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Indole Diterpene Synthetic Studies: Development of a Second-Generation Synthetic Strategy for (+)-Nodulisporic Acids A and B

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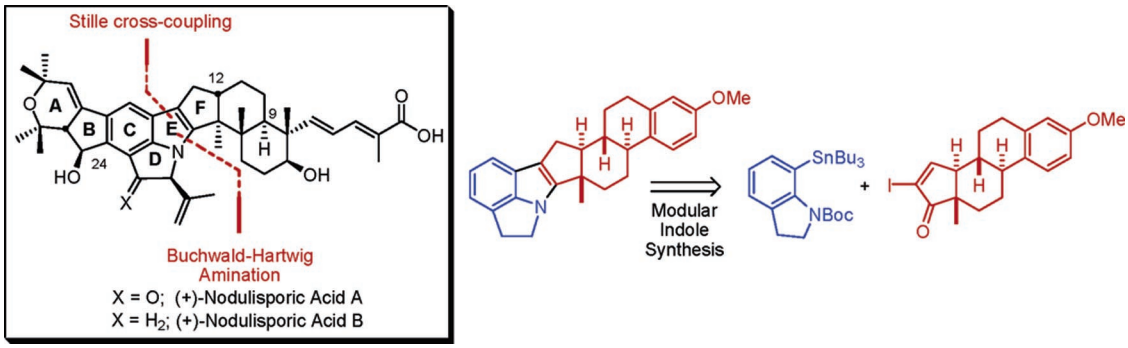

A second-generation strategy for construction of (+)-nodulisporic acids A and B based on the development of a new, effective modular indole synthesis exploiting a sequential Stille cross-coupling/Buchwald−Hartwig union/cyclization tactic is disclosed. This strategy evolved due to the considerable acid instability of the C(24) hydroxyl group observed in several advanced intermediates during our first-generation approach.

Introduction

The nodulisporanes comprise a new class of insecticidal indole diterpenes (Figure 1). Structurally the most complex member, (+)-nodulisporic acid A (**1**), was isolated by Ondeyka and co-workers at Merck Research Laboratories in 1997.[1,2] Given the architectural novelty of the nodulisporanes, in conjunction with their potential use as commercial insecticides, we initiated a synthetic program in 2000 to devise a modular strategy that would permit construction, not only of the naturally occurring nodulisporic acids, but also of the congeners not readily available by chemical modification of the natural products.[3,4] In the preceding paper,[5] we outlined a first-generation strategy (Scheme 1) for (+)-nodulisporic acids A (**1**) and B (**2**) based on the indole construction tactic (**6**+**7**, Scheme 1) that we developed in the mid 1980s[6,7] and subsequently exploited for the total syntheses of several related indole diterpenoid natural products, including (−)-21-isopentenylpaxilline[8] and (−)-penitrem D.[9,10] Specifically, we envisioned late-stage attachment of the highly strained nodulisporic acid D-ring

(1) Ostlind, D. A.; Felcetto, T.; Misura, A.; Ondeyka, J.; Smith, S.; Goetz, M.; Shoop, W.; Mickle, W. *Med. Vet. Entomol.* **1997**, *11*, 407−408.

(2) Ondeyka, J. G.; Helms, G. L.; Hensens, O. D.; Goetz, M. A.; Zink, D. L.; Tsipouras, A.; Shoop, W. L.; Slayton, L.; Dombrowski, A. W.; Polishook, J. D.; Ostlind, D. A.; Tsou, N. N.; Ball, R. G.; Singh, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 8809−8816.

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(6) Smith, A. B., III; Visnick, M.; Haseltine, J. N.; Sprengeler, P. A. *Tetrahedron* **1986**, *42*, 2957−2969.

(7) Smith, A. B., III; Visnick, M. *Tetrahedron Lett.* **1985**, *26*, 3757−3760.

(8) Smith, A. B., III; Cui, H. *Org. Lett.* **2003**, *5*, 587−590.

(9) Smith, A. B., III; Kanoh, N.; Ishiyama, H.; Hartz, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 11254−11255.

(10) Smith, A. B.; Kanoh, N.; Ishiyama, H.; Minakawa, N.; Rainier, J. D.; Hartz, R. A.; Cho, Y. S.; Cui, H.; Moser, W. H. *J. Am. Chem. Soc.* **2003**, *125*, 8228−8237.

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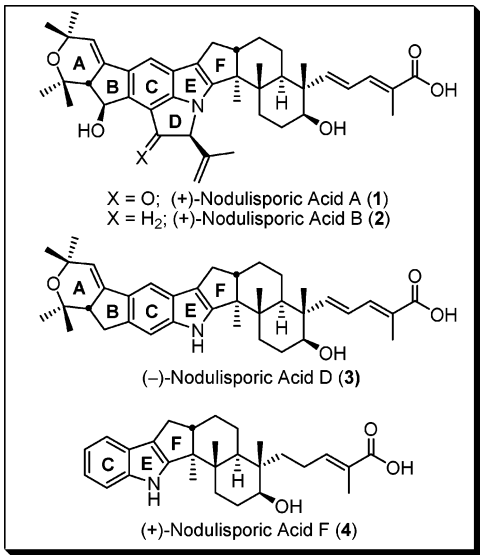
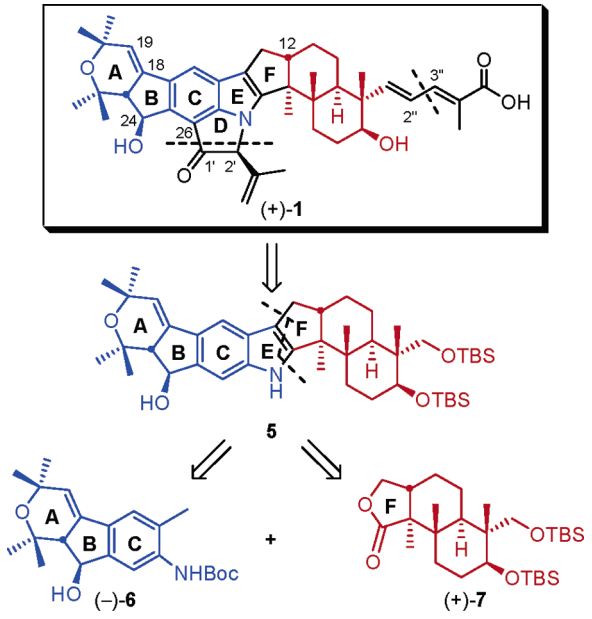


FIGURE 1. Representative nodulisporic acid congeners.

onto an advanced heptacyclic intermediate (cf. **5**) employing the acylation conditions developed by Hendrickson.[11] The requisite dienoic side chain would then be installed via a Stille cross-coupling tactic.[12]

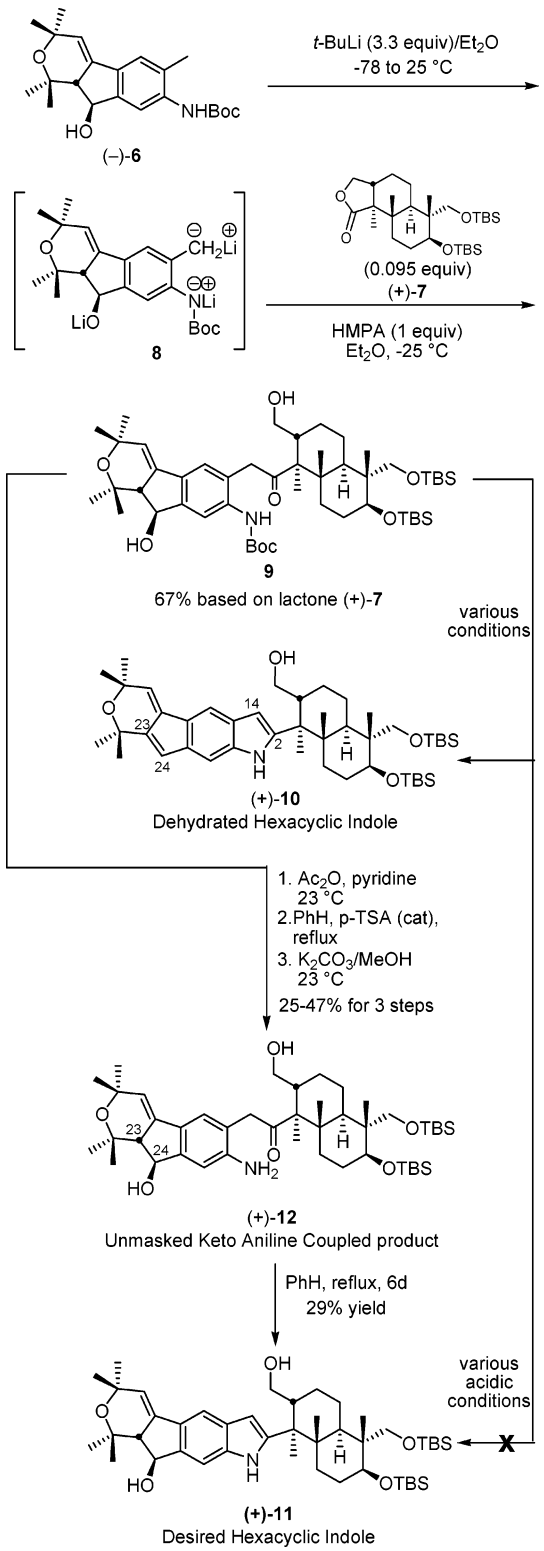
SCHEME 1. First-Generation Retrosynthetic Analysis of Nodulisporic Acid A (1)



Results and Discussion

A First-Generation Strategy for Nodulisporic Acid A: Challenges and Frustrations. Pleasingly, our indole synthetic tactic proved successful for the union of the requisite structurally complex western and eastern hemisphere tricyclic aniline (−)-**6** and lactone (+)-**7** to furnish aniline **9** (Scheme 2).[5] We anticipated that the Boc group could be readily removed under mild acidic or basic conditions and the resulting amino ketone

SCHEME 2. Union of Aniline (−)-6 with Lactone (+)-7 and Indole Formation Studies with Keto Aniline 9



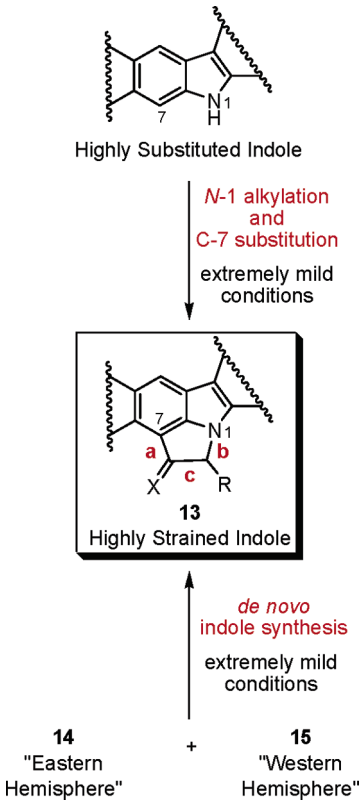
in turn induced to undergo facile cyclodehydration to complete construction of the desired hexacyclic indole **11**. Unfortunately, selective removal of the Boc group, even under extremely mild acidic conditions (e.g., SiO_2, PPTS, etc.), could not be achieved without effecting C(24) hydroxyl dehydration to furnish the hexacyclic indole **10** (Scheme 2). Ultimately, we did achieve removal of the Boc group, but only after acetylation of the two

(11) Hendrickson, J. B.; Hussoin, M. S. *J. Org. Chem.* **1989**, *54*, 1144−1149.

(12) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652.

hydroxyl groups, followed by exposure to *p*-toluenesulfonic acid (Scheme 2). Removal of the acetates (K_2CO_3/MeOH) then led to the unmasked amino ketone (+)-**12**, albeit in modest yield (three steps, ca. 25−47%). Indole formation was then achieved under neutral conditions by heating in benzene at reflux for 6 days; the long exposure time, however, permitted isolation of (+)-**11** in only 29% yield. The modest efficiency of the overall indole ring construction, in conjunction with the considerable lability of the C(24) hydroxyl clearly foreshadowed difficulty with the proposed D-ring installation exploiting the earlier proposed (vide infra) acidic Hendrickson acylation protocol. We therefore developed a second-generation strategy (Scheme 3); two strategic alternatives were envisioned to construct ring D. The first, as with the Hendrickson scenario, would entail use of a pre-existing indole moiety, onto which the C(7)−N(1) two-

SCHEME 3. Possible Approaches to the Highly Strained Indole 13



carbon bridge would be installed. Mild conditions would be paramount to avoid elimination of the C(24) hydroxyl. The second alternative would require the development of a de novo indole synthesis, again employing mild reaction conditions. Central to the latter scenario would be preservation of the convergency of the overall synthetic sequence, thereby permitting the union of two modestly re-engineered advanced hemispheres (e.g., **14** and **15**).[13] To elaborate the D-ring employing an already existing indole nucleus, three bonds (**a**, **b**, and **c**) were considered for disconnection. We were of course cognizant of the considerable strain inherent in the central CDE ring system of the nodulisporic acids. In this regard, only two reports exist wherein a two-carbon bridge has been successfully installed between the C(7) and N(1) (nodulisporic acid numbering) on a substituted indole or indoline ring. The first entailed construction of the highly strained 1,7-annulated system **16** (Figure 2).[14] Not surprisingly, indole **16** was reported to be quite unstable, readily reacting with various nucleophiles (e.g., alcohols and amines)

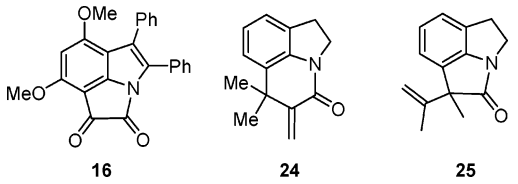


FIGURE 2. Literature examples of 1,7-annulated indoles.[14,15,17]

to relieve the ring strain (i.e., relatively weak C−N bond). The second example was recorded as part of a study by Dankwardt et al.[15] on the structural requirements for a 5-*exo*-trig versus 6-*endo*-trig Pd-catalyzed Heck reaction (cf. **24** and **25**).[16−18] Notwithstanding the foreboding literature precedent, we briefly explored several seemingly straightforward approaches to install the C(7)−N(1) bridge. The first involved intramolecular nucleophilic substitution to form the C−N bond (bond **b**, Scheme 3). Toward this end, α-bromo ketone **27** was prepared from α-diazoketone **26** via treatment with HBr.[19] We envisioned either heating **27** in a nonpolar solvent or exposure to K_2CO_3 or LiHMDS might permit the indolyl nitrogen to displace the α-bromine atom. Unfortunately, both reactions proved unsuccessful. Presumably, the ring strain in conjunction with stereoelectronic alignment prevents the nitrogen anion from developing sufficient overlap with the σ^* orbital of the C−Br bond.

(13) Smith, A. B., III; Kürti, L.; Davulcu, A. H. *Org. Lett.* **2006**, *8*, 2167−2170.

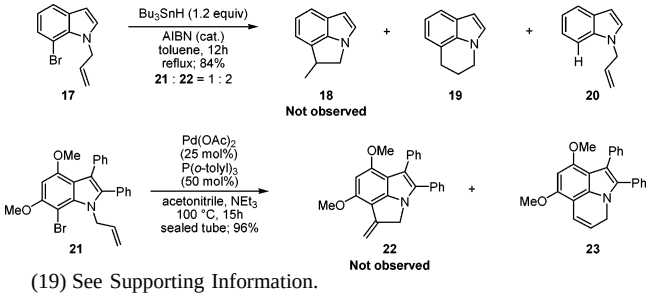
(14) Black, D. S. C.; Bowyer, M. C.; Catalano, M. M.; Ivory, A. J.; Keller, P. A.; Kumar, N.; Nugent, S. J. *Tetrahedron* **1994**, *50*, 10497−10508.

(15) Dankwardt, J. W.; Flippin, L. A. *J. Org. Chem.* **1995**, *60*, 2312−2313.

(16) Dankwardt and co-workers also examined the effect of the ring size on the mode of ring closure and therefore prepared an *N*-acryloyl-8-bromotetrahydroquinoline derivative upon Heck cyclization, and the ratio of the 5-*exo*-trig versus the 6-*endo*-trig products was reversed, favoring the former mode of cyclization. The authors concluded that the 6-*endo*-trig cyclization mode is only favored in systems (i.e., indoles and indolines) wherein the strain of the transition state would severely suppress the 5-*exo*-trig mode of ring closure.

(17) For a few examples of radical or Pd-catalyzed cyclization of *N*-allyl-7-bromoindoles (Scheme 4), see: (a) Dobbs, A. P.; Jones, K.; Veal, K. T. *Tetrahedron Lett.* **1997**, *38*, 5379−5382. (b) Black, D. S. C.; Keller, P. A.; Kumar, N. *Tetrahedron* **1992**, *48*, 7601−7608.

(18) Intramolecular reactions between carbon-centered radicals and olefins prefer to proceed via a kinetic 5-*exo*-trig cyclization for stereoelectronic reasons. However, in the case of compound **17**, only the corresponding 6-*endo*-trig cyclization product **19** was obtained along with some reduced product **20**. Similar observations were obtained with the Pd-catalyzed cyclization of indole **21**. The authors[14] attributed the observed selectivity favoring the 6-*endo*-trig cyclization to the considerable strain and distortion in the transition state leading to the five-membered 1,7-annulated products.



(19) See Supporting Information.

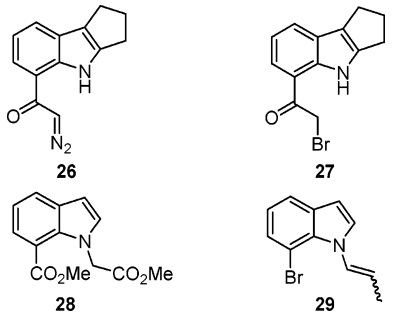


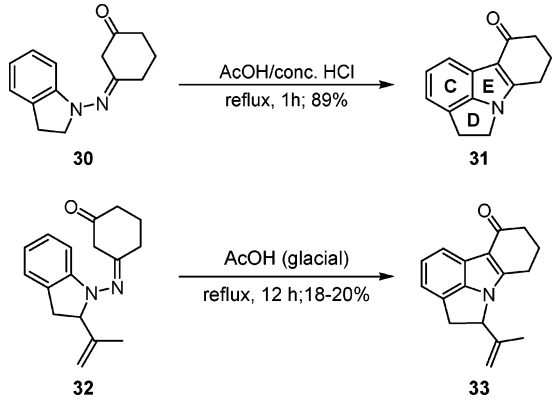
FIGURE 3. Unsuccessful approaches for the construction of ring D.

We next considered an intramolecular carbenoid insertion promoted by rhodium.[20−23] Required here was **26** (Figure 3). Two Rh carboxylate catalysts were explored. The common dirhodium tetraacetate [$Rh_2(OCOCH_3)_4$] catalyst[24] led rapidly to decomposition. The less common catalyst, dirhodium tetraoctanoate,[24] also led at room temperature to no reaction, while at the reflux temperature of dichloroethane, complete decomposition occurred. Again, ring strain in conjunction with the stereoelectronics presumably precluded bond formation.

We turned next to the possibility of bond **c** construction (Scheme 3). Two approaches were explored: a Dieckmann condensation[25] and a Heck carbonylation.[26,27] The requisite Dieckmann substrate was diester **28**.[19] No products were observed employing a variety of bases (e.g., NaH, NaOMe, LiHMDS). Similarly, treatment of **29** with a series of palladium catalysts, solvents, and temperature regiments failed to generate the D-ring. Again the ring strain was presumably too high to permit cyclization. Taken together, these observations compelled us to abandon installation of the C(7)−N(1) two-carbon bridge (D-ring) onto a pre-existing indole nucleus. This decision had two important consequences: first, a new convergent indole synthesis was mandated to assemble the highly strained CDE tricycle; second, the new union tactic would require at least modest re-engineering of the original eastern and western hemispheres (**6** and **7**).

Turning to the literature for alternative construction of the CDE tricycle, we noted the work of Wijngaarden and coworkers[28] who subjected hydrazone **30** to the classic Fischer indole synthetic protocol [HCl/AcOH] (Scheme 4). Tetracyclic

SCHEME 4. The Fischer Indole Synthesis Approach



indole **31** was formed in excellent yield. We reasoned that a similar tactic might provide a convergent synthetic strategy for the core of the nodulisporic acids. The prospect of generating a fully elaborated D-ring during to the union of an eastern and western fragment was clearly appealing. To test the viability of this approach, we turned to the preparation of tetracyclic indole **33**, bearing an isopropenyl substituent on the D-ring as found in nodulisporic acid B (Scheme 4). The requisite hydrazine, efficiently constructed from isopropenyl indoline[29] in two steps, was condensed with 1,3-cyclohexanedione.[30] In addition to the expected hydrazone **32** (50%), we obtained a very modest yield (ca. 9%) of the desired tetracyclic indole **33**. However, when the pure hydrazone **32** was subjected to the same or related Fischer indole protocols, the yield of **33** improved only slightly (ca. 10−20%), presumably due to the instability of **33** to the reaction conditions. The structure of **33** was confirmed via single-crystal X-ray crystallography (Figure 4). Examination of the bond angles in **33** not surprisingly revealed significant bond angle distortions. Particularly noteworthy, one of the bond angles in ring C deviated by 12.3° from the expected angle of 120° for benzene. Similar transformations with the hydrazones derived from either cyclopentanedione or cyclopentanone however led only to decomposition. Again, the issue of ring strain under the thermodynamic conditions prevented indole ring formation.

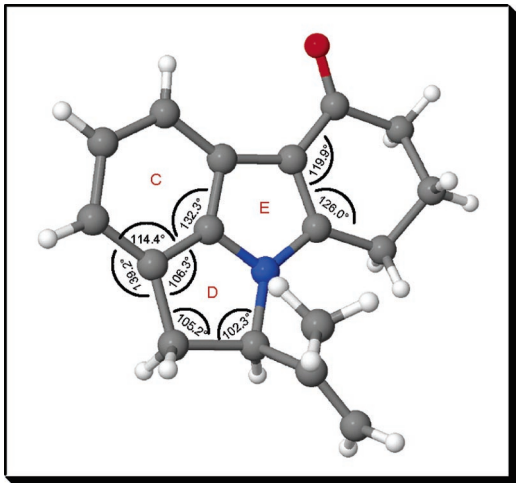


FIGURE 4. Bond angles of tetracyclic indole **33** as determined from the single-crystal X-ray structure (Jmol Viewer version 10).

At this juncture, we reasoned that access to the γ-amino ketone that serves as the cornerstone of the Fischer indole tactic

(20) Doyle, M. P. *Top. Organomet. Chem.* **2004**, *13*, 203−222.
(21) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091−1160.
(22) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385−5453.
(23) Burke, S. D.; Grieco, P. A. *Org. React.* **1979**, *26*, 361−475.
(24) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765−1808.
(25) Davis, D. R.; Garratt, P. J. In *Comprehensive Organic Syntheses*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 795−863.
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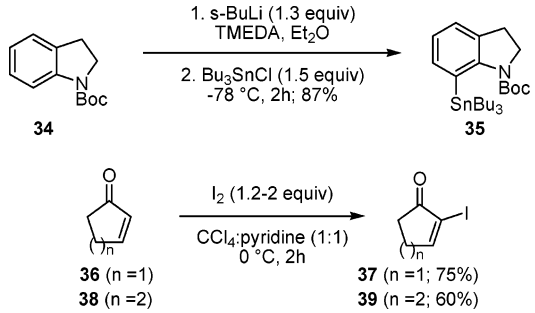
(30) Generally, absolute ethanol at reflux is sufficient for the preparation of hydrazones; however, even after 12 h at reflux, we observed less than 5% of hydrazone **32**, accompanied by significant decomposition of the hydrazine. Acetic acid was therefore added to catalyze the transformation.

might permit the development of a new, modular indole synthetic protocol. This line of analysis suggested that α-arylation of ketones, as introduced by Buchwald and Hartwig,[31,32] might be well-suited to permit access to the requisite γ-amino ketones. Although we were able to reproduce successfully several α-ketone arylations as reported by Buchwald et al.,[31] treatment of 7-bromoindoline or the *N*-Boc derivative with either cyclohexanone or 1,3-cyclohexanedione led only to recovery of starting materials. We suspect that the necessary oxidative addition most likely fails to take place, again due to steric reasons. Indeed a careful literature search revealed the lack of *o*-haloanilines participating in the Buchwald−Hartwig ketone arylation process. We therefore halted further efforts to obtain the required γ-amino ketone intermediates via the Buchwald−Hartwig protocol.

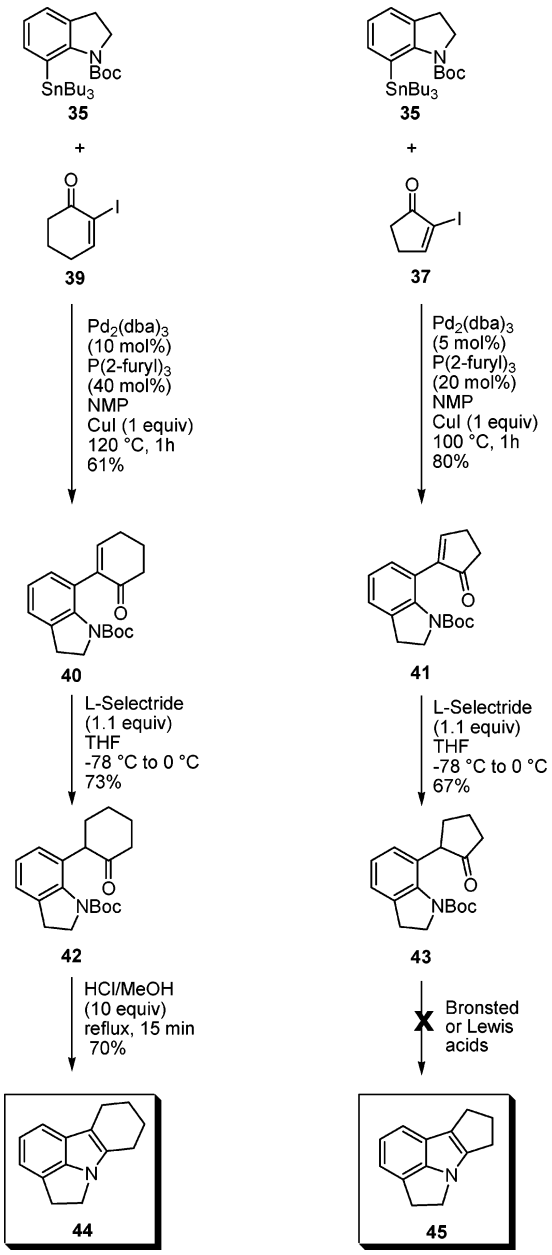
Still intrigued by the possibility of α-ketone arylations, we turned to other cross-coupling reactions (i.e., Suzuki or Stille cross-coupling).[12] Overman and co-workers,[33,34] en route to the total synthesis of (−)-idiospermuline, reported the union of a complex 7-iodo-*N*-Boc indoline with an aliphatic vinylstannane. To explore this possibility, we constructed model substrates (**35**, **37**, and **39**), albeit reversing the functional groups compared to the Overman example (Scheme 5). Specifically *N*-Boc indoline **34** was *ortho*-lithiated, and the resulting aryllithium reacted with tributylstannyl chloride to furnish arylstannane **35**.[35] The

SCHEME 5. Preparation of Substrates for the Stille Cross-Coupling



requisite α-iodoenones **37** and **39** were prepared using the procedure developed by Johnson et al.[36] We began with the Stille cross-coupling reaction of enone **37** with arylstannane **35** (Scheme 6). No reaction was observed at room temperature employing the Overman conditions. However, as the reaction temperature was raised (ca. >80 °C), the yield of **41** progressively increased. Optimum conditions entailed 1.5 equiv of **35** at ca. 100 °C. When less than 1.5 equiv of **35** was employed, a sharp drop in the yield was observed.[37] In similar fashion, the Stille cross-coupling of 2-iodocyclohexenone **39** with **35** furnished **40**; however, to obtain a high yield, the catalyst and

SCHEME 6. The Stille Cross-Coupling Approach



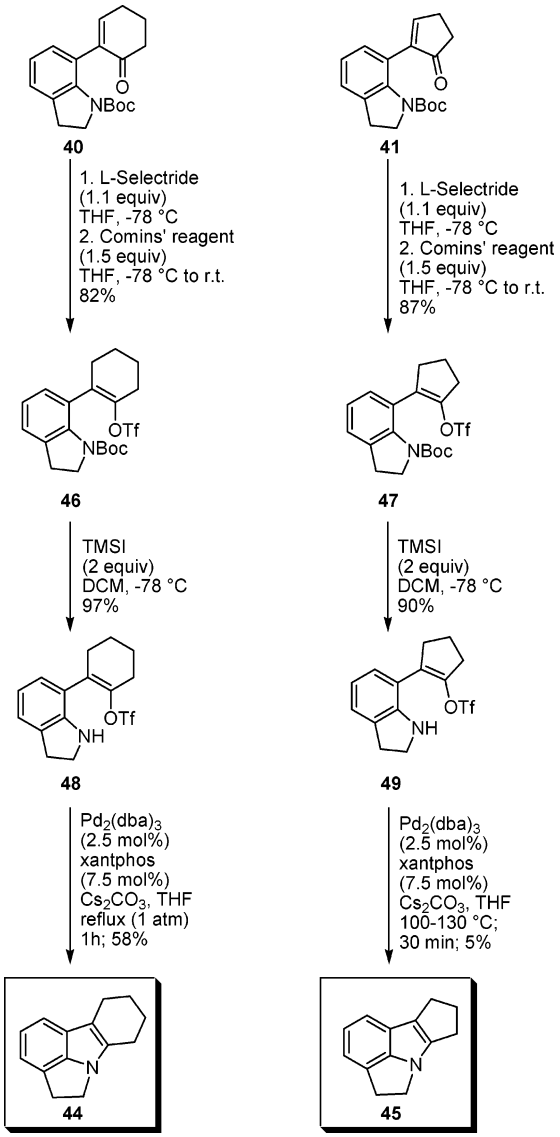
ligand loadings had to be increased (Scheme 6). Reduction of enones **40** and **41** with L-Selectride in 1,4 fashion furnished the desired α-arylcycloalkanones **42** and **43**, respectively.[38] Again cognizant of the core CDE ring strain, we turned to the critical cyclodehydration. Gratifyingly, exposure of **42** to methanolic HCl at reflux furnished the desired tetracyclic indole **44** in 70% yield. Treatment of **43**, however, with a variety of Brønsted and Lewis acids (e.g., HCl/MeOH, TFA, TMSI, $MgBr_2$, *p*-TsOH) even under forcing conditions, led only to decomposition. Presumably, the ring strain in indole **45** is again sufficiently high to prevent indole formation under thermodynamic conditions. This result suggests that even if we had succeeded in

(31) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360−1370.
(32) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234−245.
(33) Overman, L. E.; Peterson, E. A. *Tetrahedron* **2003**, *59*, 6905−6919.
(34) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.
(35) Diep, V.; Dannenberg, J. J.; Franck, R. W. *J. Org. Chem.* **2003**, *68*, 7907−7910.
(36) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 917−918.
(37) The reaction was also found to be very sensitive to the anhydrous state of the NMP; that is, not sufficiently dried NMP caused the arylstannane **35** to undergo significant protodestannylation at the reaction temperature. The protodestannylation was found to be much faster than the cross-coupling; in some cases, no coupling product (**40**) was observed.
(38) A survey of the literature revealed that this transformation might prove quite challenging since a mixture of 1,2- and 1,4-reduction products had been reported for many combination of enones and reducing agents: (a) Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194−2200. (b) Kowalski, C. J.; Weber, A. E.; Fields, K. W. *J. Org. Chem.* **1982**, *47*, 5088−5093. (c) Lee, H.-Y.; An, M. *Tetrahedron Lett.* **2003**, *44*, 2775−2778.

facilitating the [3,3]-sigmatropic rearrangement (i.e., in the proposed Fischer indole synthesis) employing the cyclopentanone and 1,3-cyclopentanedione-derived hydrazones, the resulting γ-amino ketone intermediates would not likely have undergone cyclization to furnish tetracyclic indoles.

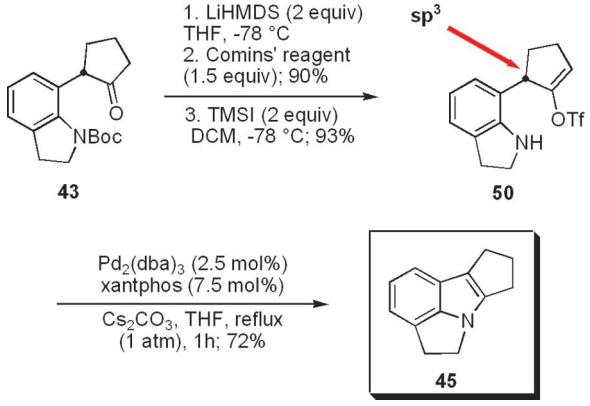
The Buchwald−Hartwig Amination: A Kinetically Controlled Protocol. At this juncture, we recognized that construction of the requisite C−N bond would require a kinetically controlled process. We selected the transition-metal-catalyzed C−N bond formation known as the Buchwald−Hartwig amination.[39] A thorough literature search revealed that examples of the amination between enol triflates and aliphatic or aromatic amines were not well precedented.[40−42] Only one report by Willis et al.[41] featured secondary amines as the coupling partner. All of the examples, however, were intermolecular reactions.[43,44] Nonetheless, we proceeded with the expectation that the right combination of catalyst, ligand, base, and solvent would permit formation of the C−N bond under kinetically controlled conditions (Scheme 7). Given the availability of the Stille cross-

SCHEME 7. Initial Buchwald−Hartwig Cyclization Studies



coupling products **40** and **41**, formation of the requisite enol triflates **46** and **47** appeared straightforward. To this end, α-aryl cycloalkenones **40** and **41** were reduced with L-Selectride and the resulting lithium alkoxides captured as the enol triflates with the Comins reagent.[45] Enol triflates **46** and **47** were produced in excellent yields. Removal of the Boc protecting groups was then achieved with TMSI[46] to furnish free amines **48** and **49**. We next screened the most commonly used catalysts [i.e., $Pd(OAc)_2$ and $Pd_2(dba)_3$], ligands [i.e., BINAP and xantphos], bases [i.e., NaO*t*-Bu, LiHMDS, Cs_2CO_3], and solvent systems [i.e., toluene, THF] to achieve the Buchwald−Hartwig amination. We quickly recognized that the use of strong bases, such as NaO*t*-Bu and LiHMDS, would not be compatible with the enol triflate moiety. Rapid decomposition occurred within minutes even at room temperature. Eventually we discovered that the combination of a mild base (Cs_2CO_3) and THF as solvent effected cyclization of enol triflate **48** to furnish the corresponding tetracyclic indole **44** in 58% yield (Scheme 7). However, the identical reaction conditions [2.5 mol % of $Pd_2(dba)_3$, 7.5 mol % of xantphos, 2 equiv of Cs_2CO_3 in THF at reflux] failed to effect the cyclization of enol triflate **49**. Formation of tetracyclic indole **45** did occur, albeit in low yield (ca. 5%) when the reaction mixture was heated to 100−130 °C in a sealed tube. This observation again attests to the fact that the activation energy for cyclization of **49** to **45** is considerably higher than for the cyclization of **48**. We next reasoned that, if we were to prepare the kinetically derived enol triflate **50** from ketone **43**, the presence of an sp^3-hybridized carbon at the benzylic position might permit a less strained transition state for the conversion of **50** to **45** (Scheme 8). Pleasingly, treatment of enol triflate **50**, derived from **43**, under the optimum

SCHEME 8. Buchwald−Hartwig Coupling of Kinetic Enol Triflate 50

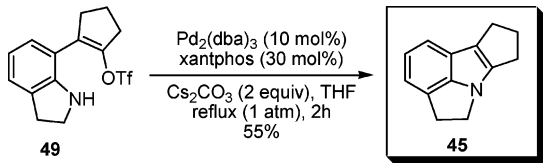


cyclization conditions developed for the conversion of **48** to **44** furnished the highly strained tetracyclic indole **45** in 72% yield. From the perspective of the nodulisporic acids, this result clearly demonstrated that an indole such as **45** could indeed be formed in high yield and, importantly, was stable under the reaction conditions. However, still determined to define condi-

(39) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131−209.
(40) Hicks, F. A.; Brookhart, M. *Org. Lett.* **2000**, *2*, 219−221.
(41) Willis, M. C.; Brace, G. N. *Tetrahedron Lett.* **2002**, *43*, 9085−9088.
(42) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 403−406.
(43) Barluenga, J.; Valdes, C. *Chem. Commun.* **2005**, 4891−4901.
(44) Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun.* **2005**, 973−986.
(45) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299−6302.

tions that would convert the thermodynamically derived enol triflate **49** to indole **45**, we turned to increasing the catalyst load, a tactic known in some cases to bring about difficult transition-metal-catalyzed transformations, given the issue of catalyst decomposition. Gratifyingly, doubling the catalyst load resulted in product formation in THF at reflux. Optimum conditions required a 4-fold increase in both catalyst and ligand (Scheme 9).[47] Several hundred milligrams of the tetracyclic indoles **44**

SCHEME 9. Buchwald−Hartwig Cyclization of Thermodynamic Enol Triflate 49



and **45** were readily prepared. Structure confirmation was achieved by single-crystal X-ray crystal analysis. As with indole **33**, significant bond angle distortion was observed in **44** and **45** (Figure 5).

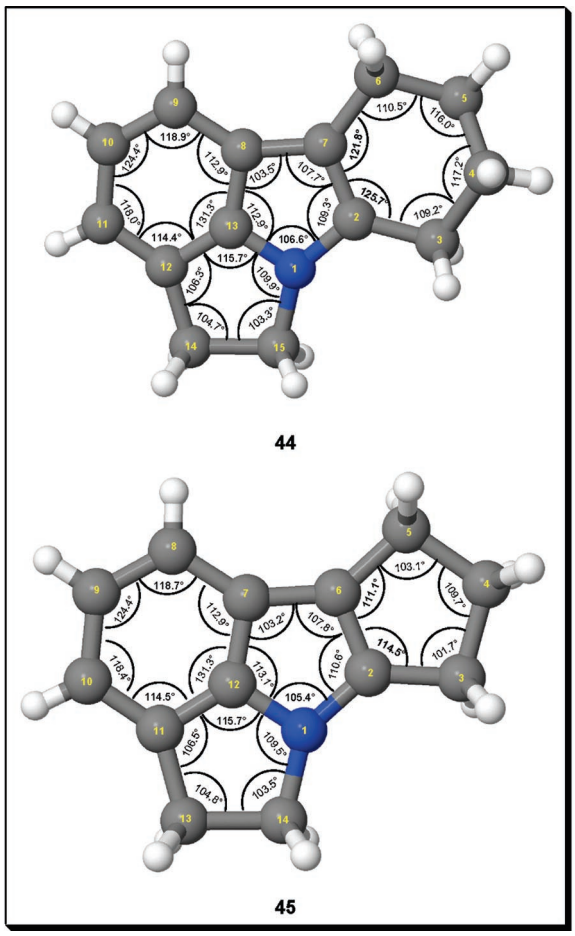
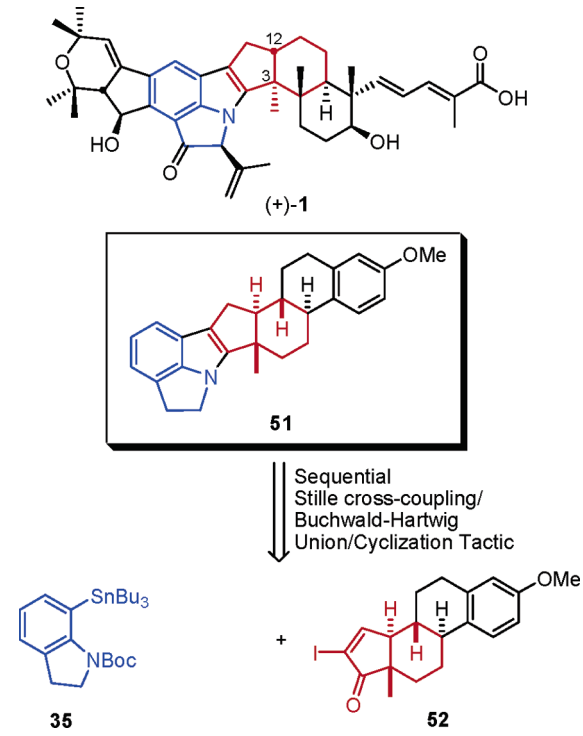


FIGURE 5. Bond angles of tetracyclic indoles **44** and **45** as determined from the single-crystal X-ray structures (Jmol Viewer version 10).

To demonstrate that the sequential Stille cross-coupling/Buchwald−Hartwig union/cyclization tactic could be employed to access a more complex indole that would more closely resemble the substitution pattern found in (+)-nodulisporic acid A (**1**), we searched for an appropriate model ketone possessing a quaternary stereocenter at the α-position. We eventually selected (+)-estrone methyl ether[48] which possesses the same substitution pattern as (+)-nodulisporic acid A (**1**) at C(3) and C(12), except having the opposite absolute stereogenicity (Scheme 10). Construction of the requisite vinyl iodide (−)-**52** was achieved in three steps, involving Saegusa oxidation of the enol ether derived from (+)-estrone methyl ester to install the requisite α,β-unsaturation in enone moiety,[49,50] followed by iodination employing the method of Johnson et al.[36]

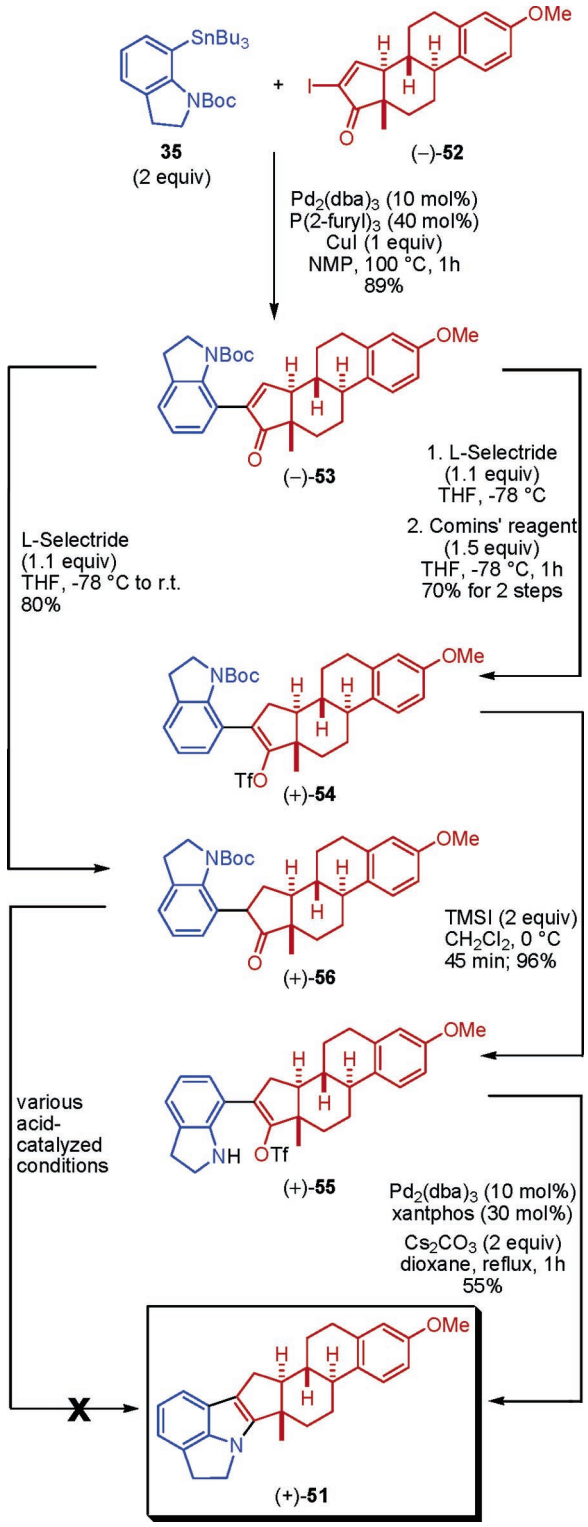
SCHEME 10. Design of a Heptacyclic Strained Indole [(+)-51] That Resembled Nodulisporic Acid A (+)-1 in Substitution Pattern at C(3) and C(12)



Pleasingly, the Stille cross-coupling between arylstannane **35** and (−)-**52** proved successful; the best conditions entailed 10 mol % of catalyst, 40 mol % of ligand, with 2 equiv of arylstannane. Ketone (−)-**53** was obtained in excellent yield (ca. 89%). L-Selectride reduction then furnished (+)-**56** in 80% yield. Given our earlier model studies, we were not surprised to find that all attempts to achieve cyclization of (+)-**56** to heptacyclic indole (+)-**51** under thermodynamic conditions (e.g., acid) failed; only decomposition occured. The Buchwald−Hartwig amination protocol, however, proved quite successful. Treatment of (−)-**53** with L-Selectride followed by lithium enolate capture with the Comins reagent[45] furnished the *N*-Boc enol triflate (+)-**54**. Removal of the Boc group with TMSI, followed by application of the optimized amination cyclization conditions (ca. 10 mol % of catalyst, 30 mol % of ligand, Cs_2-

(46) Lott, R. S.; Chauhan, V. S.; Stammer, C. H. *J. Chem. Soc., Chem. Commun.* **1979**, 495−496.
(47) Further increase in catalyst and ligand loadings did not result in higher yields of tetracyclic indole **45**.
(48) Xie, W.; Peng, H.; Kim, D. I.; Kunkel, M.; Powis, G.; Zalkow, L. H. *Bioorg. Med. Chem.* **2001**, *9*, 1073−1083.
(49) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011−1013.
(50) Egner, U.; Fritzemeier, K.-H.; Halfbrodt, W.; Heinrich, N.; Kuhnke, J.; Muller-Fahrnow, A.; Neef, G.; Schollkopf, K.; Schwede, W. *Tetrahedron* **1999**, *55*, 11267−11274.

SCHEME 11. Preparation of the Highly Strained Heptacyclic Indole (+)-51



CO_3 (2 equiv) in dioxane), completed construction of (+)-**51** in 55% yield (Scheme 11).[51] Single-crystal X-ray crystallography confirmed the structure (Figure 6). We again note considerable bond angle distortions were observed in the aromatic ring (see Supporting Information).

Having demonstrated the efficiency of the sequential Stille cross-coupling/Buchwald−Hartwig union/cyclization tactic, we have now revised our first-generation synthetic analysis of (+)-nodulisporic acids A (**1**) and B (**2**) to involve arylstannane **59** and vinyl iodide **58** (Scheme 12). Importantly, the proposed second-generation synthetic strategy not only preserves the convergency of the original approach, but also holds the potential for increased convergency by permitting the union of more elaborate fragments.

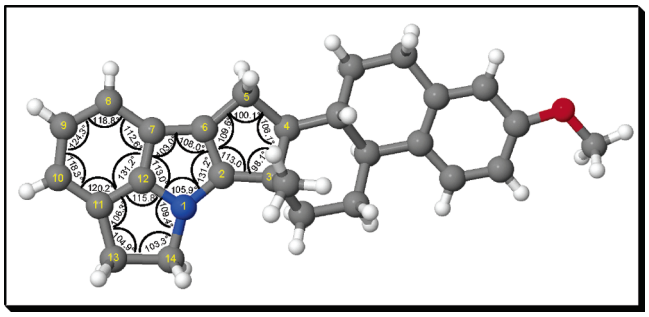
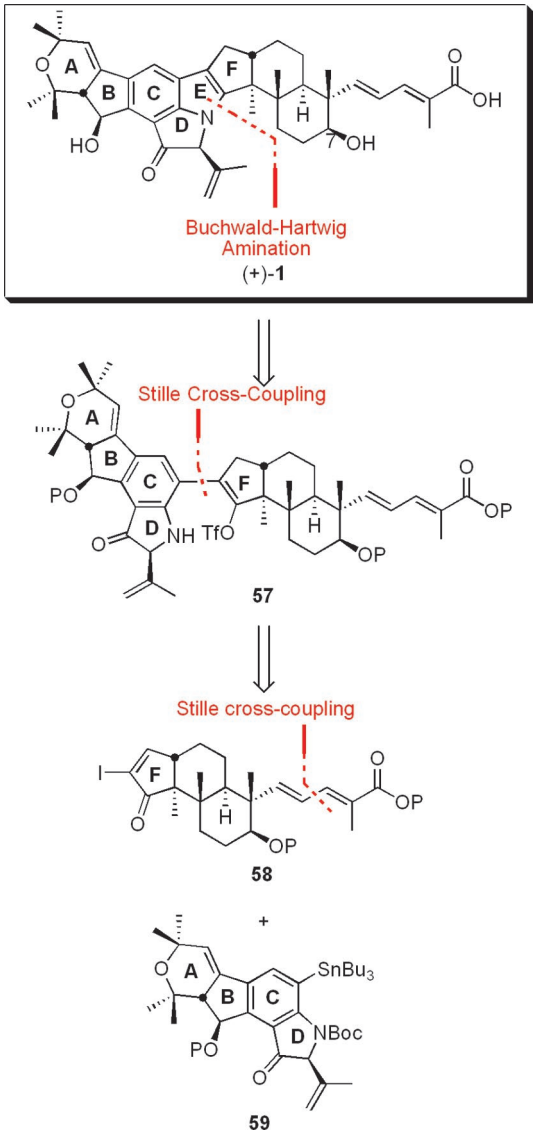


FIGURE 6. Single-crystal X-ray structure of indole (+)-**51** (Jmol Viewer version 10).

SCHEME 12. Second-Generation Retrosynthetic Analysis of (+)-Nodulisporic Acid A (1)



Summary

A second-generation strategy for construction of (+)-nodulisporic acids A and B, based on the development of a new, highly efficient, modular indole synthesis exploiting a sequential Stille cross-coupling/Buchwald−Hartwig union/cyclization tactic, has been developed. Construction of the requisite redesigned eastern and western hemispheres **58** and **59** for (+)-nodulisporic acids A and B is currently underway. Progress concerning their union and future elaboration to (+)-nodulisporic acids A and B will be reported in due course.

Experimental Section

Preparation of Tetracyclic Indole (44). To a 10 mL round-bottom flask, equipped with a PTFE-coated stirbar and a reflux condenser, were charged ketone **42** (70 mg, 0.222 mmol, 1 equiv) and deoxygenated HPLC grade MeOH (2 mL). In the meantime, acetyl chloride (174 mg, 2.22 mmol, 10 equiv) was carefully added to deoxygenated MeOH (2 mL) at 0 °C to produce anhydrous HCl in MeOH. After 5 min, this freshly prepared MeOH/HCl solution was added in one portion to a solution of **42** in MeOH at room temperature, and the resulting mixture was heated at reflux for 15 min. The solvent and excess HCl were removed in vacuo, and the crude product was purified by preparative TLC (1000 μm plate) eluted with hexanes/EtOAc = 3:1, affording **44** as a white solid after the removal of the solvents in vacuo (31 mg, 70%): mp = 149−150 °C; R_f = 0.7 (hexanes/EtOAc = 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, J = 7.7 Hz, 1H), 6.94 (t, J = 7.3 Hz, 1H), 6.85 (d, J = 6.7 Hz, 1H), 4.35 (t, J = 7.1 Hz, 2H), 3.74 (t, J = 7.1 Hz, 2H), 2.75 (m, 4H), 1.91 (m, 2H), 1.86 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.9, 134.8, 123.9, 120.7, 119.6, 115.6, 114.2, 113.4, 47.9, 34.0, 23.3, 23.0, 22.9, 22.6; IR (neat) 3046 (w), 2937 (s), 2912 (s), 2845 (s), 1651 (w), 1507 (w), 1418 (m), 1336 (w), 1309 (m), 1292 (s), 1193 (w), 743 (s), 582 (w). HRMS (CI−MS) calcd for $C_{14}H_{15}N$ [M^+] 197.1204, found 197.1201.

Preparation of Tetracyclic Indole (45). To a 25 mL round-bottom flask, equipped with a PTFE-coated stirbar and a reflux condenser, were charged Cs_2CO_3 (451 mg, 1.386 mmol, 2 equiv), THF (10 mL), $Pd_2(dba)_3$·$CHCl_3$ (71 mg, 0.07 mmol, 10 mol %), and xantphos (121 mg, 0.208 mmol, 30 mol %). The resulting solution was stirred for 5 min and then treated with a solution of enol triflate **49** (231 mg, 0.693 mmol, 1 equiv) in THF (2 mL), and the resulting mixture was heated at reflux for 2 h. The reaction mixture was then cooled to room temperature, quenched with saturated aqueous NH_4Cl (15 mL), and extracted with Et_2O (3 × 30 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude material was adsorbed onto silica gel (3 g) and subjected to column chromatography (hexanes/EtOAc = 30:1), affording **45** as a white solid (69 mg, 55%): mp = 109−110 °C; R_f = 0.7 (hexanes/EtOAc = 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, J = 7.8 Hz, 1H), 6.97 (dd, J = 7.8, 6.8 Hz, 1H), 6.86 (d, J = 6.8 Hz, 1H), 4.42−4.38 (m, 2H), 3.75 (t, J = 7.1 Hz, 2H), 2.84 (m, 4H), 2.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1, 143.3, 124.6, 122.3, 121.0, 117.3, 115.8, 113.8, 48.6, 34.1, 28.8, 24.9, 24.7; IR (KBr pellet) 3047 (s), 3015 (w), 2956 (m), 2929 (m), 2901 (m) 2852 (s), 1646 (s), 1496 (s), 1478 (m), 1465 (s), 1456 (m), 1437 (s), 1379 (m), 1368 (m), 1338 (s), 1294 (m), 1269 (s), 1215 (w), 1174 (m), 1156 (w), 1096 (w), 1040 (w), 1012 (m), 951 (w), 822 (w), 752 (s), 743 (s), 617 (w), 588 (w), 517 (w). HRMS (CI-MS) calcd for $C_{13}H_{13}N$ [M^+] 183.1048, found 183.1051.

(51) When THF was used as the solvent, we isolated a side product in 10% yield in which the triflate functionality was reduced and the indoline ring was oxidized to the corresponding indole. This oxidation most likely occurred via air oxidation during the purification stage. However, we later found that, when THF was replaced with dioxane as the solvent, only the desired heptacyclic indole (+)-**51** was obtained.

Preparation of (−)-53. To a 50 mL round-bottom Schlenk flask, equipped with a PTFE-coated stirbar, were charged 7-tributylstannyl-*N*-Boc indoline **359** (1.02 g, 2.00 mmol, 2 equiv), NMP (20 mL), $Pd_2(dba)_3$·$CHCl_3$ (104 mg, 0.100 mmol, 10 mol %), and P(2-furyl)$_3$ (93 mg, 0.400 mmol, 40 mol %), and the resulting solution was purged with deoxygenated Ar for 15 min. Afterward, a solution of (−)-**52** (409 mg, 1.00 mmol, 1 equiv) in NMP (5 mL) was added via syringe, followed by flame-dried CuI (191 mg, 1.00 mmol, 1 equiv). The reaction vessel was then fitted with a reflux condenser and heated at 100 °C for 1 h to give a dark green mixture. The reaction mixture was then slowly poured into saturated NH_4OH (75 mL) and Et_2O (75 mL) with vigorous stirring. The aqueous layer was extracted with Et_2O (3 × 30 mL) and EtOAc (1 × 30 mL), and the combined organic layers were washed with brine (4 × 25 mL), dried over $MgSO_4$, concentrated in vacuo, and adsorbed onto silica gel (10 g). Flash chromatographic purification (hexanes/EtOAc = 6:1) furnished (−)-**53** as an amorphous white solid (445 mg, 89%): mp = 164−165 °C; $[\alpha]_D^{20}$ = −39.25 (*c* 0.53, $CHCl_3$); R_f = 0.52 (hexanes/EtOAc = 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.24 (dd, J = 7.9, 5.7 Hz, 2H), 7.15 (d, J = 7.3 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 6.75 (dd, J = 8.6, 2.3 Hz, 1H), 6.69 (d, J = 2.0 Hz, 1H), 4.33−3.95 (m, 2H), 3.80 (s, 3H), 3.03 (t, J = 7.9 Hz, 2H), 3.00−2.94 (m, 2H), 2.69 (d, J = 11.5 Hz, 1H), 2.51−2.36 (m, 2H), 2.31−2.19 (m, 1H), 2.07 (d, J = 12.8 Hz, 1H), 1.93−1.68 (m, 3H), 1.66−1.55 (m, 1H), 1.46 (s, 9H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.5, 157.6, 152.5, 149.6, 143.1, 140.6, 137.6, 134.4, 132.2, 128.4, 126.0, 124.1, 123.7, 121.9, 113.9, 111.5, 80.1, 55.2, 54.6, 51.5, 49.8, 45.2, 35.8, 29.8, 29.4, 29.0, 28.4, 26.8, 25.6, 21.1; IR (neat) 2929 (br s), 2858 (m), 1711 (s), 1609 (m), 1576 (w), 1500 (s), 1447 (s), 1434 (s), 1389 (s), 1368 (s), 1336 (s), 1280 (m), 1244 (s), 1163 (s), 1135 (m), 1104 (w), 1075 (w), 1050 (m), 1007 (m), 983 (m), 910 (m), 869 (w), 821 (w), 799 (w), 767 (m), 734 (m), 647 (w), 592 (w). HRMS (ESI-MS) calcd for $C_{32}H_{37}NO_4Na$ [(M + Na)$^+$] 522.2620, found 522.2591.

Preparation of (+)-56. To a 25 mL round-bottom flask, equipped with a PTFE-coated stirbar, were charged enone (−)-**53** (122 mg, 0.240 mmol, 1 equiv) and THF (10 mL), and the resulting solution was cooled to −78 °C. Next, a 1.0 M solution of L-Selectride in THF (0.27 mL, 0.27 mmol, 1.1 equiv) was introduced over 1 min. The cold bath was then removed, and the reaction mixture was warmed to 0 °C and stirred at that temperature for 1 h. The reaction mixture was then quenched with 2 N NaOH (10 mL) and subsequently extracted with Et_2O (15 mL). The resulting organic layer was then washed with water (20 mL) followed by brine (20 mL). The aqueous phase was extracted with EtOAc (2 × 15 mL), and the combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and adsorbed onto silica gel (3 g). Flash column chromatography (hexanes/EtOAc = 5:1) afforded (+)-**56** as a white solid (98 mg, 80%): mp = 193−195 °C (dec); $[\alpha]_D^{20}$ = +170.00 (*c* 0.23, $CHCl_3$); R_f = 0.58 (hexanes/EtOAc = 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, J = 8.7 Hz, 1H), 7.08 (d, J = 6.9 Hz, 1H), 7.02 (td, J = 14.8, 7.3 Hz, 2H), 6.73 (dd, J = 8.6, 2.5 Hz, 1H), 6.65 (d, J = 2.2 Hz, 1H), 4.23 (t, J = 8.6 Hz, 1H), 4.09 (dtd, J = 18.5, 11.2, 7.6 Hz, 2H), 3.79 (s, 3H), 3.05−2.93 (m, 2H), 2.91 (dd, J = 8.7, 3.9 Hz, 2H), 2.64 (dd, J = 13.1, 5.0 Hz, 1H), 2.47−2.37 (m, 1H), 2.33 (s, 1H), 2.18−1.91 (m, 2H), 1.71−1.51 (m, 6H), 1.53 (s, 9H), 0.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.4, 157.6, 153.6, 142.0, 137.8, 135.2, 132.2, 129.6, 126.2, 126.0, 124.8, 122.9, 113.9, 111.5, 80.7, 55.2, 52.8, 51.0, 48.9, 48.7, 44.1, 37.9, 32.1, 29.8, 29.6, 29.5, 28.4, 26.8, 26.0, 13.7; IR (neat) 2930 (br s), 1736 (s), 1702 (s), 1641 (w), 1609 (m), 1549 (w), 1529 (w), 1500 (m), 1479 (w), 1449 (m), 1433 (m), 1369 (s), 1335 (m), 1281 (w), 1243 (m), 1160 (s), 1125 (m), 1053 (m), 1010 (w), 908 (m), 849 (w), 822 (w), 767 (w), 732 (s), 647 (w). HRMS (ESI-MS) calcd for $C_{32}H_{40}NO_4$ [(M + H)$^+$] 502.2957, found 502.2953.

Preparation of (+)-54. To a 25 mL round-bottom flask, equipped with a PTFE-coated stirbar, were charged enone (−)-**53**

(375 mg, 0.750 mmol, 1 equiv) and THF (10 mL), and the resulting solution was cooled to −78 °C. Next, a 1.0 M solution of L-Selectride in THF (0.83 mL, 0.830 mmol, 1.1 equiv) was added at −78 °C over 3 min, and the resulting yellow solution was stirred at −78 °C for 15 min. Next, a solution of Comins' reagent (442 mg, 1.125 mmol, 1.5 equiv) in THF (4 mL) was introduced over 1 min, and the resulting mixture was stirred for 20 min at −78 °C. The −78 °C reaction mixture was then poured into saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (4 × 10 mL) and EtOAc (1 × 10 mL). The combined organic layers were washed with brine (2 × 20 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude material was adsorbed onto silica gel (3 g) and subjected to flash chromatography (hexanes/EtOAc = 20:1) affording (+)-**54** as a thick, colorless oil which solidified upon standing to a white solid (320 mg, 67%): mp = 79−80 °C; $[\alpha]_D^{20}$ = +46.59 (*c* 0.43, $CHCl_3$); R_f = 0.60 (hexanes/EtOAc = 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.6 Hz, 1H), 7.14 (d, *J* = 7.0 Hz, 1H), 7.04 (td, *J* = 14.5, 7.08 Hz, 2H), 6.73 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.66 (d, *J* = 2.7 Hz, 1H), 4.13 (ddd, *J* = 11.0, 9.3, 6.0 Hz, 1H), 3.99 (ddd, *J* = 11.0, 9.3, 8.0 Hz, 1H), 3.79 (s, 3H), 3.20−2.83 (m, 5H), 2.78−2.58 (m, 2H), 2.37 (td, *J* = 10.8, 10.4 Hz, 2H), 2.11 (dt, *J* = 11.2, 7.06 Hz, 1H), 1.99 (m 1H), 1.93−1.86 (m, 1H), 1.78 (dt, *J* = 12.7, 3.84 Hz, 1H), 1.72−1.57 (m, 2H), 1.50 (s, 9H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 153.0, 151.0, 140.3, 137.8, 134.5, 132.4, 131.4, 127.4, 125.9, 124.2, 123.6, 122.6, 122.1, 119.6, 117.0, 114.5, 113.9, 111.5, 111.5, 80.2, 55.2, 52.9, 49.6, 46.1, 44.2, 36.8, 33.5, 29.6, 29.0, 28.5, 26.8, 26.0, 15.3 (the CF_3 group shows up as a quartet and all four peaks are reported); IR (neat) 2976 (m), 2935 (br s), 1709 (s), 1609 (m), 1575 (w), 1500 (m), 1478 (m), 1447 (m), 1435 (m), 1412 (s), 1378 (s), 1338 (m), 1281 (w), 1241 (s), 1210 (s), 1161 (s), 1140 (s), 1107 (w), 1059 (m), 1036 9 m), 1010 (w), 957 (w), 911 (m), 858 (m), 846 (m), 813 (w), 768 (w), 735 9m0, 653 (w), 608 (m), 567 (w), 504 (w). HRMS (ESI-MS) calcd for $C_{33}H_{38}F_3NO_6SNa$ [$(M + Na)^+$] 656.2270, found 656.2281.

Preparation of Enol Triflate (+)-55. To a 10 mL round-bottom flask, equipped with a PTFE-coated stirbar, were charged (+)-**54** (203 mg, 0.321 mmol, 1 equiv) and CH_2Cl_2 (5 mL), and the resulting solution was cooled to 0 °C. Next, TMSI (129 mg, 91 μL, 2 equiv) was added at 0 °C over 1 min, and the resulting mixture was stirred for 45 min at 0 °C. The reaction was then quenched with saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo, affording analytically pure (+)-**55** as a yellow oil (165 mg, 96%): $[\alpha]_D^{20}$ = +27.72 (*c* 0.29, $CHCl_3$); R_f = 0.35 (hexanes/EtOAc = 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.6 Hz, 1H), 7.09 (dd, *J* = 7.2, 0.8 Hz, 1H), 6.90 (dd, *J* = 7.7, 0.5 Hz, 1H), 6.73 (td, *J* = 15.0, 5.1 Hz, 2H), 6.66 (d, *J* = 2.6 Hz, 1H), 3.79 (s, 3H), 3.59 (dt, *J* = 8.5, 1.25 Hz, 2H), 3.06 (t, *J* = 8.4 Hz, 1H), 2.92 (dd, *J* = 9.3, 6.5 Hz, 2H), 2.67 (dd, *J* = 14.9, 6.4 Hz, 1H), 2.48−2.40 (m, 3H), 2.37 (dd, *J* = 11.0, 4.3 Hz, 1H), 2.08−1.99 (m, 1H), 1.99−1.91 (m, 3H), 1.82 (dt, *J* = 12.7, 4.2 Hz, 1H), 1.63 (m, 2H), 1.48 (ddd, *J* = 23.2, 11.2, 7.4 Hz, 1H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 153.0, 149.0, 137.7, 132.1, 130.0, 129.9, 126.7, 125.9, 124.6, 122.1, 119.6, 118.6, 117.0, 116.1, 114.6, 113.9, 111.5, 55.2, 52.6, 47.1, 46.1, 44.1, 36.7, 33.4, 33.3, 29.8, 29.4, 26.7, 25.9, 15.8 (the CF_3 group shows up as a quartet and all four peaks are reported); IR (neat) 3328 (br w), 2934 (br s), 1608 (m), 1500 (m), 1452 (m), 1414 (s), 1282 (m), 1210 (s), 1139 (s), 1059 (m), 1036 (m), 911 (m), 847 (m), 735 (m), 650 (w), 608 (m). HRMS (ESI-MS) calcd for $C_{28}H_{31}F_3NO_4S$ [$(M + H)^+$] 534.1926, found 534.1908.

Preparation of Heptacyclic Indole (+)-51 Derived from Estrone. To a 25 mL round-bottom Schlenk flask, equipped with a PTFE-coated stirbar, were charged Cs_2CO_3 (202 mg, 0.62 mmol, 2 equiv), dioxane (8 mL), xantphos (54 mg, 0.09 mmol, 30 mol %), and $Pd_2(dba)_3{\cdot}CHCl_3$ (32 mg, 0.031 mmol, 10 mol %) to give a deep brownish red solution. The resulting solution was stirred for 5 min, then treated with a solution of the enol triflate (+)-**55** (165 mg, 0.309 mmol, 1 equiv) in THF (3 mL). Next, the Schlenk flask was fitted with a reflux condenser, and the reaction mixture was brought to reflux, yielding a dark brownish yellow solution. After 50 min, the reaction was cooled to room temperature and poured into a vigorously stirred mixture of Et_2O (20 mL) and saturated aqueous NH_4Cl (20 mL). The aqueous layer was then extracted with Et_2O (2 × 15 mL), and the combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and adsorbed onto silica gel (2 g). Flash chromatography (hexanes/EtOAc = 12:1) furnished (+)-**51** as a white crystalline solid (65.4 mg, 55%): mp = 204−205 °C (dec);$[\alpha]_D^{20}$ = +64.20 (*c* 0.26, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 1H), 6.96 (dd, *J* = 7.8, 6.8 Hz, 1H), 6.85 (d, *J* = 6.8 Hz, 1H), 6.74 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.68 (d, *J* = 2.6 Hz, 1H), 4.47 (dt, *J* = 9.3, 4.6 Hz, 1H), 4.39 (dt, *J* = 9.4, 5.9 Hz, 1H), 3.80 (s, 3H), 3.79 (m, 1H), 3.73 (dq, *J* = 8.9, 4.4 Hz, 1H), 3.09−2.87 (m, 2H), 2.81 (dd, *J* = 13.4, 6.2 Hz, 1H), 2.43 (m, 3H), 2.26 (ddd, *J* = 10.6, 8.3, 4.7 Hz, 1H), 2.11−2.01 (m, 2H), 1.90 (dt, *J* = 12.7, 3.7 Hz, 1H), 1.77 (dtd, *J* = 16.2, 11.9, 3.4 Hz, 2H), 1.54 (dq, *J* = 12.0, 6.6 Hz, 1H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 152.3, 151.6, 138.0, 132.7, 126.0, 124.6, 121.2, 119.7, 117.7, 115.9, 113.9, 113.7, 111.5, 60.1, 55.2, 48.3, 44.5, 41.7, 37.4, 34.7, 34.3, 29.8, 27.4, 26.3, 26.0, 17.9; IR (neat) 2947 (br m), 1499 (m), 1497 (m), 1456 (m), 1447 (m), 1372 (w), 1362 (w), 1329 (w) 1280 (w), 1245 (m), 1182 (w), 1143 (w), 1046 (w), 909 (w), 732 (m). HRMS (ESI-MS) calcd for $C_{27}H_{30}NO$ [$(M + H)^+$] 384.2327, found 384.2326.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for all other new compounds. Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. Crystallographic information files (CIF) of compounds **33**, **44**, **45**, and **51**. This material is available free of charge via the Internet at http://pubs.acs.org.

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