; Arseniyadis, S.; Cossy, J. *Adv. Synth. Catal.* **2007**, *349*, 152–156. (b) Hoffman, T. J.; Rigby, J. H.; Arseniyadis, S.; Cossy, J. *J. Org. Chem.* **2008**, *73*, 2400–2403. For applications in natural product synthesis, see: (c) Gebauer, J.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2007**, *9*, 3425–3427. (d) Gebauer, J.; Arseniyadis, S.; Cossy, J. *Eur. J. Org. Chem.* **2008**, 2701–2704.

(8) For the development of an enantioselective organocatalytic conjugate reduction of β-azole α,β-unsaturated aldehydes and its application in natural product synthesis, see: Hoffman, T. J.; Dash, J.; Rigby, J. H.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2009**, *11*, 2756–2759.

(9) Hatakeyama et al. have very recently used a similar procedure in their synthesis of phoslactomycin B; see: Shibahara, S.; Fujino, M.; Tashiro, Y.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2008**, *10*, 2139–2142.

(10) (a) Evans, D. A.; Kim, A. S. In *Handbook of Reagents for Organic Synthesis: Reagents, Auxiliaries, and Catalysts for C−C bond Formation*; Coates, R. M., Denmark, S. E., Eds.; John Wiley and Sons: New York, 1999; pp 91−101. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichimica Acta* **1997**, *30*, 3–12. (c) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23–32. (d) Smith, T. E.; Richardson, D. P.; Truran, G. A.; Belecki, K.; Onishi, M. *J. Chem. Ed.* **2008**, *85*, 695–697.

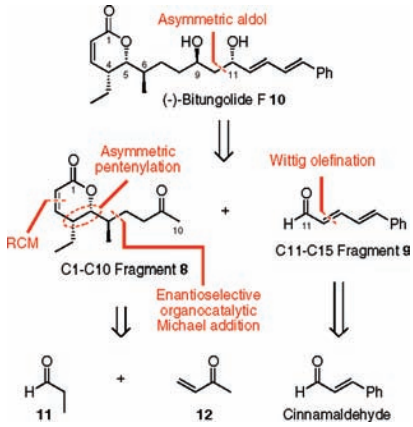
(11) The second diastereomer could not be detected by either ^{1}H or ^{13}C NMR of the crude reaction mixture, thus suggesting a dr > 95:5.

(12) Smith, A. B., III; Lee, D. *J. Am. Chem. Soc.* **2007**, *129*, 10957–10962.

(13) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293–294.

(14) (a) Schlosser, A.; Despond, O.; Lehmann, R.; Moret, E.; Rauchschwalbe, G. *Tetrahedron* **1993**, *49*, 10175–10203. (b) Schlosser, A.; Hartmann, J. *J. Am. Chem. Soc.* **1976**, *98*, 4674–4676. (c) Roush, W.; Adam, M.; Walts, A.; Harris, D. *J. Am. Chem. Soc.* **1986**, *108*, 3422–3434.

Scheme 3. Second Strategy for the Synthesis of (−)-Bitungolide F



led to the corresponding aldehyde **5**, which was engaged in a newly developed boron-mediated asymmetric pentenylation reaction[6] inspired by the asymmetric crotylation procedure developed by Brown et al.[13] Hence, aldehyde **5** was subjected to a chiral (*Z*)-pentenylborane reagent generated *in situ* from (*Z*)-2-pentene [*n*-BuLi/*t*-BuOK, (−)-Ipc$_2$B(OMe), BF$_3$•OEt$_2$, THF, −78 °C][14] affording the corresponding homoallylic alcohol **6** (dr = 9:1) in 59% yield (2 steps) with a complete control of the *syn*-relationship between the two substituents at C4 and C5.[15] The latter was then efficiently converted into the corresponding α,*β*-unsaturated *δ*-lactone using an acylation/RCM sequence, thus affording compound **7** in 67% yield over the two steps.[16] The ketone was eventually deprotected[17] upon refluxing in an acetone/H_2O mixture in the presence of a catalytic amount of *p*-TsOH (95%), thus setting the stage for the chiral boron enolate mediated asymmetric aldol reaction.[18] In order to perform this key transformation, we first needed to prepare the required (*E*,*E*)-dienal **9**. The latter was synthesized in 75% overall yield starting from cinnamaldehyde *via* a three-step sequence that involved a Wittig olefination ($Ph_3P{=}C(Me)CO_2Et$, THF, rt), a DIBAL-H mediated reduction, and a final oxidation with MnO_2.[19] With the two units **8** and **9** in hand, we were finally ready to perform the key chiral boron-mediated aldol reaction that would lead to the entire carbon backbone of (−)-bitungolide F. Ketone **8** was thus treated with (+)-Ipc$_2$BCl (Et_3N, Et_2O, −78 °C) to afford the chiral boron

(15) The second diastereomer could not be detected by either ^{1}H or ^{13}C NMR of the crude reaction mixture, thus suggesting a a dr > 95:5.

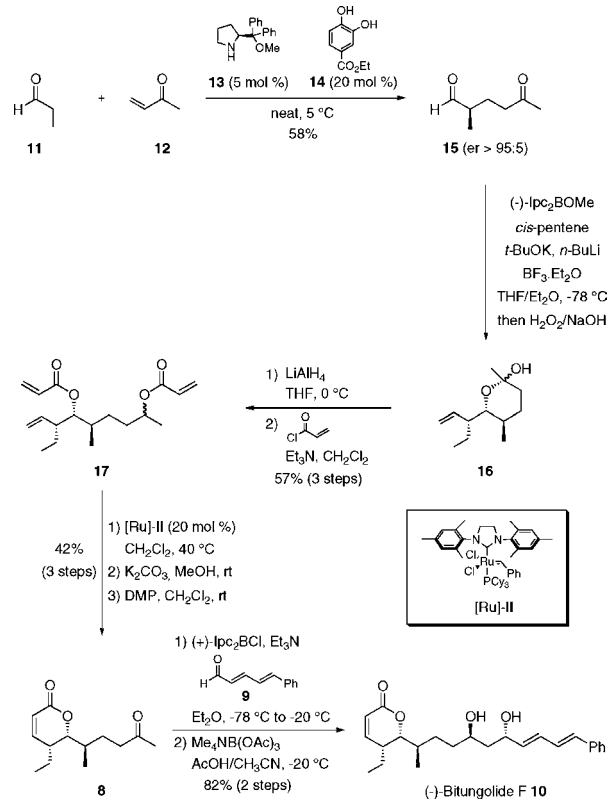
(16) (a) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136. (b) Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651–4654. (c) Cossy, J.; Bauer, D.; Bellosta, V. *Tetrahedron Lett.* **1999**, *40*, 4187–4188. (d) Boucard, V.; Broustal, G.; Campagne, J. M. *Eur. J. Org. Chem.* **2007**, 225–236.

(17) Meissner, R. S.; Perkins, J. J.; Duong, L. T.; Hartman, G. D.; Hoffman, W. F.; Huff, J. R.; Ihle, N. C.; Leu, C.-T.; Nagy, R. M.; Naylor-Olsen, A.; Rodan, G. A.; Rodan, S. B.; Whitman, D. B.; Wesolowski, G. A.; Duggan, M. E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 25–29.

(18) (a) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1–200. (b) Paterson, I.; Goodman, J. M. *Tetrahedron Lett.* **1989**, *30*, 997–1000. (c) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663–4684. (d) Cergol, K. M.; Coster, M. J. *Nat. Protoc.* **2007**, *10*, 2568–2573.

(19) Cao, X.-P. *Tetrahedron* **2002**, *58*, 1301–1307.

Scheme 4. Synthesis of (−)-Bitungolide F *via* an Enantioselective Organocatalyzed Michael Addition



enolate intermediate, which was then reacted with aldehyde **9**. The resulting aldol adduct (dr = 5:1) was directly reduced to the corresponding 1,3-*anti* diol ($Me_4NB(OAc)_3$, AcOH/CH_3CN, −20 °C) in order to prevent any partial elimination that could occur on such systems.[20] To our delight, we were able to isolate (−)-bitungolide F as a single diastereoisomer in 82% yield (2 steps). As expected, the spectroscopic and physical data of **10** were identical with those reported for the natural product except for the optical rotation, which was of opposite sign {$[\alpha]^{20}_D$ −51.6 (*c* 1.56, $CHCl_3$); lit.[4] $[\alpha]^{22}_D$ +43.0 (*c* 0.85, $CHCl_3$)}.

Having completed the synthesis of (−)-bitungolide F, we continued our efforts to conceive a slightly more flexible route, which would allow access to a variety of analogues for further biological screening and structure−activity relationship (SAR) studies. In this context, we decided to modify the synthesis of fragment **8** while keeping the asymmetric aldol/1,3-*anti* reduction end game. In order to gain maximum versatility, we therefore devised our synthesis around an enantioselective organocatalyzed Michael addition, which would afford the C5−C10 aldehyde in one step, and the boron-mediated asymmetric pentenylation/acylation/RCM sequence disclosed previously (Scheme 3).

The synthesis of ketone **8** commenced with Chi's and Gellman's recently reported highly enantioselective organo-

(20) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.

catalytic Michael addition of simple aldehydes to non-activated enones (Scheme 4).[21] Hence, by subjecting propanal **11** and methyl vinyl ketone **12** to diphenylprolinol methyl ether **13** (5 mol %) and catechol **14** (20 mol %), we were able to isolate aldehyde **15** in a moderate 58% yield but with an excellent enantioselectivity (er > 95:5).[22] The latter was then engaged in the same boron-mediated asymmetric pentenylation reaction as previously to afford the corresponding homoallylic alcohol, which spontaneously underwent hemiketalization.[23] After failing to selectively acylate the homoallylic alcohol by pushing the hemiacetal/hydroxy ketone equilibrium, we decided to directly reduce the crude reaction mixture with $LiAlH_4$ (THF, 0 °C, 94%) and bis-acylate the resulting diol (acryloyl chloride, Et_3N, CH_2Cl_2, quant). This three-step sequence resulted in the isolation of the RCM precursor **17** in 57% yield. The latter then underwent a RCM with the Grubbs second generation catalyst (CH_2Cl_2, 40 °C, 66%), followed by the saponification of the acrylate (K_2CO_3, MeOH, rt, 75%) and the oxidation of the resulting secondary alcohol (DMP, CH_2Cl_2, rt, 84%) to give the desired ketone **8** in seven steps and 13.9% overall yield starting from propanal **11** and methyl vinyl ketone **12**. (−)-Bitungolide F was eventually isolated after the chiral boron-mediated aldol reaction/1,3-*anti* reduction sequence thus validating this second strategy.

In conclusion, we have completed the synthesis (−)-bitungolide F using two very convergent routes that feature an asymmetric boron-mediated pentenylation, a stereoselective aldol and a hydroxyl-directed 1,3-*anti*-reduction to control the stereogenic centers at C4, C5, C9 and C11. The first strategy was achieved in 11 steps and 14.6% overall yield using an Evans-type asymmetric alkylation to control the stereogenic centers at C6, while the second strategy was completed in only nine steps and 11.4% overall yield using a highly enantioselective organocatalytic Michael addition. It is worth pointing out that while both syntheses are considerably shorter than the ones reported so far,[24] the second approach is particularly appealing as it is highly flexible, does not involve the use of any protecting group, and is therefore amenable to a wide variety of potentially useful synthetic analogues.

Acknowledgment. We would like to thank Generalitat de Catalunya and the Ministère de l'Enseignement Supérieur et de la Recherche for financial support to A.E. and A.C., respectively.

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

OL101659Y

(21) Chi, Y.; Gellman, S. H. *Org. Lett.* **2005**, *19*, 4253–4256.

(22) The enantiomeric excess was determined by crude ^1H NMR analysis after subjecting aldehyde **15** to an oxidation/peptide coupling sequence, L-alanine methyl ester being the amine coupling partner.

(23) Unfortunately, we were unable to determine the selectivity of the boron-mediated asymmetric pentenylation from the crude ^1H NMR due to overlapping signals.

(24) She et al. synthesis of (−)-bitungolide F was achieved in 21 steps starting from (−)-malic acid, whereas Ghosh et al. synthesis of (−)-bitungolide F was completed in 22 steps starting from the same starting material.