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Pairwise Use of Complexity-Generating Reactions in Diversity-Oriented Organic Synthesis

Daesung Lee, Jason K. Sello, and Stuart L. Schreiber*

Howard Hughes Medical Institute, Department of Chemistry & Chemical Biology, Harvard Institute of Chemistry & Cell Biology, Harvard University, Cambridge, Massachusetts 02138

sls@slsiris.harvard.edu

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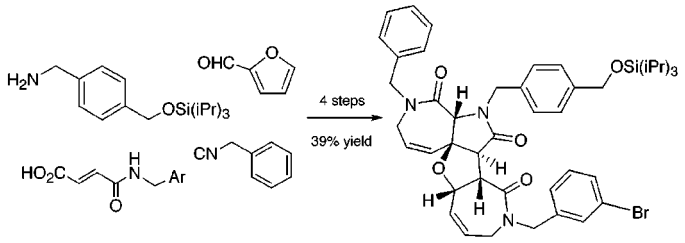
ABSTRACT



Two pairs of complexity-generating reactions with an essential product–substrate relationship along a synthetic pathway are demonstrated. This pathway illustrates a key element in a planning algorithm for diversity-oriented synthesis. This element facilitates the efficient synthesis of structurally complex compounds, and it can be integrated with ones that provide structurally diverse compounds.

Target-oriented synthesis is used widely to prepare a specific target compound (e.g., a drug or drug candidate, natural product, biological reagent) or a collection of structurally related compounds (e.g., "focused libraries" in combinatorial chemistry). Planning such syntheses invariably involves the use of retrosynthetic analysis (Figure 1A).[1]

Synthetic compounds can also be used to dissect the circuitry of cells in a way that is analogous to the use of mutations in genetics.[2] These compounds can be prepared using diversity-oriented synthesis, where the key synthesis objective is to generate a collection of structurally complex and diverse compounds capable of modulating any pathway or process of interest.[3] Complexity is important since many biological processes are critically dependent upon protein−protein interactions, and many of the small molecules known to disrupt these interactions are structurally complex natural products. Increasing the size and number of rigidifying and protein-binding elements in small molecules is generally viewed as essential for these compounds to bind to sites of protein−protein interactions, which tend to be relatively flat in comparison to the concave topography characteristic of enzyme active sites. Diversity is also important, especially in cell- or organism-based screens where small molecules are screened in search of a specific effect on a cell or organism (a "phenotypic" screen).[4] Since there is no one particular target in such screens, and an eventual target could be any one of the cell's or organism's entire collection of macromolecules, the structural diversity of the collection of small molecules will be critically linked to a successful outcome.

Since diversity-oriented syntheses are not aimed at a single structural type, retrosynthetic analysis is not readily applicable. Having an interest in preparing and using synthetic compounds in the manner described above,[4,5] we have been

(1) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; John Wiley & Sons: New York, 1989.

(2) (a) Mitchison, T. J. *Chem. Biol.* **1994**, *1*, 3−6. (b) Schreiber, S. L. *Bioorg. Med. Chem.* **1998**, *6*, 1127−1152. (c) Crews, C. M.; Splittgerber, U. *Trends Biochem. Sci.* **1999**, *24*, 317−320.

(3) Spaller, M. R.; Burger, M. T.; Fardis, M.; Bartlett, P. A. *Curr. Opin. Chem. Biol.* **1997**, *1*, 47−53.

(4) (a) Mayer, T. U.; Kapoor, Tarun M.; Haggarty, S. J.; King, R. W.; Schreiber, S. L.; Mitchison, T. J. *Science* **1999**, *286*, 971−974. (b) Haggarty, S. J.; Mayer, T. U.; Miyamoto, D. T.; Fathi, R.; King, R. W.; Mitchison, T. J.; Schreiber, S. L. *Chem. Biol.*, in press.

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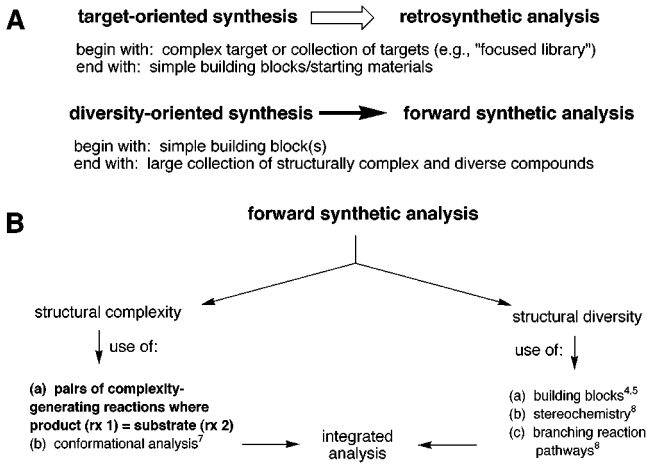


Figure 1. (A) Schematic of strategic considerations in target-oriented and diversity-oriented organic synthesis. (B) Dissecting forward synthetic analysis in diversity-oriented organic synthesis. Since the objective is to synthesize a collection of structurally complex and diverse compounds effective in modulating the complex circuitry of cells, it is easiest to first consider separately the factors that lead to complex and diverse compounds. In this Letter, we demonstrate examples of the pairwise identification of complexity-generating reactions with the indicated relationship.

developing a strategic planning algorithm to assist in the development of effective synthetic pathways in diversity-oriented synthesis. Diversity-oriented syntheses are analyzed in the direction of the chemical reactions, i.e., from reactants to products (Figure 1A). This is analogous to target-oriented synthesis in its early days, prior to the development of retrosynthetic analysis.[1] Planning such syntheses in a way that provides large collections of spatially segregated small molecules requires only the use of split-pool synthesis,[6] preferably encoded split-pool synthesis so that compounds scored as positives in screens can be readily characterized structurally.[7] Planning in a way that achieves structural complexity and diversity requires considerably more thought. Nevertheless, guiding principles have emerged that provide a means to plan such syntheses systematically, in analogy to retrosynthetic analysis in target-oriented synthesis. These are outlined in Figure 1B.

The goals of achieving structural complexity and diversity in synthetic pathways initially can be analyzed separately, but these analyses eventually should be melded. Structural diversity can be achieved in diversity-oriented syntheses by at least three methods (right side of Figure 1B). Incorporating diverse building blocks is the most obvious one.[4,5] Diversity can also arise from the synthesis of stereoisomeric products, although conformational analysis will often be required since certain combinations of stereocenters may present obstacles in a synthesis.[8] The design of branching reaction pathways that result in structures with widely varying connectivity ("scaffolds") are both highly desirable and challenging.[8] In this process, reagents are added to reaction vessels following a split step that causes the skeletal backbone to be altered, rather than the simpler process of adding reagents that couple building blocks to a common skeletal backbone.

The primary focus of this work is on a simple planning technique aimed at generating structural complexity in synthetic products in a minimal number of steps (left side in bold-face type in Figure 1B). Pairs of complexity-generating reactions are identified where the product of the first reaction is a substrate for the second reaction.[9] This is related to the case of "tandem reactions" in target-oriented synthesis, but here a premium is placed on reactions that have a dramatic impact on the complexity index of the product.[10] The examples provided in this report illustrate syntheses of structurally complex compounds containing five-, six-, and seven-membered rings. Conformational analysis can play an important role in diversity-oriented syntheses of compounds containing macrocyclic rings.[8]

Examples of the pairwise use of complexity-generating reactions involving the Ugi-4 component, intramolecular Diels−Alder, and ring-opening-closing olefin metathesis reactions are provided in Figures 2 and 3. A tandem Ugi-4 component coupling and intramolecular Diels−Alder reaction[11] was first achieved in the solution phase by using furfural, benzyl isocyanide, fumaric acid (3-bromobenzyl)-monocarboxamide, and (triisopropylsilyloxy)methylbenzylamine in methanol (the triisopropylsilyl protecting group was use to mimic a silicon-based linker used subsequently in solid-phase experiments) (Figure 2). Key to this process and an earlier related one[11] is to use a diene and a dienophile as two of the four components in the Ugi reaction. After the reaction mixture was stirred at an ambient temperature for 48 h, the intramolecular Diels−Alder adduct was isolated (67%) after purification as a single stereoisomer (the relative stereochemistry of this compound was established by the X-ray diffraction analysis).[12]

(5) (a) Tan, D. S.; Foley, M. A.; Shair, M. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 8565−8566. (b) Tan, D. S.; Foley, M. A.; Stockwell, B. R.; Shair, M. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9073−9087.

(6) (a) Furka, A.; Sebestyén, F.; Asgedom, M.; Dibó, G. Proceedings of the 14th International Congress of Biochemistry, Prague, Czechoslovakia, 1988; VSP: Ultrecht, The Netherlands, 1988; Vol. 13, p 47. (b) Furka, A.; Sebestyén, F.; Asgedom, M.; Dibó, G. Poster presented at the Xth International Symposium on Medicinal Chemistry, Budapest, 1988. (c) Furka, A.; Sebestyén, F.; Asgedom, M.; Dibó, G. *Int. J. Peptide Prot. Res.* **1991**, *37*, 487−493. (d) Houghten, R. A.; Pinilla, C.; Blondelle, S. E.; Appel, J. R.; Dooley, C. T.; Cuervo, J. H. *Nature* **1991**, *354*, 84−86. (e) Lam, K. S.; Salmon, S. E.; Hersh, E. M.; Hruby, V. J.; Kazmierski, W. M.; Knapp, R. J. A. *Nature* **1991**, *354*, 82−84.

(7) (a) Kerr, J. M.; Banville, S. C.; Zuckermann, R. N. *J. Am. Chem. Soc.* **1993**, *115*, 2529−2531. (b) Nikolaiev, V.; Stierandová, A.; Krchák, V.; Seligmann, B.; Lam, K. S.; Salmon, S. E.; Lebl, M. *Peptide Res.* **1993**, *6*, 161−170. (c) Ohlmeyer, M. H. J.; Swanson, R. N.; Dillard, L. W.; Reader, J. C.; Asouline, G.; Kobayashi, R.; Wigler, M.; Still, W. C. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 10922−10926.

(8) Lee, D.; Sello, J. K.; Schreiber S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10648−10649.

(9) For recent examples, see: (a) Heerding, D. A.; Takata, D. T.; Kwon, C.; Huffman, W. F.; Samanen, J. *Tetrahedron Lett.* **1998**, *39*, 6815−6818. (b) de Meijere, A.; Nüske, H.; Es-Sayed, M.; Labahn, T.; Schroen, M.; Bräse, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3669−3672. (c) Brooking, P.; Crawshaw, M.; Hird, N. W.; Jones, C.; MacLachlan, W. S.; Readshaw, S. A.; Wilding, S. *Synthesis* **1999**, 1986−1922. (d) Schürer, S. C.; Blechert, S. *Synlett* **1999**, *12*, 1879−1882.

(10) (a) Bertz, S. H. *J. Am. Chem. Soc.* **1981**, *103*, 3599−3601. (b) Bertz, S. H.; Sommer, T. J. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, pp 67−92.

(11) Paulvannan, K. *Tetrahedron Lett.* **1999**, *40*, 1851−1854.

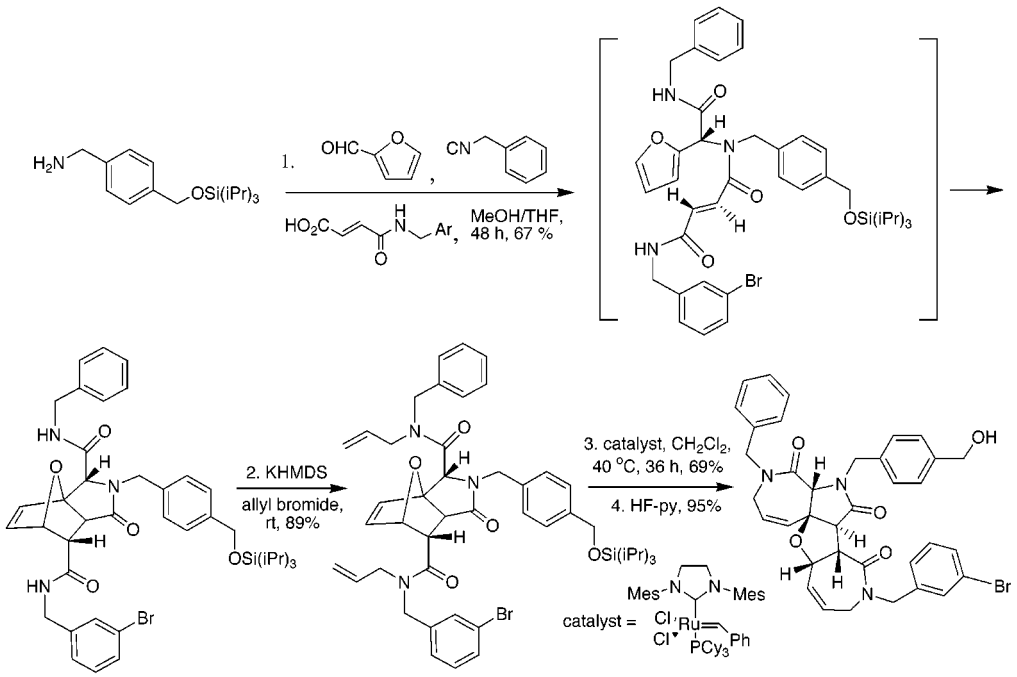
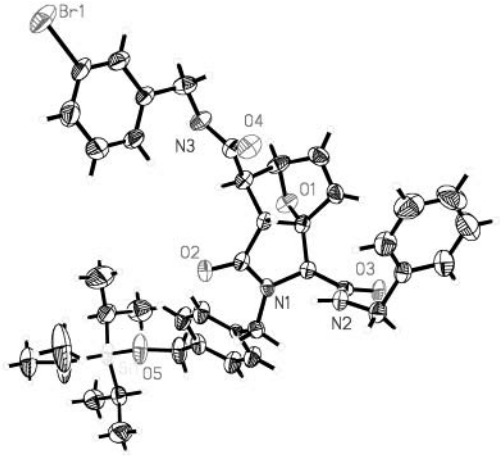


Figure 2. Solution-phase studies of 7-5-5-7 polycyclic ring synthesis.

The resulting cycloadduct contains a strained alkene that we envisioned as a substrate for another complexity-generating reaction, the ring opening−closing metathesis reaction.[13] In contrast to the first pair of reactions which have the described product−substrate relationship, coupling a metathesis reaction to a Diels−Alder reaction requires an intermediate step. Bis(allylation) of the secondary amides was achieved by treating the cycloadduct with excess KHMDS and allyl bromide in THF at an ambient temperature (89%). Reaction of this bis(allyl) amide with a ruthenium-based olefin metathesis catalyst containing 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene[14] in CH_2Cl_2 (3 mM) for 36 h under reflux followed by purification provided the 7-5-5-7 fused ring product in 69% yield.

For this chemistry to benefit from the numerics of split-pool synthesis, it is necessary to adapt it to the solid phase (Figure 3).[15] In research to be described elsewhere, a collaborative effort has led to the large scale synthesis of high-capacity polystyrene beads (500−560 μm) containing a carbon-and-silicon-only extender that allows attachment and release of ca. 100 nmol of small molecules via a silicon−

(12) Crystallographic data: monoclinic single crystal (0.10 × 0.05 × 0.05 mm^3, space group $P2(1)/c$, unit cell constants a = 18.092(1) Å, b = 14.6615(8) Å, c = 14.9414(9) Å, α = 90°, β = 97.633(1)°, γ = 90°, V = 3928.2(4) Å^3, Z = 4, D_x = 1.305 g/cm^3). X-ray diffraction data were collected using a Bruker SMART CCD diffractometer equipped with an LT-2 low-temperature apparatus at 213 K. Data were measured using ω scans of 0.3° per frame for 45 s. A total of 1271 frames were collected with a maximum resolution of 0.80 Å. Cell parameters were retrieved using SMART software and refined using SAINT on all observed reflections. Data reduction was performed with SAINT, and the structures are solved by the direct method using the SHELXS-97 program incorporated in SHELXTL-PC V 5.10 and refined by theleast-squares method on F^2. The final agreement factors are $R(F)$ = 0.1105, $R_w(F)$ = 0.1192.



(13) (a) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634−6640. (b) Zuercher, W. J.; Scholl, M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 4291−4298. (c) Stragies, R.; Blechert, S. *Tetrahedron* **1999**, *55*, 8179−8188.

(14) For the most efficient ring opening−closing metathesis reaction, the ruthenium-based catalyst containing 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene in refluxing CH_2Cl_2 was necessary. (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956. (b) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751−1753. (c) Huang, J. K.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674−2678.

(15) Recent reviews of solid-phase organic reactions: (a) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527−4554. (b) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643−5678. (c) Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288−2337. (d) Dolle, R. E.; Nelson, K. H., Jr. *J. Comb. Chem.* **1999**, *1*, 236−282. (e) Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997−10998. (f) Simon, R. J.; Kaina, R. S.; Zuckermann, R. N.; Huebner, V. D.; Jewell, D. A.; Banville, S.; Ng, S.; Wang, L.; Rosenberg, S.; Marlowe, C. K.; Spellmeyer, D. C.; Tan, R.; Frankel, A. D.; Santi, D. V.; Cohen, F. E.; Bartlett, P. A. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 9367−9371. (g) DeWitt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Cody, D. M. R.; Pavia, M. R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 6909−6913.

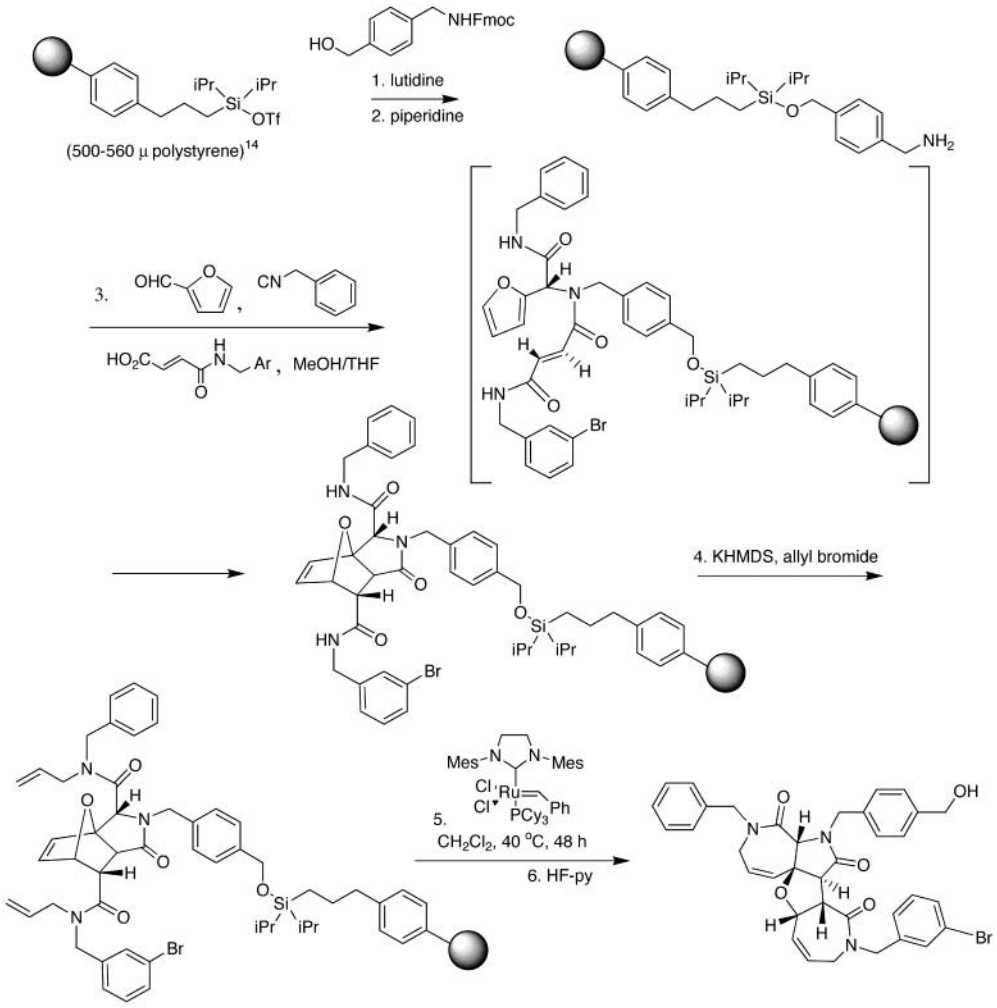


Figure 3. Solid-phase studies of 7-5-5-7 polycyclic ring synthesis.

oxygen bond.[16] The free alcohol of the amine component of the Ugi reaction was attached to the large beads by displacement of the silyl triflate element on the linker. The resulting immobilized amine was treated with excess (10 equiv) furfural, benzyl isocyanide, and fumaric acid (3-bromobenzyl)monocarboxamide in MeOH−THF (2:1) for 60 h. After thorough washing and drying of the large beads, they were treated with an excess amount of KHMDS and allyl bromide in THF. The beads were tumbled for 5 h, washed, dried, and then subjected to metathesis conditions (20 mol % of catalyst, CH_2Cl_2, 40 °C) for 60 h. The beads were treated with HF−pyridine in CH_2Cl_2 for 2 h, resulting in the release of product that was shown to be identical to that of the solution-phase synthesis.[17]

We are currently optimizing the individual steps of this solid-phase synthesis and testing related building blocks for future split-pool syntheses. As an example of melding analyses that are initially focused separately on structural complexity and diversity, we are also planning and developing related diversity-oriented synthetic pathways where pairs of complexity-generating reactions are coupled to both branching and building block coupling reactions.

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(16) Tallarico, J. A.; Depew, K. M.; Pelish, H.; Athanasopoulos, J.; Lindsley, C.; Westwood, N.; King, R. W.; Schreiber, S. L.; Shair, M. D.; Foley, M. A., unpublished results.

(17) Spectroscopic data for the final product: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41−7.14 (m, 13H), 6.24 (d, J = 10.7 Hz, 1H), 5.94 (m, 1H), 5.85 (m, 2H), 5.36 (d, J = 14.7 Hz, 1H), 4.79 (d, J = 15.2 Hz, 1H), 4.71 (s, 1H), 4.69 (d, J = 13.7 Hz, 1H), 4.65 (s, 1H), 4.57 (m, 1H), 4.50 (d, J = 14.6 Hz, 1H), 4.39 (d, J = 15.2 Hz, 1H), 4.08 (m, 1H), 4.02 (d, J = 5.9 Hz, 1H), 3.99 (s, 1H), 3.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.4, 139.0, 136.2, 134.9, 133.6, 131.1, 130.8, 130.6, 130.1, 129.6, 128.6, 128.5, 128.3, 127.7, 127.4, 127.3, 126.5, 122.5, 80.7, 76.3, 69.0, 64.8, 54.4, 51.6, 51.2, 50.7, 46.1, 42.9, 42.0; HRMS (ES) calcd for $C_{36}H_{34}BrN_3O_5$ $(M + H)^+$ 668.1760, found 668.1736.