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Diazonamide Synthesis Studies: Use of Negishi Coupling to Fashion Diazonamide-Related Biaryls with Defined Axial Chirality

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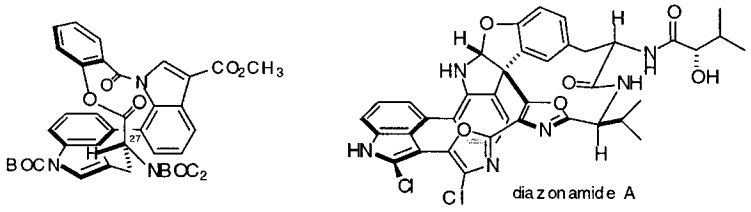
ABSTRACT



The syntheses of a bis indole and an indole salicylate with the required axial chirality for diazonamide A are reported. Atropselectivity in these biaryl systems is enforced by an sp³ stereogenic center in a lactone tether in both cases.

The control of biaryl atropselectivity remains an enduring challenge in the synthesis of structurally and functionally complex natural products biosynthesized via oxidative coupling of component aryl residues.[1] One prominent target in this context is the marine principle diazonamide A,[2,3] an ascidian isolate notable for both its high potency against several cancer cell lines and its architectural novelty. A truly remarkable chapter in the diazonamide story was added recently by Harran and co-workers,[3b] who showed convincingly that the natural product possesses the structure **2** and not the previously assigned **1**.

A longstanding interest in developing methods for diastereoselective biaryl synthesis[4] drew us to the diazonamide problem, and initially a synthesis route was conceived that relied on two key strategic elements: (1) late-stage biomimetic (?) transannular oxidative cyclization of a macrolactam precursor **3** to set the stereochemistry at both C(10) and the C(24)/C(26) bond and (2) establishment of the pivotal C(16)−C(18) axial chirality via the conformational preferences dictated by an sp³ stereogenic center at C(27), **4**, Scheme 1. In light of Harran's report, the specifics of this approach must be modified. Nevertheless, molecular mechanics (MM) calculations suggest that the juxtaposition of C(10) and C(30) in a now bis indole analogue of **3** (3.51 Å in the low-energy conformer **3**, P = P_1 = H)[5] might still be used to advantage in a synthesis route to **2**, again provided that the central C(16)−C(18) stereochemical relationship can be established correctly and maintained throughout the effort.

(1) Lessene, G.; Feldman, K. S. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: New York, 2002.

(2) Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303−2304.

(3) Leading references to the work of several groups can be found in: (a) Li, J.; Jeong, S.; Esser, L.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4765−4770. (b) Li, J.; Burgett, A. W. G.; Esser, L.; Amezeva, C.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4770−4773. (c) Nicolaou, K. C.; Huang, X.; Guiseppone, N.; Bheema Rao, P.; Bella, M.; Reddy, M. V.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4705−4709. (d) Bagley, M. C.; Moody, C. J.; Pepper, A. G. *Tetrahedron Lett.* **2000**, *41*, 6901−6904. (e) Magnus, P.; Lescop, C. *Tetrahedron Lett.* **2001**, *42*, 7193−7196. (f) Vedejs, E.; Zajac, M. A. *Org. Lett.* **2001**, *3*, 2451−2454. (g) Hang, H. C.; Drotleff, E.; Elliott, G. I.; Ritsema, T. A.; Konopelski, J. P. *Synthesis* **1999**, 398−400. (h) Wipf, P.; Methot, J.-L. *Org. Lett.* **2001**, *3*, 1261−1264. (i) Boto, A.; Ling, M.; Meek, G.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 8167−8170. (j) Fuerst, D. E.; Stoltz, B. M.; Wood, J. L. *Org. Lett.* **2000**, *2*, 3521−3523.

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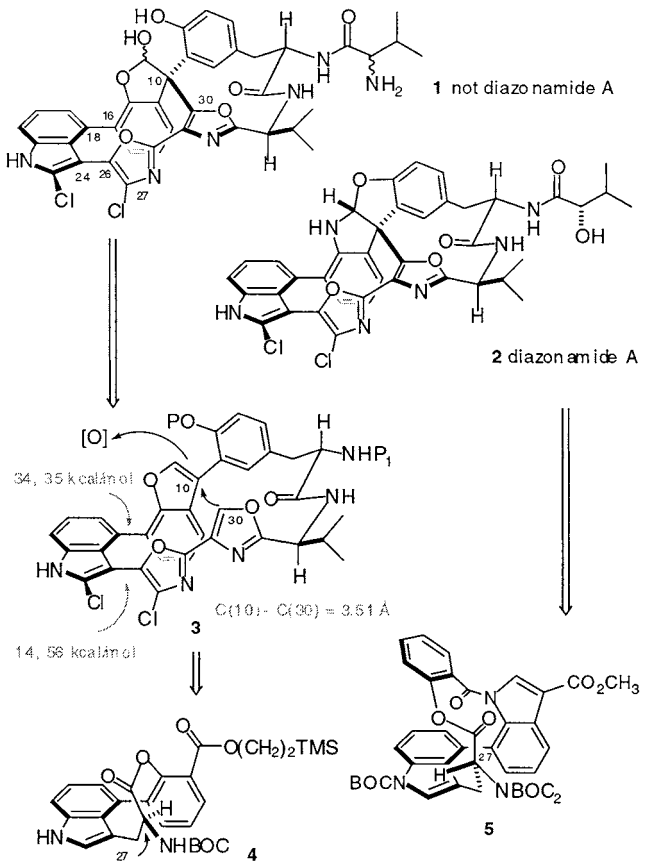
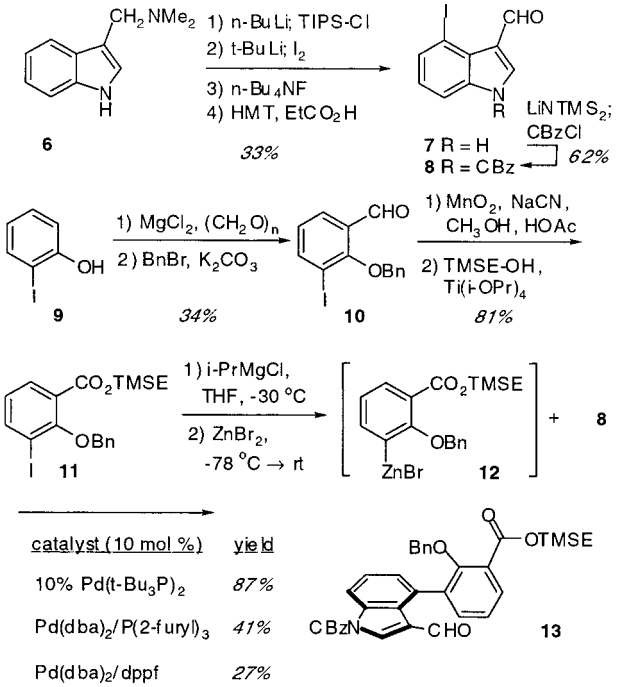
Scheme 1



The synthesis of both biaryl **4** and biaryl **5** are described herein. In both cases, a Negishi coupling[6] is used to link C(16) with C(18) in good yield, an approach distinct from that pursued by other workers in this area. Subsequent elaboration of the tether bearing a stereogenic center provides single diastereomers of the target biaryls, in accordance with the MM-generated expectations that a proton rather than an NHBOC will project toward the peri-positioned aryl residue in **4**, whereas in **5**, a proton rather than an $NBOC_2$ will project toward the adjacent indole C(2) hydrogen.

The synthesis of biaryl lactone **4** commences with *N*-carbobenzyloxy-4-iodo-indole-3-carboxaldehyde (**8**), which could be prepared conveniently from gramine (**6**) in five steps,[7] Scheme 2. A shorter (two-step) synthesis of **7** from indole itself (3-formylation via $POCl_3$/DMF, 4-iodination with $Tl(TFA)_3$/CuI/KI) has been described,[8] but inconsistent yields

Scheme 2



upon scale-up and concerns about the toxicity of thallium salts made the longer route a more attractive option. The zincate precursor **11** can be synthesized from *o*-iodophenol (**9**) through initial *o*-formylation under Skattebøl's conditions[9] followed by protection and oxidation steps. The key coupling reaction between **8** and **11** followed the procedure of Knochel[10] as modified by Fu.[11] Initial magnesiation of **11** was sensitive to reaction temperature, and optimum yields were achieved at −30 °C without any detectable decomposition of the arylmagnesium product. Transmetalation to zinc during slow warming from −78 °C to room-temperature preceded addition of the indole iodide **8** and the palladium catalyst. TLC analysis indicated that coupling proceeded rapidly at room temperature without any substantial decomposition of components. Some exploration of different palladium/ligand recipes with **11** (or its PMB ether analogue) (see Scheme 2) revealed that the $Pd(t\text{-}Bu_3P)_2$-based protocol provided the most consistently high yields of biaryl product **13** at gram-scale reaction.

Continuing elaboration of the coupled product **13** required introduction of tryptophan functionality at C(3) on the indole

(5) A 10 000-step conformational search of **3** (P = P_1 = H) using the directed Monte Carlo algorithm of Macromodel 6.5 (cf.: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467) led to a family of four low-energy conformers corresponding to the four possible atropisomers about the indicated biaryl linkages. Two of these species were of equivalently low energy, **3** as shown and its rotomer about the C(24)/C(26) bond. However, only **3** among these conformers brings C(10) and C(30) within bonding distance, 3.51 Å. The enthalpies of rotation about the C(24)/C(25) and C(16)/C(18) bonds were estimated by the difference between the "global minimum" conformer **3** and planar versions of **3** where the relevant biaryl dihedral was locked at either 0° or 180°, The four values obtained (two rotational directions per bond) are shown with **3**. Only rotation about the C(24)/C(26) bond in one direction is predicted by this analysis to be facile at room temperature ($\Delta H^{\ddagger} \approx 14$ kcal/mol).

(6) Negishi, E.-i. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; pp 1−47.

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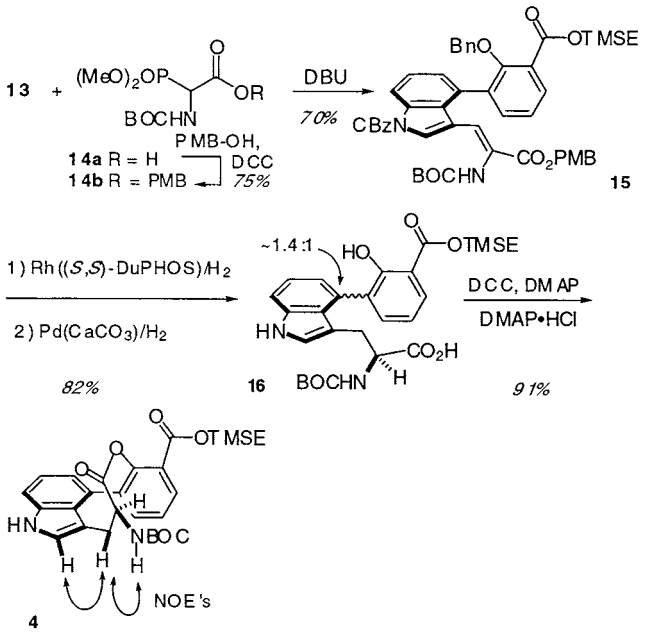
(9) Hofsløkken, N. U.; Skattebøl, L. *Acta Chem. Scand.* **1999**, *53*, 258−262.

(10) (a) Rottländer, M.; Palmer, N.; Knochel, P. *Synlett* **1996**, 573−575. (b) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4414−4435.

(11) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719−2724.

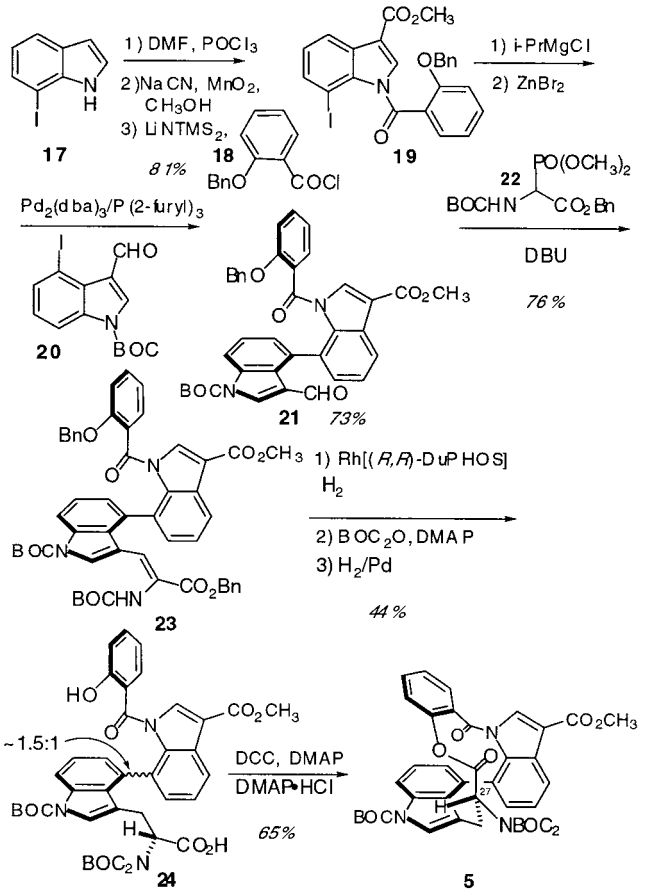
Scheme 3



unit, Scheme 3. Emmons−Horner extension of the aldehyde in **13** with phosphonate **14b**, itself available from the known acid **14a**,[12] provided predominantly the (*Z*)-alkene-containing product **15** (10:1 *Z*/*E*) in good yield. The incorporation of the *p*-methoxybenzyl group in **15** was in response to the unsatisfactory performance in subsequent steps of the more obvious choice, a benzyl ester. The use of Schmidt's conditions (DBU in CH_2Cl_2)[13] was critical for success of this Wittig transformation, as other bases (*t*-BuOK, NaH, tetramethylguanidine) either failed to deliver acceptable yields of **15** or produced *E*/*Z* mixtures of product. Asymmetric hydrogenation of **15** mediated by (*S*,*S*)-DuPHOS ligated rhodium provided a ~1.4:1 mixture of diastereomeric 4-aryl tryptophan derivatives in almost quantitative yield. Palladium-catalyzed hydrogenolysis of the benzyl functionalities in this intermediate furnished the phenoxy acid derivative **16**, which was cyclized under Keck's modification of Steglich esterification conditions to provide the desired lactone **4** in excellent yield.[14] The fact that a nearly unbiased mixture of diastereomeric hydroxy acids **16** was converted into a single diastereomer of lactone **4** is consistent with a scenario wherein the biaryl linkage in **16** is freely rotating under the reaction conditions and only one diastereomer cyclizes rapidly to a lactone. DNOE measurements (cf. **4**) secure the relative stereochemical assignment. The absolute stereochemistry has not been rigorously established, but an earlier description of the DuPHOS-promoted asymmetric hydrogenation of a dehydrotryptophan derivative suggests that the (*S*)-configuration at C(27) (diazonamide numbering) of **16** was obtained.[15] Further studies to determine the enantiomeric excess were deferred in light of the reorienting results of Harran. However, acquisition of **4** as essentially a single diastereomer serves as a proof-of-concept for the thesis that the C(16)−C(18) bond in a putative diazonamide precursor can be set under the influence of a proximal sp^3 stereogenic center.

The extension of this strategy to the bis indole **5** relevant to the revised diazonamide A structure is shown in Scheme 4. 4,7′-Bis indoles have been identified as minor components

Scheme 4



of complex mixtures derived from shotgun oligomerization of 5,6-dihydroxyindole, but deliberate preparations of this biaryl unit have yet to be described. Thus, application of the Negishi protocol successful with **8** and **11** to 4,7′-bis indole formation remained an open question. In particular, the presumably increased steric demand of the *N*-salicamide unit in **19**, absent in the **8**/**11** coupling, posed a concern. In the event, the known 7-iodoindole (**17**)[16] was converted into the coupling partner **19** without incident, and exposure of the derived zinc reagent to 4-iodoindole **20** under palladium catalysis provided the desired 4,7′-bis indole product **21** in

(12) Travins, J. M.; Etzkorn, F. A. *J. Org. Chem.* **1997**, *62*, 8387−8393.
(13) Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487−490.
(14) (a) Bolden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394−2395. (b) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522−524.
(15) Wang, W.; Xiong, C.; Yang, J.; Hruby, V. J. *Tetrahedron Lett.* **2001**, *42*, 7717−7719.
(16) Somei, M.; Saida, Y.; Funamoto, T.; Ohta, T. *Chem. Pharm. Bull.* **1987**, *35*, 3146.

excellent yield. In this Negishi coupling, optimum yields attended use of P(2-furyl)$_3$ as the stabilizing ligand, in contrast to the P(*t*-Bu)$_3$ alternative favored with the salicylate-derived zinc reagent **12**. Similar Emmons−Horner homologation of the hindered aldehyde in **21** with phosphonate **22**,[17] followed by rhodium(I)-mediated asymmetric hydrogenation of the derived alkene in **23** with (*R*,*R*)-DuPHOS as a chiral director, provided the expected tryptophan derivative. Nitrogen protection of the NHBOC unit within this species with a second BOC group followed by hydrogenolysis of the benzyl groups afforded the free phenoxy acid **24**. The use of the (*R*,*R*)-DuPHOS reagent in this instance was prompted by the requirement for the (*R*)-configuration at C(27) to lock the biaryl linkage in the desired (*R*)-axial chirality. As with **16**, the hydrogenation product existed as a ∼1.5:1 mixture of diastereomers.

The phenoxy acid **24** was cyclized by treatment with Keck's modified Steglich esterification conditions to furnish the lactone **5** in good yield. The gross structure and stereochemistry of the lactone **5** was ascertained by single-crystal X-ray analysis (see Supporting Information for details).[18] As with **16**, the presumably equilibrating mixture of diastereomers **24** apparently cyclized through only the one isomer featuring a proton (rather than the $NBOC_2$ group) projected toward the adjacent indole's C(2) hydrogen. The second BOC group on the tryptophan nitrogen provided the necessary steric bulk to enforce formation of a single atropisomeric lactone. Earlier studies demonstrated that when this nitrogen bore only a single BOC group, the derived lactone was formed as a 1:1 mixture of isomers. Chiral HPLC analysis of **5** using an ss-Welk-01 column (95:5 hexane/2-propanol as the eluent) provided an indirect assay of the enantioselectivity of the DuPHOS-mediated hydrogenation. By this protocol, the lactone **5** exists as a 75:25 ratio of enantiomers.

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Supporting Information Available: Spectral data (^{1}H NMR, ^{13}C NMR, IR, MS), combustion analysis for select compounds, and copies of ^{1}H NMR and ^{13}C NMR spectra for **4**, **5**, **8**, **10**, **11**, **13**, **14b**, **15**, **16**, **19**, **21**, **23**, and **24**, HPLC traces of lactone **5** derived from both (*R*,*R*)- and (*S*,*S*)-DuPHOS-mediated hydrogenation of **23**, a thermal ellipsoid representation from the X-ray analysis of **5**, and the accompanying CIF. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Horenstein, B. A.; Nakanishi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6242.

(18) Lactone **5** was crystallized from ethyl acetate and pentane. The difference Fourier map shows electron density at and around the special position (0.50, 0.638, 0.25). However, neither ethyl acetate nor pentane could be successfully fitted into the density present due to the crystallographic symmetry involved. This feature, in addition to the high value for R_{int} of 0.09 (after absorption correction), limits the crystallographic *R*-factor to 0.18 for this structure. Nevertheless, the relative stereochemical assignment of interest here is unambiguous.