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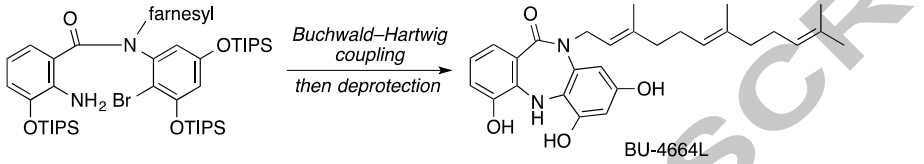

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First synthesis of BU-4664L

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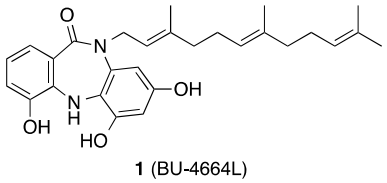
ABSTRACT

The first synthesis of BU-4664L, an actinomycte-produced *N*-farnesylated dibenzodiazepinone with important biological activities, has been achieved in 18% overall yield from a known benzoic acid derivative by a nine-step sequence that involves an intramolecular Buchwald–Hartwig coupling of a sterically demanding bromo amine intermediate to install the unique tricyclic ring system.

BU-4664L (**1**) was first discovered by Bristol-Myers Squibb in the fermentation broth of the actinomycete *Micromonospora* sp. M990-6 and shown to exhibit rat 5-lipoxygenase inhibitory activity (IC_{50}, 1.7 μM), significant in vitro cytotoxicity against several tumor cell lines (IC_{50}, 1.1–18 μM), and in vivo antitumor activity against P388 leukemia and B16 melanoma (Figure 1).[1] This compound was later reisolated from other *Micromonospora* strains by some research groups[2–6] and has also been referred to as ECO-04601 (or ECO-4601),[2,7] TLN-4601,[8] or diazepinomicin.[3] Other important biological properties of **1** such as antimicrobial activity,[3] binding ability to peripheral benzodiazepine receptor,[9,10] anti-invasive and anti-angiogenic activities,[11] Ras-MAPK signaling pathway inhibitory effect,[8,12] and antioxidant as well as anti-protease activities,[5] have also been reported so far. From a structural viewpoint, it is worth mentioning that BU-4664L (**1**) is the only natural product that incorporates a 5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one core. The structural uniqueness of **1** as well as the intriguing biological activities prompted its biosynthetic and structure–activity relationship (SAR) studies,[1,7,11,13–17] the latter of which led to some promising analogs with better pharmacological profiles.[7,11] Most analogs employed in the SAR studies were prepared by directly derivatizing **1** of natural origin,[1,7,13,11] while, for *N*-farnesylated dibenzodiazepinone analogs with simpler substitution patterns on the benzene rings, intramolecular condensation of amino carboxylic acid intermediates was utilized for the formation of the tricyclic fused ring system.[17] Despite the appearance of a considerable number of SAR studies involving analog synthesis, the synthesis of BU-4664L itself has never been reported to date. We describe herein the first synthesis of **1**, which would endow SAR studies on **1** with more flexibility in analog design.



1 (BU-4664L)

Figure 1. Structure of BU-4664L (**1**).

Scheme 1 outlines our retrosynthetic analysis of BU-4664L (**1**). We planed to install the seven-membered diazepinone ring in **1** by the intramolecular Buchwald–Hartwig coupling of **2**; global deprotection of the resulting tricyclic product would afford the target molecule **1**. The bromo amine intermediate **2** should readily be prepared by reduction of nitro compound **3**, which would be obtainable by amide bond formation between benzoic acid derivative **4** and protected 3,5-dihydroxyaniline **5**.

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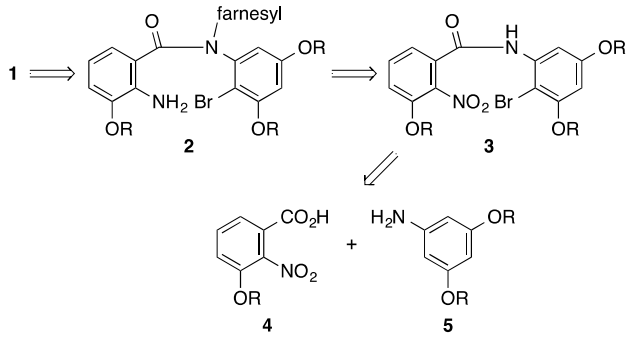
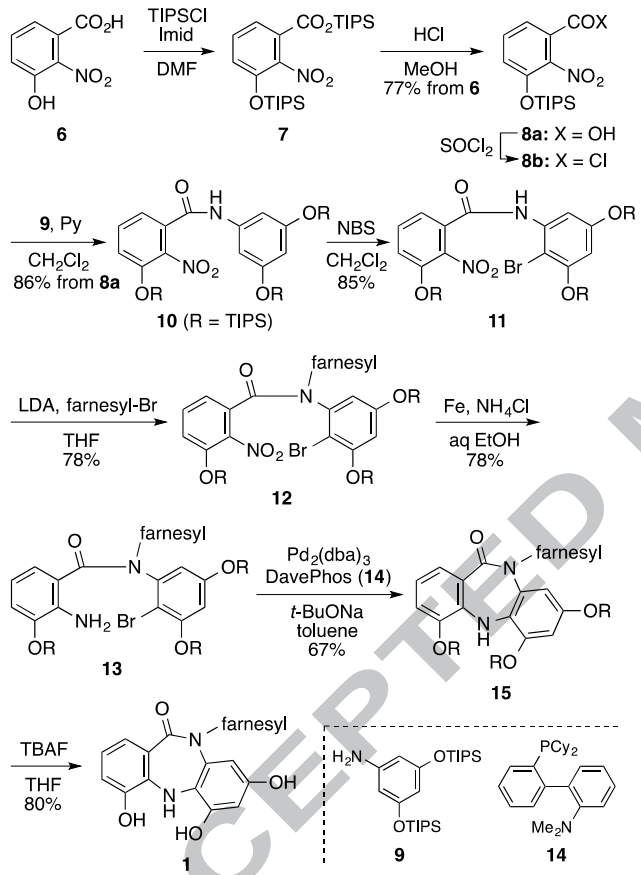


Scheme 1. Retrosynthetic analysis of **1**.



Scheme 2. Synthesis of BU-4664L (**1**).

Our synthesis of **1** began with the preparation of carboxylic acid **8a** (Scheme 2). Treatment of commercially available hydroxy acid **6** with an excess amount of TIPSCl and imidazole in DMF gave **7**, the selective methanolysis of which under acidic conditions afforded **8a** in 78% yield for the two steps. The aromatic acid **8a** was activated by converting into the corresponding acid chloride **8b** and then condensed with bis-TIPS-protected 3,5-dihydroxyaniline **9** to give amide **10** in 86% yield. Compound **9**, in turn, could readily be obtained from 5-aminoresorcinol by treatment with TIPSCl and imidazole in DMF or from phloroglucinol in two steps based on literature protocols.[18,19] Bromination of **10** with NBS in CH_2Cl_2 proceeded regioselectively to afford **11**. Installation of a farnesyl side chain into **11** was performed by deprotonation of the amide hydrogen with LDA followed by *N*-alkylation of the resulting anion with farnesyl bromide to give **12** in 78% yield. The *N*-farnesylation of **11** could also be effected in 82% yield by using NaH as the base instead of LDA, but the use of LDA was superior to that of NaH in reproducibility. Reduction of the nitro group in **12** with Fe and NH_4Cl in aqueous EtOH gave **13** in 78% yield, which set the stage for the installation of the dibenzodiazepinone ring system by the intramolecular Buchwald–Hartwig coupling. Despite our concern that the steric congestion around both the amino group and the bromine substituent of **13** might hamper the intramolecular ring formation, treatment of **13** with $Pd_2(dba)_3$ (30 mol%) and P(*o*-tolyl)$_3$ (60 mol%) in refluxing toluene in the presence of *t*-BuONa afforded desired product **15**, albeit in a modest yield of 34%.[20,21] Fortunately, this cyclization could be improved significantly by using a catalyst system composed of $Pd_2(dba)_3$, DavePhos (**14**) and *t*-BuONa;[22,23] refluxing a mixture of **13**, $Pd_2(dba)_3$ (10 mol%), **14** (20 mol%), and *t*-BuONa in toluene furnished **15** in an acceptable yield of 67%.[24] Finally, removal of the three TIPS groups with TBAF in 80% yield completed the synthesis of BU-4664L (**1**), the ^{1}H and ^{13}C NMR spectra of which were identical with those of an authentic material.[4]

In conclusion, the first synthesis of BU-4664L (**1**) was achieved in 18% overall yield from the commercially available benzoic acid derivative **6** by a 9-step sequence involving the intramolecular Buchwald–Hartwig coupling of the highly sterically demanding bromo amine **13** as the key step. The successful completion of the synthesis of **1** would enable the preparation of BU-4664L analogs with various side chains via *N*-alkylation of intermediate **11**, and thereby make it possible to evaluate biological activities of thitherto unprepared analogs of **1** that possess an *N*-substituent other than sesquiterpenoidal fifteen-carbon chains, such as a geranyl or a geranylgeranyl group, while maintaining the substitution pattern on the two benzene ring of **1**.

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Supplementary data

Supplementary data (experimental procedures, characterization data, and copies of NMR spectra for new compounds) associated with this article can be found, in the online version, at doi:

References and notes

1. Ohkuma, H.; Kobaru, S. U.S. Patent 5,541,181, 1996.
2. Bachmann, B. O.; McAlpine, J. B.; Zazopoulos, E.; Farnet, C. M.; Piraee, M. WO 2004/065591A1, 2004.
3. Charan, R. D.; Schlingmann, G.; Janso, J.; Bernan, V.; Feng, X.; Carter, G. T. *J. Nat. Prod.* **2004**, *67*, 1431–1433.
4. Igarashi, Y.; Miyanaga, S.; Onaka, H.; Takeshita, M.; Furumai, T. *J. Antibiot.* **2005**, *58*, 350–352.
5. Abdelmohsen, U. R.; Szesny, M.; Othman, E. M.; Schirmeister, T.; Grond, S.; Stopper, H.; Hentschel, U. *Mar. Drugs* **2012**, *10*, 2208–2221.
6. Songsumanus, A.; Kudo, T.; Igarashi, Y.; Tanasupawat, S. *Malays. J. Microbiol.* **2013**, *9*, 260–269.
7. McAlpine, J. B.; Banskota, A. H.; Aouidate, M. U.S. Patent 7,304,054, 2007.
8. Campbell, P. M.; Boufaied, N.; Fiordalisi, J. J.; Cox, A. D.; Falardeau, P.; Der, C. J.; Gourdeau, H. *J. Mol. Signal.* **2010**, *5*, 18.
9. Gourdeau, H.; McAlpine, J. B.; Ranger, M.; Simard, B.; Berger, F.; Beaudry, F.; Falardeau, P. *Cancer Chemother. Pharmacol.* **2008**, *61*, 911–921.
10. Bertomeu, T.; Zvereff, V.; Ibrahim, A.; Zehntner, S. P.; Aliaga, A.; Rosa-Neto, P.; Bedell, B. J.; Falardeau, P.; Gourdeau, H. *Biochem. Pharmacol.* **2010**, *80*, 1572–1579.
11. Miyanaga, S.; Sakurai, H.; Saiki, I.; Onaka, H.; Igarashi, Y. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 963–965.
12. Mason, W. P.; Belanger, K.; Nicholas, G.; Vallières, I.; Mathieu, D.; Kavan, P.; Desjardins, A.; Omuro, A.; Reymond, D. *J. Neurooncol.* **2012**, *107*, 343–349.
13. McAlpine, J. B.; Banskota, A. H.; Charan, R. D.; Schlingmann, G.; Zazopoulos, E.; Piraee, M.; Janso, J.; Bernan, V. S.; Aouidate,

M.; Farnet, C. M.; Feng, X.; Zhao, Z.; Carter, G. T. *J. Nat. Prod.* **2008**, *71*, 1585–1590.
14. Ratnayake, A. R.; Janso, J. E.; Feng, X.; Schlingmann, G.; Goljier, I.; Carter, G. T. *J. Nat. Prod.* **2009**, *72*, 496–499.
15. Feng, X.; Ratnayake, A. S.; Charan, R. D.; Janso, J. E.; Bernan, V. S.; Schlingmann, G.; He, H.; Tischler, M.; Koehn F. E.; Carter, G. T. *Bioorg. Med. Chem.* **2009**, *17*, 2154–2161.
16. Bonitz, T.; Zubeil, F.; Grond, S.; Heide, L. *PLoS One* **2013**, *8*, e85707.
17. Yu, Y.; Wu, J.; Lei, F.; Chen, L.; Wan, W.; Hai, L.; Guan, M.; Wu, Y. *Lett. Drug Des. Discov.* **2013**, *10*, 369–373.
18. Thorn, M. A.; Denny, G. H.; Babson, R. D. *J. Org. Chem.* **1975**, *40*, 1556–1558.
19. Peterca, M.; Imam, M. R.; Ahn, C.-H.; Balagurusamy, V. S. K.; Wilson, D. A.; Rosen, B. M.; Percec, V. *J. Am. Chem. Soc.* **2011**, *133*, 2311–2328.
20. Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1995**, *34*, 1348–1350.
21. Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805–818.
22. Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722–9723.
23. Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27–50.
24. For analogous cyclization of halo amines leading to dibenzodiazepinone derivatives, see: (a) Beccalli, E. M.; Broggini, G.; Paladino, G.; Zoni, C. *Tetrahedron* **2005**, *61*, 61–68; (b) Majumdar, K. C.; Ganai, S. *Synlett* **2011**, 1881–1887.