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C−C Bond Formation via C−H Bond Activation: Synthesis of the Core of Teleocidin B4

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The practice of organic synthesis has been fundamentally changed by the introduction of metal-mediated coupling reactions, for instance, the Heck and Suzuki reactions, the α-arylation of carbonyl compounds,[1] and multiple bond metathesis.[2] However, these now routine reactions require that both reactants contain a reactive functional group. Thus, it seems logical that the next frontier in organic synthesis will center on reducing the number of required functionalities in coupling processes, namely C−C bond formation via C−H activation.[3] This would represent a powerful synthetic method in which *only one component of the coupling reaction need to possess a reactive group*.[4]

To demonstrate this point, we herein report a synthesis of the teleocidin B4 core, a complex fragment of a natural product containing two quaternary stereocenters and a penta-substituted benzene ring.[5] We envisioned that the final product would be constructed from an *ortho*-*tert*-butylaniline in four key C−C bond-forming steps, wherein the central piece of the assembly requires two tandem cycles of directed C−H bond functionalization of the *tert*-butyl group (Figure 1).[6]

According to the synthetic plan outlined above, we set out to prepare intermediate **4** through alkenylation of a *tert*-butyl aniline derivative (Scheme 1). We envisioned that a new transformation of this type might be accomplished via sequential cyclometalation and transmetalation. Consequently, Schiff base **1** was prepared (see the Supporting Information) and submitted to a systematic screening of metal salts in the context of directed C−H bond activation (cyclometalation). We found that Pd(II) salts were the only reagents capable of furnishing the desired and stable metallacycle products (cf. **2**).[7] Thus, stoichiometric $PdCl_2$ (1.2 equiv) in the presence of NaOAc (3 equiv) led to quantitative conversion of the starting material, affording 75% yield of pure palladacycle **2**. Although two methoxy substituents on the aldehyde portion of **1** were initially incorporated to protect the ortho positions of the aryl imine (metalation of arene C−H bonds is usually preferred over those of alkanes), they emerged as an important part of the directing element. No cyclopalladation occurred with the free aniline.

While palladacycle intermediates have been known to undergo numerous functionalization reactions, including carbonylation, alkylation, alkene, and alkyne insertion, halogenation, and oxygen transfer,[8] to our knowledge transmetalation with boronic acids has not been reported.[9] Therefore, we were delighted to find that palladacycle **2** and vinyl boronic acid **3** yielded desired alkene **4** in the presence of Ag_2O to furnish 86% yield of compound **4**. This two-step sequence (**1** → **2** → **4**) not only provided the desired alkenylation product **4**, but moreover set the stage for the development of a new catalytic transformation.[10]

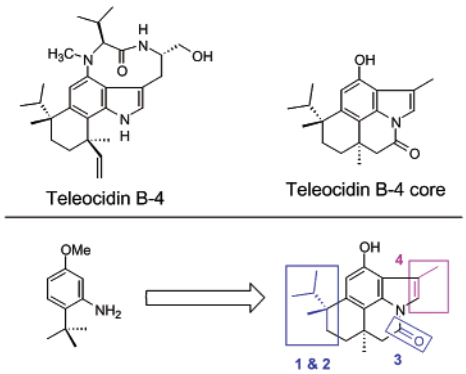

Figure 1. Teleocidin core was assembled in four key C−C bond-forming steps (1−4): (1) alkenylation of unactivated alkyl group (*tert*-butyl); (2) Friedel−Crafts reaction (racemic); (3) diastereoselective carbonylation of an unactivated methyl group; (4) alkenylation of phenol.

The subsequent step in the route centered on the closure of the cyclohexane ring through a formal hydroarylation process.

In this instance, the presence of the methoxy group meta to the amine facilitated the Friedel−Crafts reaction mediated by methanesulfonic acid,[11] providing racemic compound **5** in 83% yield (Scheme 1). Note that under anhydrous conditions, the Schiff base protection was retained, and the resultant product was ready for the second cycle of C−H activation/C−C bond formation without interruption.

At this stage of the synthesis, a diastereoselective one-carbon homologation of the methyl group anti to the isopropyl group (1,4-chiral transfer) was required (Scheme 1). Thus, intermediate **5** was again treated with $PdCl_2$ and NaOAc to yield a mixture of diastereomeric palladacycles (cf. **6**), followed by addition of CO(g) and methanol. The resulting methyl esters were not isolated, but instead acidic hydrolysis of the Schiff base, accompanied by spontaneous cyclization, furnished lactams **7** and **8**. This three-step sequence converted compound **5** to the desired lactam without isolation of a single intermediate. The yields and selectivity were identical at both the cyclopalladate and the lactam stage and varied with reaction temperature (70−100 °C). The lower end of this temperature range (70 °C) led to both highest yield and selectivity (65%, 6:1, **7**/**8**). The fortunate stereochemical outcome suggested that in the preferred transition state of the C−H activation step, the isopropyl group occupied the pseudo-equatorial position, therefore making the anti methyl group, also in the pseudo-equatorial position, accessible to the metal center.

The desired isomer **7** was obtained in diastereomerically pure form by crystallization, and the X-ray structure was solved to confirm the stereochemical assignment (Figure 2). In the final stage of the assembly, the indole ring was synthesized via intramolecular coupling between the phenol and the vinyl bromide **9**.[12] Thus, the allylation of lactam **7**, followed by removal of the methyl group

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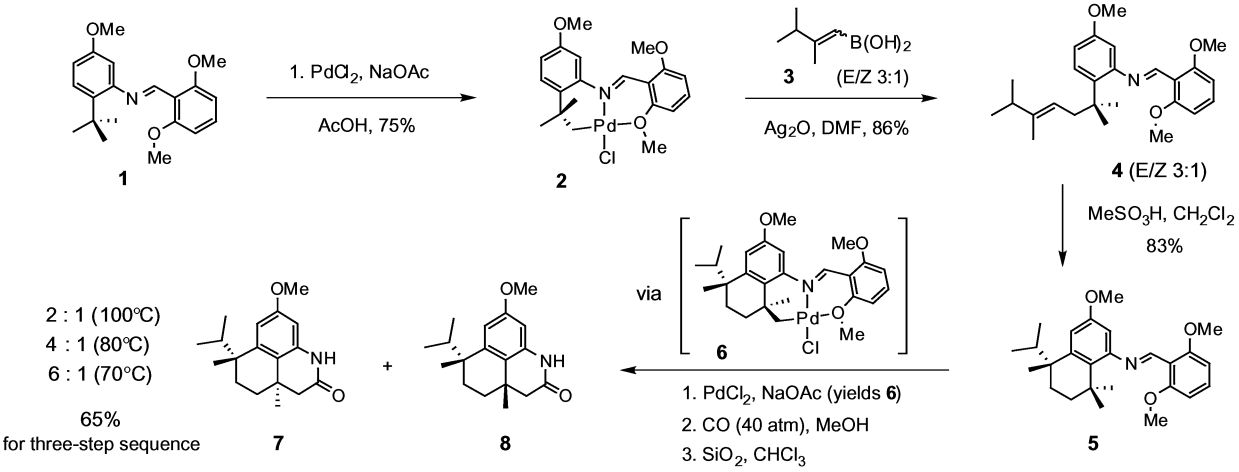
Scheme 1. Two Tandem Cycles of C−H Bond Functionalization Render Two Quaternary Centers of the Teleocidin Core



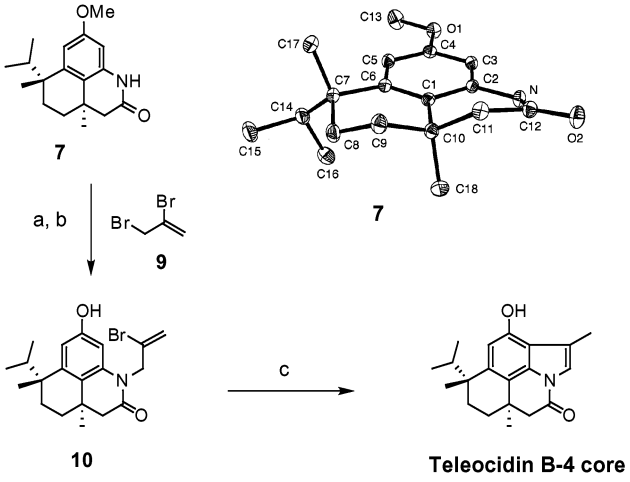


Figure 2. The final stage of the teleocidin core assembly: indole synthesis. Conditions: (a) **9**, ^{t}BuOK, THF, 71%; (b) BBr_3, CH_2Cl_2, 96%; (c) Pd(OAc)$_2$ (15 mol %), P(^{t}Bu)$_3$ (30 mol %), Cs_2CO_3, DMA, 57%. For crystallographic data of **7**, see the Supporting Information.

by the action of BBr_3, afforded the required phenol **10**. The subsequent intramolecular alkenylation coupling, catalyzed by Pd(OAc)$_2$, produced the final product, the teleocidin B4 core. A systematic optimization showed that the ratio of the desired indole formation to the allyl group removal was improved by the use of tri-*tert*-butylphosphine as the ligand and Cs_2CO_3 as the base, to furnish the final target molecule in 57% yield.

In summary, the core of teleocidin B4 was synthesized in four C−C bond-forming steps starting from *tert*-butyl derivative **1** (nine steps in total). The key sequence of the synthesis consisted of two C−H bond functionalization cycles, alkenylation and oxidative carbonylation of two methyl groups. Thus, the consideration of nontraditional disconnections in the context of synthetic strategy has significant consequences; not only do new perspectives on organic compounds emerge, but the development of new chemical transformations is further inspired.

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Supporting Information Available: Experimental procedures, preparation, and spectral data for compounds **1**−**10** (PDF). Crystallographic data for **7** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Miyaura, N. *Cross-Coupling Reactions, A Practical Guide*. *Top. Curr. Chem*.; Springer: New York, 2002; Vol. 219.
(2) (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (b) Fürstner, A. *Angew. Chem., Int. Ed*. **2000**, *39*, 3012−3043.
(3) (a) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res*. **2001**, *34*, 633−639. (b) Dyker, G. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 103−105. (c) Kakiuchi, F.; Murai, S. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, 1999; pp 47−79. (d) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev*. **2002**, *102*, 1731−1769.
(4) Metal-carbene insertions serve as successful examples of this concept: (a) Taber, D. F.; Stribia, S.-E. *Chem.-Eur. J*. **1998**, *4*, 990−992 and references therein. (b) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc*. **2000**, *122*, 3063−3070.
(5) (a) Teleocidin structure: Hitotsuyanagi, Y.; Fujiki, H.; Suganuma, M.; Aimi, N.; Sakai, S.; Endo, Y.; Shudo, K.; Sugimura, T. *Chem. Pharm. Bull*. **1984**, *32*, 4233−4236 and references therein. (b) Previous synthesis: Nakatsuka, S.; Masuda, T.; Goto, T. *Tetrahedron Lett*. **1986**, *27*, 6245−6248. Nakatsuka, S.; Masuda, T.; Goto, T. *Tetrahedron Lett*. **1987**, *28*, 3671−3674. Okabe, K.; Muratake, H.; Natsume, M. *Tetrahedron* **1991**, *47*, 8559−8572 and references therein. (c) Teleocidins are potent protein kinase C (PKC) activators: Kishi, Y.; Rando, R. R. *Acc. Chem. Res*. **1998**, *31*, 163−172.
(6) Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc*. **2002**, *124*, 6900−6903.
(7) (a) Dunina, V. V.; Zalevskaya, O. A.; Potapov, V. M. *Russ. Chem. Rev*. **1988**, *57*, 250−269. (b) Ryabov, A. D. *Chem. Rev*. **1990**, *90*, 403−424.
(8) (a) Ryabov, A. D. *Synthesis* **1985**, 233−252. (b) Baldwin, J. E.; Jones, R. H.; Najera, C.; Yus, M. *Tetrahedron* **1985**, *41*, 699−711. (c) Balavoine, G.; Clinet, J. C. *J. Organomet. Chem*. **1990**, *390*, C84−C88 and references therein. (d) Dyker, G. *Chem. Ber./Recueil* **1997**, *130*, 1567−1578.
(9) Arylation of the Herrmann palladacycle with phenylstannane has been reported: Louie, J.; Hartwig, J. F. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 2359−2361.
(10) The catalytic arylation and alkenylation of *tert*-butyl aniline have been achieved in our laboratory. Exploration and optimization of this reaction will be the subject of a separate communication.
(11) Corey, E. J.; Lazerwith, S. E. *J. Am. Chem. Soc*. **1998**, *120*, 12777−12782.
(12) Hennings, D. D.; Iwasa, S.; Rawal, V. H. *Tetrahedron Lett*. **1997**, *38*, 6379−6382.

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