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Highly Substituted Oxabicyclic Derivatives from Furan: Synthesis of (±)-Platensimycin

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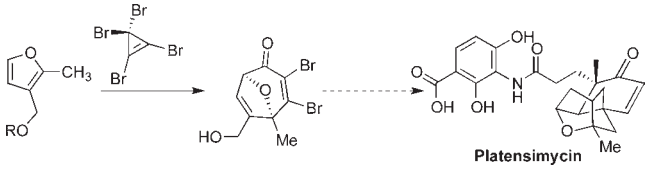
ABSTRACT



A stereocontrolled approach to a key platensimycin intermediate was achieved from a commercially available furylcarboxylate. Key to our approach is the highly efficient formal [4 + 3] cyclocondensation of a substituted furan with tetrabromocyclopropene along with an intramolecular γ-alkylation to construct the final ring of the caged intermediate.

Platensimycin and platencin[1] (Figure 1) are unusual bridged bicyclic natural products isolated from *Streptomyces platensis* during a screen for novel antibiotic chemotypes.[2] These compounds showed broad-spectrum activity against several pathogenic Gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA). Platensimycin and platencin inhibit the enzyme FabF, also known as β-ketoacyl-(acyl carrier protein (ACP)) synthase I, an essential component of the fatty acid biosynthesis machinery in bacteria.[3] This biosynthetic pathway is crucial for bacterial cell growth, and there are already clinically used antibacterial agents such as triclosan[4] and isoniazid[5] that target other enzymes on this pathway. The novel structure and exciting antimicrobial activity of these compounds have made them popular targets for total synthesis.[6]

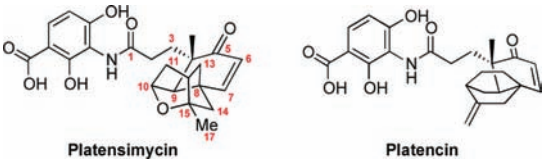


Figure 1. Structures of new antibiotics from *Streptomyces platencis*.

We have been interested in the development of bridged bicyclic adducts derived from perhalocyclopropenes and various dienes as key intermediates for the synthesis of natural products.[7] Of particular interest have been the oxabicylco[3.2.1]octane adducts derived in a single step through cyclocondensation of furans and tetrabromocyclopropene (TBCP). These compounds have been studied as versatile precursors to highly substituted cycloheptanes, furans, and pyrans through cleavage of one of the three unique bridges present in the adduct.

(1) (a) Singh, S. B.; Jayasuriya, H.; Ondeyka, J. G.; Herath, K. B.; Zhang, C.; Zink, D. L.; Tsou, N. N.; Ball, R. G.; Basilio, A.; Genilloud, O.; Diez, M. T.; Vicente, F.; Pelaez, F.; Young, K.; Wang, J. *J. Am. Chem. Soc.* **2006**, *128*, 11916–11920. (b) Singh, S. B.; Herath, K. B.; Wang, J.; Tsou, N.; Ball, R. G. *Tetrahedron Lett.* **2007**, *48*, 5429–5433.

(2) (a) Wang, J.; Soisson, S. M.; Young, K.; Shoop, W.; Kodali, S.; Galgoci, A.; Painter, R.; Parthasarathy, G.; Tang, Y. S.; Cummings, R.; Ha, S.; Dorso, K.; Motyl, M.; Jayasuriya, H.; Ondeyka, J.; Herath, K.; Zhang, C.; Hernandez, L.; Allocco, J.; Basilio, A.; Tormo, J. R.; Genilloud, O.; Vicente, F.; Pelaez, F.; Colwell, L.; Lee, S. Ho.; Michael, B.; Felcetto, T.; Gill, C.; Silver, L. L.; Hermes, J. D.; Bartizal, K.; Barrett, J.; Schmatz, D.; Becker, J. W.; Cully, D.; Singh, S. B. *Nature* **2006**, *441*, 358–361. (b) Habich, D.; von Nussbaum, F. *Chem. Med. Chem.* **2006**, *1*, 951–954.

(3) White, S. W.; Zheng, J.; Zhang, Y. M.; Rock, C. O. *Annu. Rev. Biochem.* **2005**, *74*, 791–831.

(4) Zhang, Y. M.; Lu, Y. J.; Rock, C. O. *Lipids* **2004**, *39*, 1055–1060.

(5) Heath, R. J.; White, S. W.; Rock, C. O. *Appl. Microbiol. Biotechnol.* **2002**, *58*, 695–703.

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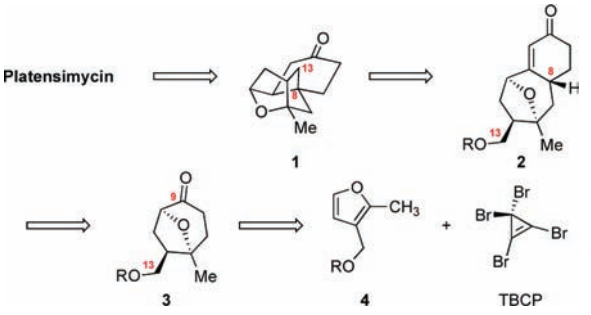
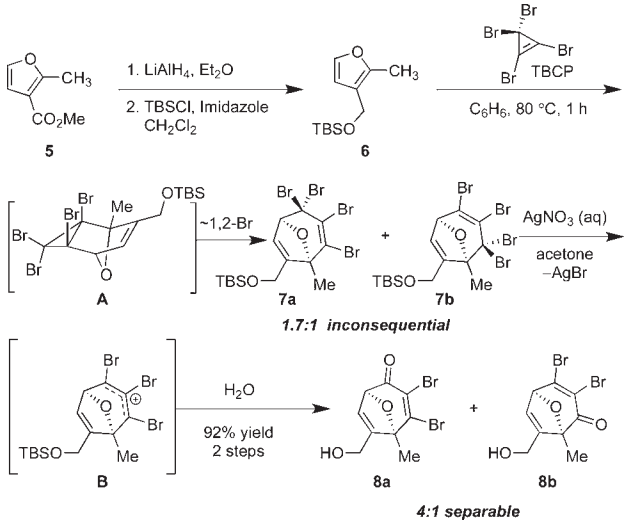
However, the identification of an intact oxabicylco-[3.2.1]octane moiety in the hydrophobic cage of platensimycin suggested that similar furan cycloaddition reactions may form an integral component of an approach to this complex antibiotic. Herein, we describe a formal total synthesis of platensimysin using a key TBCP cycloaddition reaction with a highly substituted furan. The advanced ketone **1** has previously served as a direct precursor to the natural product,[6i,j,t] and a synthetic strategy was formulated to intersect this key intermediate (Scheme 1).

Scheme 1. Retrosynthetic Analysis of Platensimycin



A retrosynthetic analysis of the caged structure **1** centered around a late-stage construction of the C8−C13 bridge from a tricyclic intermediate such as **2** which was, in turn, envisioned to arise through annulation of a cyclohexenone on to a highly substituted oxabicyclo[3.2.1]octanone **3**. Central to the overall strategy would be an efficient preparation of **3** from TBCP and a simple 2,3-disubstituted furan **4**. This strategy is somewhat unique relative to previously reported routes and may offer the ability to prepare analogs in the cyclohexenone region where subtle changes in substitution and conformation strongly influence antibacterial activity.[8] The commercially available furylcarboxylate **5** offered an economical starting material and was easily converted into the corresponding silylether **6** by reduction and protection[9] (Scheme 2).

Scheme 2. Synthesis of a Key Oxabicyclo[3.2.1]octadiene Intermediate



Reaction of this furan with TBCP led to a mixture of isomeric tetrabromides **7a/b** that were directly hydrolyzed to the dibromoenones **8a/b** by action of aqueous silver nitrate. We were pleased to observe that the bridgehead methyl substituent exerted a substantial steric effect on the attack of water on the putative allyl-cation intermediate **B** to deliver enone **8a** as the major product (4:1). The hydrolysis was accompanied by cleavage of the silyloxy protecting group as the reaction becomes quite acidic as it progresses. This high-yielding sequence allowed for the facile preparation of **8a** on a multigram scale and further elaboration to a key tricyclic enone through a subsequent Robinson annulation (Scheme 3).

Catalytic hydrogenation of the major isomer **8a** in the presence of triethylamine effected simultaneous reduction of the dibromoalkene and saturation of the C11−C12 olefin. Reduction of the alkene occurred with complete selectivity from the less encumbered *exo*-face to correctly set the key stereogenic center at C12. A Robinson annulation

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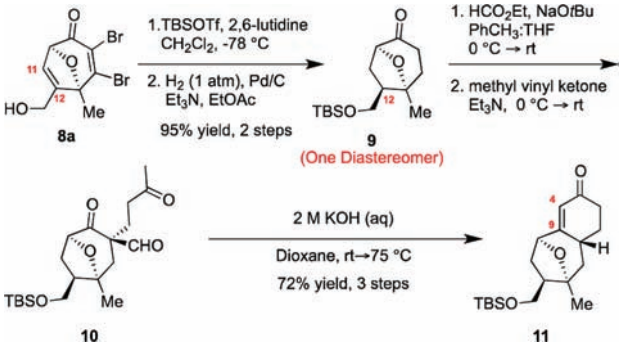
(8) (a) Nicolaou, K. C.; Stepan, A. F.; Lister, T.; Li, A.; Montero, A.; Tria, G. S.; Turner, C. I.; Tang, Y.; Wang, J.; Denton, R. M.; Edmonds, D. J. *J. Am. Chem. Soc.* **2008**, *130*, 13110–13119. (b) Shen, H. C.; Ding, F.-X.; Singh, S. B.; Parthasarathy, G.; Soisson, S. M.; Ha, S. N.; Chen, X.; Kodali, S.; Wang, J.; Dorso, K.; Tata, J. R.; Hammond, M. L.; MacCoss, M.; Colletti, S. L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1623–1627. (c) Wang, J.; Lee, V.; Sintim, H. O. *Chem.—Eur. J.* **2009**, *15*, 2747–2750.

(9) Paterson, I.; Mark, G.; Banks, B. J. *Tetrahedron* **1989**, *45*, 5283–5292.

strategy seemed to offer an attractive route for installation of the cyclohexenone which would ultimately lead to a C4–C9 enone. Evaluation of several Robinson variants ultimately indicated the Woodward–Wilds modification as optimal for this system.[10]

Initial formylation of ketone **9** was followed by Michael addition to methyl vinyl ketone without purification of the intermediate. Exposure of the crude ketoaldehyde **10** to strongly basic conditions triggered the final aldol/dehydration sequence and accompanying deformylation to give **11** along with a small amount of the deconjugated isomer in very good overall yield (72% from **9**). With installation of the cyclohexenone complete, we turned to closure of the final C8–C13 bridge and completion of a formal total synthesis (Scheme 4).

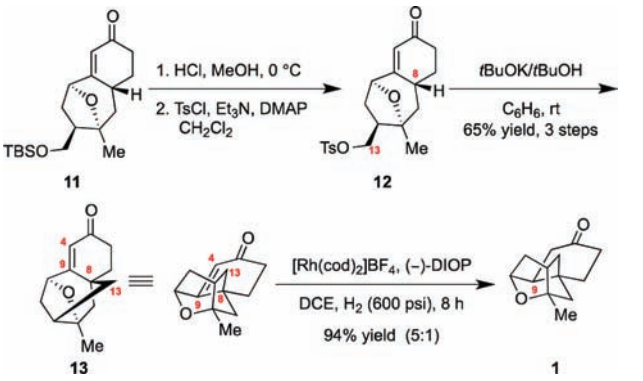
Scheme 3. Synthesis of Tricyclic Enone **11**



Final formation of the caged core structure of platensimycin would occur through a key intramolecular γ-alkylation of an endocyclic enone. Removal of the silyl protecting group under acidic conditions and activation of the alcohol as the tosylate preceded smooth ring-closure upon exposure of **12** to an alkoxide base, producing enone **13** in very good overall yield. Similar late-stage enone intermediates have been intersected with the fully constructed cage in place and found to be problematic in the ensuing reduction which establishes the bridgehead stereocenter at C9. Mulzer[6i] showed that catalytic hydrogenation of a related dienone proceeded with poor diastereoselectivity, producing mixtures at C9, as little difference exists between the two faces of the olefin. Corey and co-workers[6j] overcame this issue by recourse to a chiral hydrogenation catalyst to control the facial selectivity of the reduction. Intermediate **13** differs from the Corey substrate only slightly as that

(10) (a) Shunk, H.; Wilds, A. L. *J. Am. Chem. Soc.* **1949**, *71*, 3946–3950. (b) Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1952**, *74*, 4223–4251.

Scheme 4. Completion of a Formal Total Synthesis



compound contains an additional endocyclic olefin in the form of a cross-conjugated dienone. Exposure of **13** to the same chiral rhodium complex at elevated pressure led to an excellent yield of the reduced products with the desired isomer predominating (5:1).[11] This compound matched the spectral data reported by Corey in their synthesis of platensimycin.

In this manuscript we describe a concise and direct formal total synthesis of racemic platensimycin based on the key use of a furan–tetrabromocyclopropene cycloaddition reaction. Two sequential annulations on the oxabicyclo[3.2.1]octane core establish the hydrophobic caged domain found in the natural product. Current work is focused on the utilization of this furan-based route for the preparation of novel platencimycin analogs. As this route is somewhat unique in allowing a late-stage annulation of the cyclohexanone ring onto a preformed oxabicyclic core, it should be easily adapted to allow the investigation of alternative sizes and compositions of the ring systems in this region of the natural product. This appears to be an attractive domain for analog generation as alterations to this region have been shown to have demonstrable effects on biological activity.[8]

Acknowledgment. We are grateful to the National Science Foundation (CHE-0616760) for generous support of this work.

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

(11) Catalytic hydrogenation of **13** with (bicyclo[2.2.1]hepta-2,5-diene)[1,4-bis(diphenylphosphino)butane]rhodium(I) tetrafluoroborate at elevated pressure (600 psi) furnished a 1.4:1 mixture of C9 diastereomers in favor of the undesired isomer.