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Construction of Quaternary Carbon Stereocenter of α -Tertiary Amine through Remote C–H Functionalization of Tris Derivatives: Enantioselective Total Synthesis of Myriocin

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ABSTRACT: We describe the development of a strategy for construction of quaternary carbon stereocenter of α -tertiary amines. This strategy highlights a site-selective C–H functionalization involving an alkoxy radical triggered-1,5-hydrogen transfer (1,5-HAT) reaction of a conformationally fixed spiro-compound derived from trishydroxymethylaminomethane (Tris). The utilization of this strategy enabled an enantioselective total synthesis of myriocin, a naturally occurring sphingosine analog that displays potent immunosuppressive activity.

Chiral α -tertiary amines are widely found in a variety of complex biologically active natural products, such as myriocin, salinosporamide A or tetrodotoxin, where multiple functional groups are included in the congested structures (Figure 1). The development of methods for constructing chiral α -tertiary amines has been tackled by many researchers,¹ and most of these methods rely on C–C or C–N bond formation. For instance, palladium-catalyzed asymmetric alkylations of azlactones with Trost ligands have allowed the assembly of these motifs through C–C bond formation.² Kumagai and Shibasaki et al. have developed an asymmetric amination of carbonyl compounds using a lanthane-based ternary asymmetric catalyst to construct a stereogenic α -tetrasubstituted amine through C–N bond formation.³ On the other hands, a desymmetrization-based synthetic approach can construct a chiral quaternary carbon without forming a new bond at the congested carbon center. Typically, lipase-catalyzed desymmetrization of two hydroxy groups and transition-metal-catalyzed desymmetrization of two carbon-carbon double bonds have been frequently utilized for the synthesis of complex natural products.⁴ However, to our knowledge the synthesis of an optically active α -tertiary amine based on a desymmetrization approach using C–H bond functionalization has not been reported.^{1b}

Trishydroxymethylaminomethane (Tris), which is readily available and extensively used as a reagent for biological experiments, is a characteristic densely decorated small molecule with an α -tertiary amine motif and three equivalent hydroxymethyl groups. We focused on Tris as a viable starting substrate for the efficient assembly of the quaternary carbon stereocenter

Figure 1. Structures of Myriocin and Natural Products with Chiral α -Tertiary Amines

Scheme 1. Strategy for the Construction of the Quaternary Carbon Stereocenter of an α -Tertiary Amine

Scheme 2. Strategy for the Construction of the Quaternary Carbon Stereocenter of Myriocin and the Product Distribution of the Alkoxy Radical Triggered-1,5-HAT Reaction

Scheme 3. Synthesis of Compound 4a

LED lamp = Aldrich Micro Photochemical Reactor with blue LED light (435-445 nm)

Boc = *tert*-butoxycarbonyl, DMP = 2,2-dimethoxypropane, TMAD = *N,N,N,N*-tetramethylazodicarboxamide, NMO = *N*-methylmorpholine *N*-oxide, NIS = *N*-iodosuccinimide, ND = Not detected.

of α -tertiary amines (Scheme 1). Thus, (1) functionalization of any one of the hydroxymethyl groups in Tris, (2) introduction of a chiral group, followed by (3) site-stereoselective C–H functionalization of one of the remaining hydroxymethyl groups would allow the efficient construction of the desired stereogenic center, reducing the number of steps for the C–C/C–N bond for-

mation. We planned to use an alkoxy radical triggered-1,5-hydrogen transfer (1,5-HAT) reaction⁵ for selective C–H bond functionalization controlled by the preinstalled chiral moiety (the group in blue, Scheme 1).⁶ The key to success of this tactic is the site-selective functionalization of the desired C–H bond in the presence of various functional groups.

We chose myriocin (**1**) for a model study to evaluate this working hypothesis. Myriocin (**1**) is a natural sphingosine analog isolated from the thermophiles *Myriococcum albomyces*, *Mycelia sterilia* or *Isaria sinclairii*,⁷ which has a polar moiety with three consecutive stereogenic centers including a chiral α -tertiary amine. Myriocin exhibits 10 to 100 times the immunosuppressive activity of cyclosporin A, and also has serine palmitoyltransferase inhibitory activity, which is a key enzyme of the sphingosine metabolic pathway.^{7c, 8} The biological importance of myriocin, as well as the challenge of its structural complexity, have inspired the development of numerous methods for the synthesis of myriocin.⁹ Our strategy is shown in Scheme 2. A key precursor **3** would be prepared through olefination, asymmetric dihydroxylation and oxazolidinone formation, starting from the known Tris-derived aldehyde **2**.¹⁰ We expected the 1,5-HAT-mediated site-selective C–H functionalization¹¹ of the spiro compound **3** to provide ready access to the three consecutive stereogenic centers of myriocin (**3**→**A**→**B**→**4**). Transformation of **4** to myriocin (**1**) would be then performed via carbon chain elongation of R¹ group and oxidation. The alkoxy radical in the intermediate **A** would be spatially accessible to the C–H bond of only one hydroxymethyl group because of the conformationally restricted spirocyclic structure. The 1,5-HAT reaction used in this strategy proceeds via an extremely unstable alkoxy radical, and therefore, may compete with other undesired side reactions. For example, β -scission from the alkoxy radical **A** [path (b) and (c)] would provide the side-products **5** and **6** via the radical intermediates **C** and **D**, respectively. Additionally, an undesired 1,5-HAT reaction might occur at the C–H bond on the side chain [path (d)]. Therefore, setup of appropriate reaction conditions and substrates is crucial for enabling the desired transformation in the presence of various functional groups.

Initially, we examined the appropriate alkoxy radical precursor for the site-selective C–H functionalization reaction.

Alkoxy radical chemistry is widely used in organic synthesis,^{5a, 12} and various precursors for alkoxy radicals have been developed.¹³ Among these, we chose *N*-alkoxyphthalimide and hypiodite, easily generated from the corresponding alcohol, as precursors for alkoxy radicals. However, despite several attempts, we could not obtain the substrate **3-phth** bearing an *N*-alkoxyphthalimide group (Scheme 2) because of the low reactivity of the hindered hydroxy group. Thus, we decided to use hypiodite for the generation of alkoxy radical.

The synthesis of racemic substrate **3a** is shown in Scheme 3. The known aldehyde **2** was easily prepared from Tris using a modified literature procedure.¹⁰ The Horner–Wadsworth–Emmons reaction of aldehyde **2** followed by the reduction of the ester group gave the allyl alcohol **8**. The hydroxy group was converted to a cyano group through a Mitsunobu reaction. Dihydroxylation of alkene **9** with OsO₄ and oxazolidinone formation provided the precursor **3a** for site-selective C–H functionalization. We next investigated the C–H functionalization of substrate **3a** using iodine reagents, which are well known to be used for generating an alkoxy radical from a hydroxy group under visible light irradiation. Irradiation of **3a** using LED lamp (Aldrich Micro Photochemical Reactor) in the presence of NIS did not give the desired product. By changing the iodine source from NIS to I₂/PhIO, a trace amount of the desired product **4a** was obtained. In contrast, the use of PhI(OAc)₂¹⁴ provided **4a** in 50% yield as a single diastereomer.

We next examined the C–H functionalization reaction with various substrates **3b–e** (Table 1) to optimize the substrate for the total synthesis and to reveal any inherent limitations of the reaction. The reaction of **3b** with I₂ and PhI(OAc)₂ in CH₂Cl₂ under LED irradiation gave the desired product **4b** in low yield (entry 1, 11%). The anticipated side products **10** and **11** were also observed, which can be formed through β-scission from the alkoxy radical [pathway (b) or (c) shown in Scheme 2]. Changing the solvent to cyclohexane inhibited the generation of side product **10** and improved the yield of the desired product (entry 1, 16%). Boc protection of the NH group slightly increased the yield (entry 2, 22%). The substrate **3c** with two additional methylene units to **3b**, also provided the desired product **4c** in low yield (entry 3, 25%), along with a side product obtained through the undesired abstraction of the C–H bond adjacent to the OTBDPS group [pathway (d) shown in Scheme 2]. In contrast, the substrate **3d** with one additional methylene unit to **3b**, underwent selective functionalization at the desired position to give compound **4d** in moderate yield (entry 4, 63%). The structure of **4d** was characterized by X-ray crystallography of its TBDPS-protected derivative **15** (see: Scheme 4 and Supporting Information). The Boc-protected substrate **3d'** also showed a comparable yield to that of **3d** (entry 5, 66%). The substrate **3e** (a diastereomer of **3d**) and the corresponding Boc-protected substrate **3e'** were subjected to the same reaction conditions to provide the desired products **4e** and **4e'** in 45% and 64% yields, respectively. These results indicated that the design of appropriate substrates is critical for achieving the desired transformation, while suppressing the unwanted β-scission and 1,5-HAT reactions, although the stereochemistry at the C4 position has little influence on the reaction progress. Based on these results, we selected **3d** as the substrate for the total synthesis.

Table 1. Substrate Optimization of the 1,5-HAT Reaction

entry	substrate	product	yield (%) ^b
1			16 (11) ^c
2			22 (19) ^c
3			25 (11)
4			63
5			66
6			45
7			64

^a Aldrich Micro Photochemical Reactor with blue LED light (435–445 nm) was used as the LED lamp, ^b Isolated yields. Isolated yields using CH₂Cl₂ as solvent are shown in parentheses, ^c NaHCO₃ was used as an additive.

Scheme 4. Synthesis of Myriocin

KHMDS = potassium bis(trimethylsilyl)amide, DME = 1,2-dimethoxyethane, (DHQD)PHN = dihydroquinidine 9-phenanthryl ether, TBAF = tetrabutylammonium fluoride, NaHMDS = sodium bis(trimethylsilyl)amide, TBAI = tetrabutylammonium iodide

We next turned our attention to the enantioselective total synthesis of myriocin. First, we examined the synthesis of optically active **3d**, the optimized substrate for the key C–H functionalization reaction (Scheme 4). The Julia–Kocienski olefination¹⁵ of aldehyde **2** gave the desired alkene **13** in high yield (88%) with excellent *E*-selectivity ($E:Z = > 99:1$). Next, we investigated the Sharpless asymmetric dihydroxylation¹⁶ of alkene **13**. After various experimentations, the best result was obtained using (DHQD)PHN¹⁷ as the ligand, and *t*-BuOH/H₂O as the solvent, to afford the desired diol **14** in 90% yield, 87% ee. The recrystallization of diol **14** preferentially gave racemic crystals. The racemic crystals were removed, and the mother liquid of recrystallization was recovered to provide the optically pure diol **14** (99% ee). Subsequently, treatment of the diol **14** with NaH furnished the oxazolidinone **3d** in an optically pure form. The key 1,5-HAT reaction of the oxazolidinone **3d** with I₂ and PhI(OAc)₂ in cyclohexane using a 40W Kessil LED lamp led to the formation of the desired product **4d** in 70% yield, which was reacted with TBAF to give the corresponding alcohol **15**. Next, installation of the side chain accompanying the formation of the *E*-alkene was examined. Dess–Martin oxidation of alcohol **15** followed by Julia–Kocienski olefination provided the desired coupling product **18** in a low yield as a geometrical mixture ($E:Z = \text{ca. } 3:1$, Scheme S4). We then prepared the terminal alkene **16** in 56% yield from compound **15** to test the cross metathesis reaction for the introduction of the side chain.⁹ⁿ The reaction of compound **16** with **17** using Hoveyda-Grubbs II catalyst was successfully executed to afford the desired alkene **18** in 80% yield, in favor of the *E*-isomer ($E:Z = 84:16$). The alkene **18** was used in the next step as a

mixture of isomers because of the difficulty in separation. Removal of both the acetal groups of **18** gave the lactol, which underwent NIS-mediated oxidation¹⁸ to furnish the lactone **19**^{9k}, a known intermediate for myriocin synthesis. The *E*-isomer of lactone **19** was obtained by HPLC separation, and all the spectroscopic data for **19** was in agreement with those reported in the literature ($[\alpha]_D^{26} +3.1$ (*c* 0.35, CHCl₃); lit. $[\alpha]_D^{22} +3.2$ (*c* 0.21, CHCl₃)).^{9k} Total synthesis of myriocin (**1**) was completed by hydrolysis of **19** with NaOH, according to the method of Chida et al.^{9k} and Yakura et al.⁹ⁿ ($[\alpha]_D^{25} +4.8$ (*c* 0.14, DMSO); lit.⁹ⁿ $[\alpha]_D^{23} +5.6$ (*c* 0.30, DMSO)). Additionally, the treatment of compound **19** with NaOH followed by acetylation gave the known derivative **20** (Scheme 5), the optical rotation of which was also in accordance with the literature value ($[\alpha]_D^{26} +59.5$ (*c* 0.21, CHCl₃); lit. $[\alpha]_D^{20} +53.6$ (*c* 0.71, CHCl₃)).^{9k}

Scheme 5. Synthesis of Myriocin Derivative 20

In conclusion, we have developed a strategy for generating the quaternary carbon stereocenter of α -tertiary amines through 1,5-HAT-mediated regioselective C–H functionalization of Tris derivatives. The rational design of precursors allowed practical site-selective C–H functionalization via unstable alkoxy

radicals. Implementing this strategy, we have achieved an eleven-step total synthesis of myriocin from a known Tris-derived aldehyde. Our findings thus provide insights into the utility of remote C–H functionalization through 1,5-HAT in densely functionalized substrates, and may contribute the design of synthetic route to complex compounds with chiral α -tertiary amines without accompanying bond formation for construction of the quaternary carbon center.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data for all new compounds (PDF)

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REFERENCES

- (1) (a) Bera, K.; Namboothiri, I. N. N. Asymmetric Synthesis of Quaternary α -Amino Acids and Their Phosphonate Analogues. *Asian J. Org. Chem.* **2014**, *3*, 1234-1260. (b) Hager, A.; Vrieland, N.; Hager, D.; Lefranc, J.; Trauner, D. Synthetic Approaches towards Alkaloids Bearing α -Tertiary Amines. *Nat. Prod. Rep.* **2016**, *33*, 491-522. (c) Jiang, H.; Jin, Y.; Lin, J. New Progress in Asymmetric Synthesis of Quaternary α -Amino Acids. *Mini-Rev. Org. Chem.* **2017**, *14*, 434-447.
- (2) Trost, B. M.; Lee, C. B. A New Strategy for the Synthesis of Sphingosine Analogues. Sphingofungin F. *J. Am. Chem. Soc.* **1998**, *120*, 6818-6819.
- (3) Berhal, F.; Takechi, S.; Kumagai, N.; Shibasaki, M. Catalytic Asymmetric Amination of *N*-Nonsubstituted α -Alkoxy carbonyl Amides: Concise Enantioselective Synthesis of Mycetericin F and G. *Chem. Eur. J.* **2011**, *17*, 1915-1921.
- (4) For some recent reviews of synthesis of complex natural products based on desymmetrization-based approach, see: (a) Wang, M.; Feng, M. H.; Tang, B. Q.; Jiang, X. F. Recent Advances of Desymmetrization Protocol Applied in Natural Product Total Synthesis. *Tetrahedron Lett.* **2014**, *55*, 7147-7155. (b) Inai, M.; Asakawa, T.; Kan, T. Total Synthesis of Natural Products Using a Desymmetrization Strategy. *Tetrahedron Lett.* **2018**, *59*, 1343-1347.
- (5) (a) Čeković, Ž. Reactions of δ -Carbon Radicals Generated by 1,5-Hydrogen Transfer to Alkoxy Radicals. *Tetrahedron* **2003**, *59*, 8073-8090. (b) Chu, J. C. K.; Rovis, T. Complementary Strategies for Directed C(sp³)-H Functionalization: A Comparison of Transition-Metal-Catalyzed Activation, Hydrogen Atom Transfer, and Carbene/Nitrene Transfer. *Angew. Chem., Int. Ed.* **2018**, *57*, 62-101.
- (6) For a related approach using desymmetrization of the two remaining hydroxymethyl groups of Tris based on diastereoselective acetal formation for the synthesis of lactacystin, see: Ooi, H.; Ishibashi, N.; Iwabuchi, Y.; Ishihara, J.; Hatakeyama, S. A Concise Route to (+)-Lactacystin. *J. Org. Chem.* **2004**, *69*, 7765-7768.
- (7) (a) Kluepfel, D.; Bagli, J.; Baker, H.; Charest, M.-P.; Kudelski, A.; Sehgal, S. N.; Vézina, C. Myriocin, a New Antifungal Antibiotic from *Myriococcum Albomyces*. *J. Antibiot.* **1972**, *25*, 109-115. (b) Aragozzini, F.; Manachini, P. L.; Craveri, R.; Rindone, B.; Scolastico, C. Isolation and Structure Determination of a New Antifungal α -

- Hydroxymethyl- α -Amino Acid. *Tetrahedron* **1972**, *28*, 5493-5498. (c) Fujita, T.; Inoue, K.; Yamamoto, S.; Ikumoto, T.; Sasaki, S.; Toyama, R.; Chiba, K.; Hoshino, Y.; Okumoto, T. Fungal Metabolites. Part 11. A Potent Immunosuppressive Activity Found in *Isaria sinclairii* Metabolite. *J. Antibiot.* **1994**, *47*, 208-215.
- (8) (a) Miyake, Y.; Kozutsumi, Y.; Nakamura, S.; Fujita, T.; Kawasaki, T. Serine Palmitoyltransferase is the Primary Target of a Sphingosine-Like Immunosuppressant, ISP-1/Myriocin. *Biochem. Biophys. Res. Commun.* **1995**, *211*, 396-403. (b) Chen, J. K.; Lane, W. S.; Schreiber, S. L. The Identification of Myriocin-Binding Proteins. *Chem. Biol.* **1999**, *6*, 221-235. (c) Wadsworth, J. M.; Clarke, D. J.; McMahon, S. A.; Lowther, J. P.; Beattie, A. E.; Langridge-Smith, P. R. R.; Broughton, H. B.; Dunn, T. M.; Naismith, J. H.; Campopiano, D. J. The Chemical Basis of Serine Palmitoyltransferase Inhibition by Myriocin. *J. Am. Chem. Soc.* **2013**, *135*, 14276-14285.
- (9) (a) Banfi, L.; Beretta, M. G.; Colombo, L.; Gennari, C.; Scolastico, C. Total Synthesis of (+)-Thermozymocidin (Myriocin) from D-Fructose. *J. Chem. Soc., Chem. Commun.* **1982**, 488-490. (b) Banfi, L.; Beretta, M. G.; Colombo, L.; Gennari, C.; Scolastico, C. 2-Benzoylamino-2-deoxy-2-hydroxymethyl-D-hexono-1,4-lactones: Synthesis from D-Fructose and Utilization in the Total Synthesis of Thermozymocidin (Myriocin). *J. Chem. Soc., Perkin Trans. 1* **1983**, 1613-1619. (c) Rao, A. V. R.; Gurjar, M. K.; Devi, T. R.; Kumar, K. R. A Formal Synthesis of a Novel Immunosuppressant ISP-1: Stereo-Controlled Pd(0) Catalyzed *cis*-Hydroxyamination of Carbohydrate Derived Vinyl Epoxide. *Tetrahedron Lett.* **1993**, *34*, 1653-1656. (d) Yoshikawa, M.; Yokokawa, Y.; Okuno, Y.; Murakami, N. Total Synthesis of a Novel Immunosuppressant, Myriocin (Thermozymocidin, Isp-I), and Z-Myriocin. *Chem. Pharm. Bull.* **1994**, *42*, 994-996. (e) Deloisy, S.; Thang, T. T.; Olesker, A.; Lukacs, G. Synthesis of α -Azido Aldehydes. Stereoselective Formal Access to the Immunosuppressant Myriocin. *Tetrahedron Lett.* **1994**, *35*, 4783-4786. (f) Sano, S.; Kobayashi, Y.; Kondo, T.; Takebayashi, M.; Maruyama, S.; Fujita, T.; Nagao, Y. Asymmetric Total Synthesis of ISP-I (Myriocin, Thermozymocidin), a Potent Immunosuppressive Principle in the *Isaria sinclairii* Metabolite. *Tetrahedron Lett.* **1995**, *36*, 2097-2100. (g) Yoshikawa, M.; Yokokawa, Y.; Okuno, Y.; Murakami, N. Total Syntheses of Myriocin and Z-Myriocin, Two Potent Immunosuppressants, from 2-Deoxy-D-Glucose. *Tetrahedron* **1995**, *51*, 6209-6228. (h) Hatakeyama, S.; Yoshida, M.; Esumi, T.; Iwabuchi, Y.; Irie, H.; Kawamoto, T.; Yamada, H.; Nishizawa, M. A Novel Enantioselective Synthesis of (+)-Myriocin Based on the Chemistry of 1-Trimethylsilylbuta-2,3-dienes. *Tetrahedron Lett.* **1997**, *38*, 7887-7890. (i) Torrente, S.; Alonso, R. Photoinduced Formation of β -Oxy- α,α -disubstituted- α -amino Acid Derivatives from Ketoximes. *Org. Lett.* **2001**, *3*, 1985-1987. (j) Oishi, T.; Ando, K.; Chida, N. Stereoselective Total Synthesis of (+)-Myriocin from D-Mannose. *Chem. Commun.* **2001**, 1932-1933. (k) Oishi, T.; Ando, K.; Inomiya, K.; Sato, H.; Iida, M.; Chida, N. Total Synthesis of (+)-Myriocin and (–)-Sphingofungin E from Aldoheptoses Using Overman Rearrangement as the Key Reaction. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1927-1947. (l) Lee, K.-Y.; Oh, C.-Y.; Kim, Y.-H.; Joo, J.-E.; Ham, W.-H. Total Synthesis of Myriocin. *Tetrahedron Lett.* **2002**, *43*, 9361-9363. (m) Jones, M. C.; Marsden, S. P. Total Synthesis of the Immunosuppressants Myriocin and 2-*epi*-Myriocin. *Org. Lett.* **2008**, *10*, 4125-4128. (n) Nambu, H.; Noda, N.; Niu, W.; Fujiwara, T.; Yakura, T. Stereoselective Total Synthesis of Myriocin Using Rhodium(II)-Catalyzed C–H Amination Followed by Alkylation. *Asian J. Org. Chem.* **2015**, *4*, 1246-1249. (o) Noda, N.; Nambu, H.; Ubukata, K.; Fujiwara, T.; Tsuge, K.; Yakura, T. Total Synthesis of Myriocin and Mycetericin D Employing Rh(II)-Catalyzed C–H Amination Followed by Stereoselective Alkylation. *Tetrahedron* **2017**, *73*, 868-878.
- (10) Lane, J. W.; Halcomb, R. L. *Tetrahedron* **2001**, *57*, 6531-6538.
- (11) For our recent study of 1,5-H shift-mediated C–H functionalization, see: Ikeuchi, T.; Inuki, S.; Oishi, S.; Ohno, H. Gold(I)-Catalyzed Cascade Cyclization Reactions of Allenynes for the Synthesis of Fused Cyclopropanes and Acenaphthenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 7792-7796.
- (12) Guo, J.-J.; Hu, A.; Zuo, Z. Photocatalytic Alkoxy Radical-Mediated Transformations. *Tetrahedron Lett.* **2018**, *59*, 2103-2111.

- (13) Capaldo, L.; Ravelli, D. Alkoxy Radicals Generation: Facile Photocatalytic Reduction of *N*-Alkoxyazinium or Azolium Salts. *Chem. Commun.* **2019**, 55, 3029-3032.
- (14) Concepción, J. I.; Francisco, C. G.; Hernández, R.; Salazar, J. A.; Suárez, E. Intramolecular Hydrogen Abstraction. Iodosobenzene Diacetate, an Efficient and Convenient Reagent for Alkoxy Radical Generation. *Tetrahedron Lett.* **1984**, 25, 1953-1956.
- (15) Blakemore, P. R.; Cole, W. J.; Kocineski, P. J.; Morley, A. A Stereoselective Synthesis of *trans*-1,2-Disubstituted Alkenes Based on the Condensation of Aldehydes with Metallated 1-Phenyl-1H-tetrazol-5-yl Sulfones. *Synlett* **1998**, 26-28.
- (16) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation. *Chem. Rev.* **1994**, 94, 2483-2547.
- (17) Paterson, I.; Di Francesco, M. E.; Kuhn, T. Toward the Synthesis of Peloruside A: Fragment Synthesis and Coupling Studies. *Org. Lett.* **2003**, 5, 599-602.
- (18) Hanessian, S.; Wong, D. H.; Therien, M. Oxidation of Alcohols with *N*-Halosuccinimides-New and Efficient Variants. *Synthesis* **1981**, 394-396.