Article

An Expedient Formal Total Synthesis of (–)-Diazonamide A via a Powerful, Stereoselective *O*-Aryl to *C*-Aryl Migration To Form the C10 Quaternary Center

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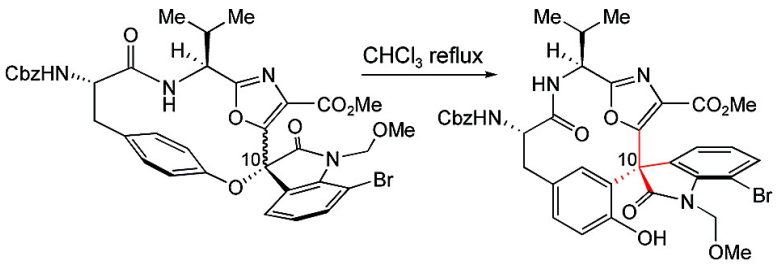

1 : 1 C10 epimers

correct C10 epimer (70%)
+ incorrect C10 epimer (30%)

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An Expedient Formal Total Synthesis of (−)-Diazonamide A via a Powerful, Stereoselective *O*-Aryl to *C*-Aryl Migration To Form the C10 Quaternary Center

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Abstract: During the course of studies on the synthesis of diazonamide A **1**, an unusual *O*-aryl into *C*-aryl rearrangement was discovered that allows partial control of the absolute stereochemistry of the C-10 quaternary stereogenic center. Treatment of **30** with TBAF/THF gave the *O*-tyrosine ethers **31** and **32** (1:1), which on heating each separately in chloroform at reflux rearranged to **33** and **34** in ratios of 84:16 and 56:44, respectively. This corresponds to a 70% yield of the correct C-10 stereoisomer **33** and a 30% yield of the wrong C-10 stereoisomer **34**. Attempts to convert **34** into **33** by *ipso*-protonation and equilibration were unsuccessful. Confirmation of the stereochemical outcome of the rearrangement was obtained by converting **33** into **37**, an advanced intermediate in the first synthesis of diazonamide A by Nicolaou et al. It was also found that the success of the above rearrangement is sensitive to the protecting group on both the tryptophan nitrogen atom and the tyrosine nitrogen atom.

Introduction

Diazonamide A **1** was isolated from the colonial ascidian *Diazona angulata*, collected from the ceilings of caves along the northwest coast of Siquijor Island in the Philippines. It exhibits potent in vitro activity against HCT-116 human colon carcinoma and B-16 murine melanoma cancer cells (IC_{50} < 15 ng/mL). The original structure, as reported in 1991 by Fenical and Clardy,[1] was corrected in 2001 to **1** by Harran, Figure 1.[2] While there has been a large number of research groups involved in the total synthesis of diazonamide A,[3a−k] only the Nicolaou[4a−d] and Harran[5] groups have so far been successful.

Our original photo-Fries rearrangement strategy as applied to the "old incorrect structure" converted **3** into **4** (76%), Scheme 1.[6] Attempted use of this strategy on the "new correct structure" required an aza photo-Fries rearrangement.[7] In the event, it was found that photolysis of **5** under a variety of conditions did not give **6**; only **5** was recovered unchanged. It was therefore decided to pursue a different strategy that involved formation of the C8−C10 bond by nucleophilic displacement of a leaving group (LG) at C10 as depicted in **2**, Figure 1. It was planned to form the C16−C18 bond by a Suzuki coupling reaction.[8]

The most significant problem in the synthesis of diazonamide A is the stereoselective formation of the crucial C10 quaternary center. Scheme 2 summarizes the results that have addressed this difficult problem, and subsequently resulted in the synthesis of diazonamide A. In the first reported total synthesis of diazonamide A **1** by the Nicolaou group, it was found that treatment of **8** [1:1 mixture of epimers at C10 (diazonamide

† Author for inquiries concerning the X-ray data.

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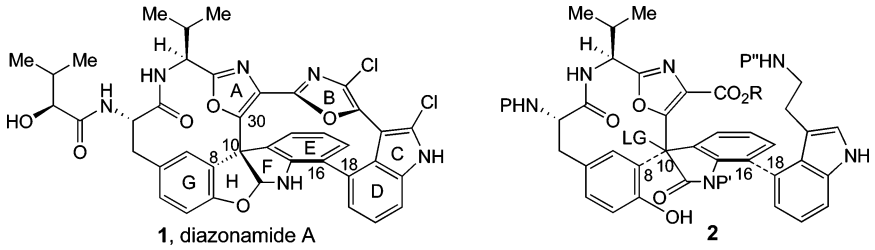
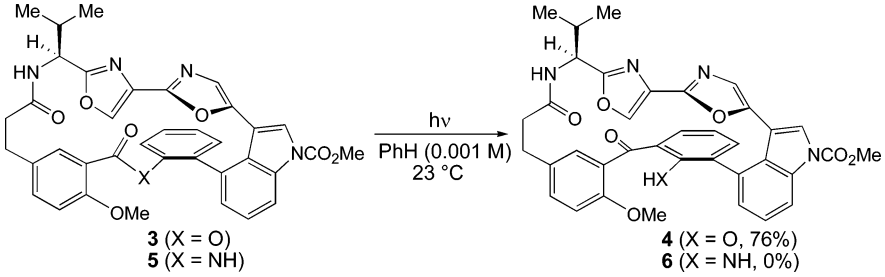
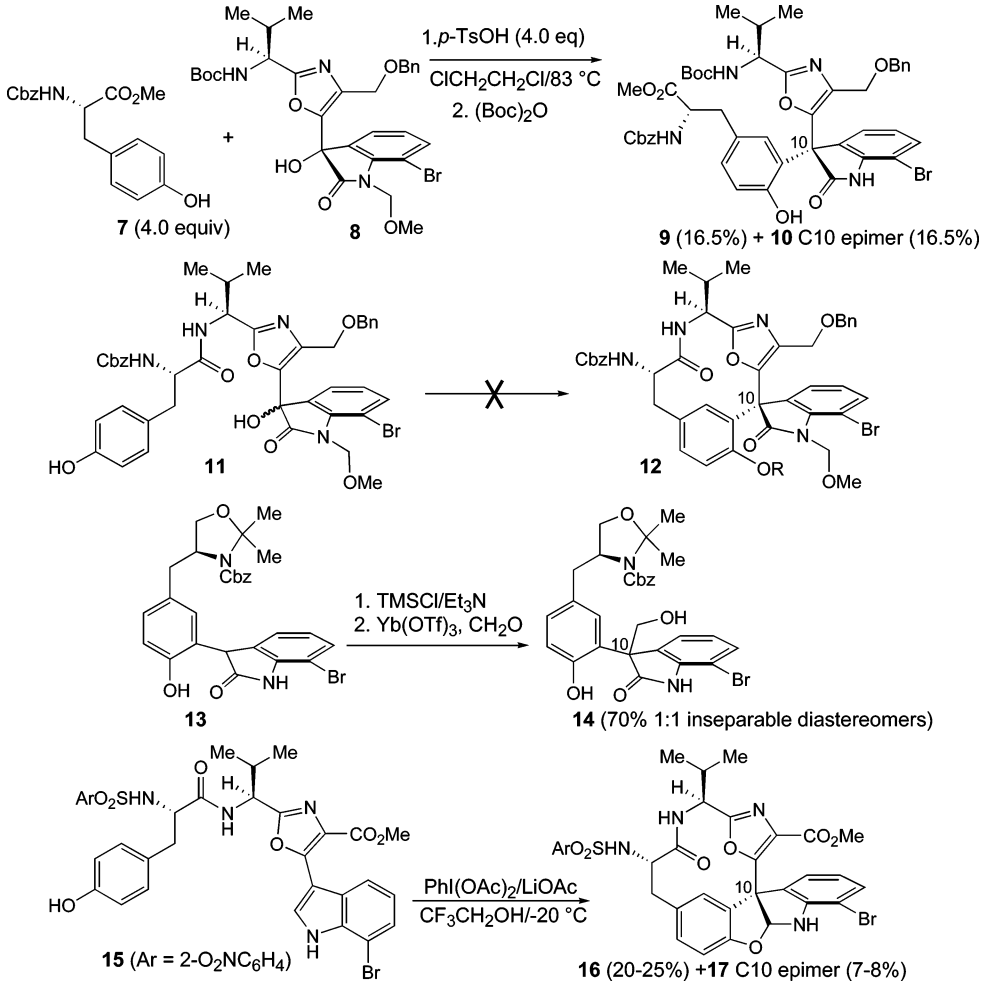


Figure 1. Structure of diazonamide A **1** and crucial disconnections **2**.

Scheme 1. Initial Photo-Fries Rearrangement Approach



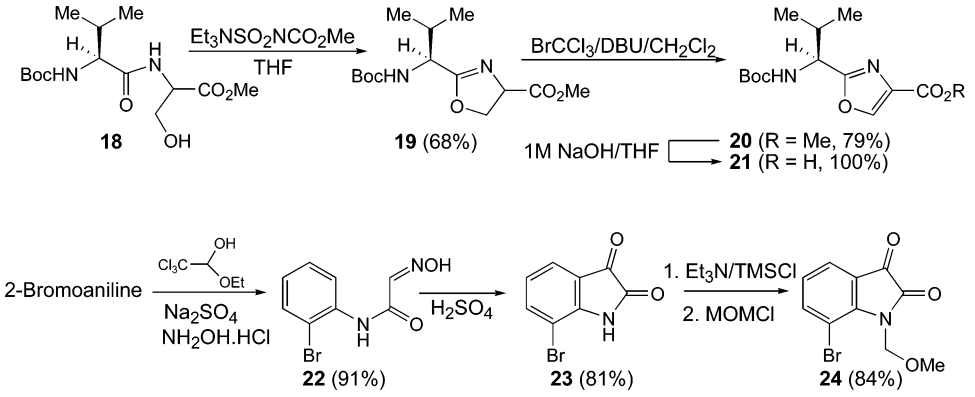
Scheme 2. Methods Used To Form the C10 Quaternary Center in the Three Syntheses of Diazonamide A



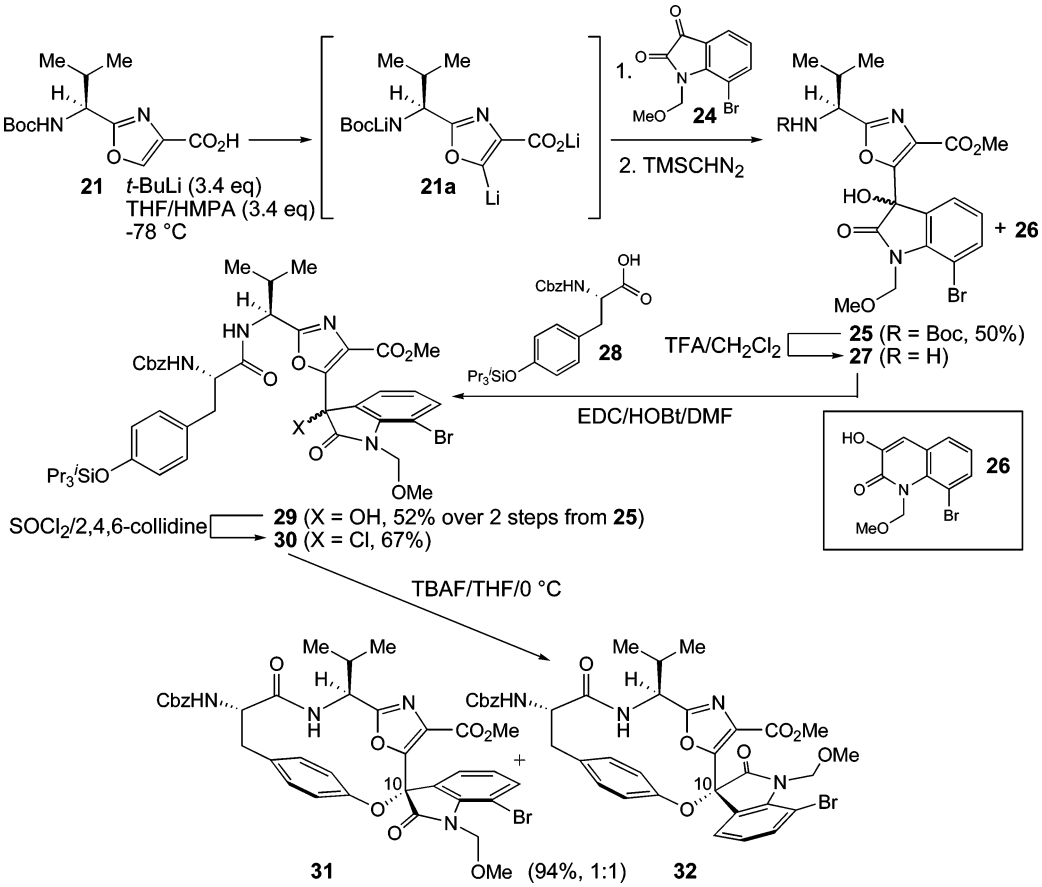
numbering)] with **7** (4 equiv) in the presence of *p*-TsOH at 83 °C in 1,2-dichloroethane gave **9** (16.5%) (after reintroduction of the Boc group), and an equal amount of the C10-epimer **10**.[4a,c] In an attempt to conduct an intramolecular version of this reaction, **11** was treated under a number of reaction conditions designed to ionize the tertiary hydroxyl group, but it did not cyclize to provide **12**.[9] In the second synthesis of **1**, Nicolaou et al. converted **13** into **14** as a 1:1 mixture of diastereoisomers in 70% yield.[4b,d]

In a tyrosine-indole oxidative coupling approach to form the C10 quaternary center, Harran et al. treated **15** with $PhI(OAc)_2$/LiOAc/CF_3CH_2OH at −20 °C to give **16** (20−25%), and its

Scheme 3. Synthesis of the Oxazole **21** and Isatin **24** Components



Scheme 4. Formation of Macrocyclic Ethers **31** and **32**



C10 epimer **17** (7−8%), along with products from other nonproductive oxidative pathways.[5]

In this Article, we describe a serendipitous solution to this problem that involves a *O*-aryl to *C*-aryl rearrangment that enables the construction of the C8−C10 bond stereoselectively and in high yield and provides a correlation with an advanced intermediate in the "first" Nicolaou synthesis of diazonamide A.[4a,c]

Results and Discussion

The known valine derived oxazole **21** was prepared by the Meyers and Williams procedures.[10] (*S*)-*N*-*t*-Butoxycarbonyl valine serine methyl ester **18** was dehydrated (Burgess reagent)[11]

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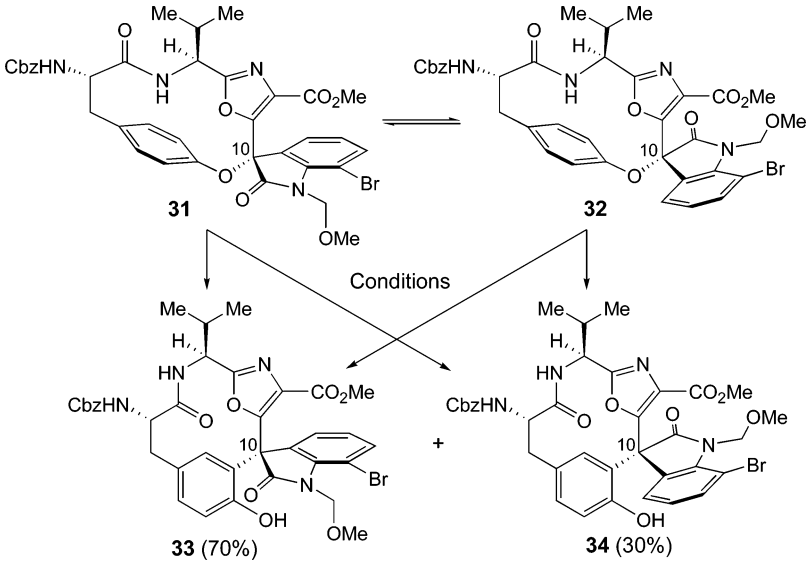
Scheme 5. *O*- to *C*-Rearrangement of **31** and **32** into **33** and **34**



to give **19** (68%), which was treated with $BrCCl_3$/DBU to provide **20** (79%). Base hydrolysis of **20** gave **21** (100%), Scheme 3.

The second component we required was 7-bromoisatin **23**.[4c] The classical isatin synthesis using the condensation of 2-bromoaniline with chloral to give **22** was not possible because chloral hydrate is no longer commercially available. However, the equivalent 2,2,2-trichloro-1-ethoxyethanol (Acros 34653 CAS [515-83-3]) is the most convenient replacement. Treatment of 2-bromoaniline with 2,2,2-trichloro-1-ethoxy-ethanol/Na_2SO_4 gave **22** (91%), which was dehydrated using concentrated H_2SO_4 resulting in **23** (81%).[12] Protection of **23** as the *N*-methoxymethyl derivative **24** was accomplished by treatment of **23** in tetrahydrofuran at 25 °C with Et_3N (5.0 equiv)/TMSCl (5.0 equiv) (heated at reflux for 2 h), followed by cooling the mixture to 0 °C and addition of methoxymethyl chloride (MOMCl, 5.0 equiv) to give **24** (84%).[13]

For the reasons indicated in ref 14, we decided to attempt to convert **21** into its derived trianion **21a** and couple it to **24**, and thus preserve the correct carboxylate oxidation level throughout the entire sequence. The acid **21** was treated with *t*-BuLi (3.4 equiv) in THF in the presence of HMPA (3.4 equiv) at −78 °C to generate the trianion **21a** (as judged by its subsequent reaction with **24**), Scheme 4.[14] Addition of 7-bromo-*N*-methoxymethylisatin **24** to the trianion **21a** (followed by workup) and treatment of the crude reaction mixture with $TMSCHN_2$ or CH_2N_2 gave **25** (35−50%). The quinolone derivative **26** was isolated in some runs of this reaction as a byproduct, which presumably was formed from the reaction of remaining **24** with $TMSCHN_2$ or CH_2N_2.

Removal of the Boc-group from **25** (TFA/CH_2Cl_2/0 °C) gave **27**, which was coupled (EDC/HOBt/DMF at 25 °C) with the *N*-Cbz/$OSiPr^i_3$ tyrosine derivative **28** to give **29** (52% over two steps) as a 1:1 mixture of diastereomers. The *t*-hydroxy functionality in **29** was converted into the chloride **30** (67%) by treatment with $SOCl_2$/collidine. When **30** was exposed to standard silyl deprotection conditions (TBAF/THF at 0 °C), it was cleanly converted into a 1:1 mixture (94%) of *O*-aryl ethers **31** and **32**, which were separable by chromatography, Scheme 4.[15] The ^1H NMR data for **31** and **32** did not allow us to assign the C10 stereochemistry, and we were unable to obtain crystals of either isomer that were suitable for X-ray crystallography.

For some time, we thought that when **31** and **32** were heated separately in chloroform at reflux (61 °C) it resulted in the

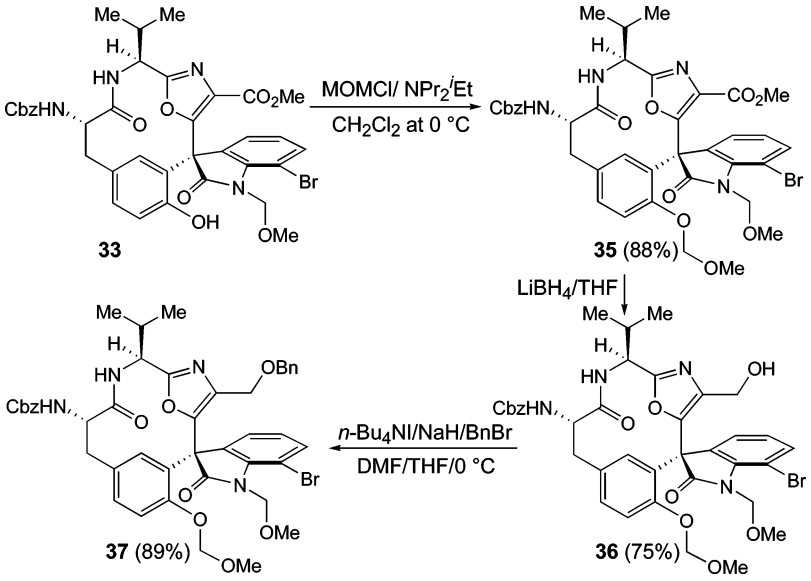
Table 1

entry, starting material	conditions	time	product (**33**:**34**)
1, **31**	solid, −20 °C	3 weeks	96:4 (42% conv.)[a]
2, **32**	solid, −20 °C	3 weeks	33:67 (27% conv.)[b]
3, **31**	solid, 83 °C	6 h	80:20
4, **32**	solid, 83 °C	6 h	18:82
5, **31**	CH_2Cl_2, −20 °C	3 weeks	96:4 (12% conv.)[c]
6, **32**	CH_2Cl_2, −20 °C	3 weeks	38:62 (4% conv.)[d]
7, **31**	CH_2Cl_2, 21 °C	7 days	82:18
8, **32**	CH_2Cl_2, 21 °C	7 days	55:45
9, **31**	CH_2Cl_2, AcOH, 21 °C	5 days	80:20
10, **32**	CH_2Cl_2, AcOH, 21 °C	5 days	53:47
11, **31**	$CHCl_3$, reflux	6 h	84:16
12, **32**	$CHCl_3$, reflux	6 h	56:44
13, **31** + **32**	$CHCl_3$, reflux	6 h	70:30
14, **31** + **32**	$(CF_3)_2CHOH$, 55 °C	6 h	58:42
15, **31** + **32**	DMSO, 55 °C	6 h	49:51
16, **31** + **32**	DMSO, 3 mol % TFA, 21 °C	6 h	49:51
17, **31** + **32**	CH_3CN, 55 °C	6 h	53:47
18, **31** + **32**	CH_3CN, 3 mol % TFA, 21 °C	6 h	58:42
19, **31** + **32**	EtOH, 55 °C	6 h	67:33
20, **31** + **32**	EtOH, 3 mol % TFA, 21 °C	6 h	61:39
21, **31** + **32**	CH_2Cl_2, 3 mol % TFA, 55 °C	6 h	66:34
22, **31** + **32**	CH_2Cl_2, cat aq HBF_4	6 h	62:38

[a] 58% returned starting material (**31**:**32** = 78:22). [b] 63% returned starting material (**31**:**32** = 20:80). [c] 88% returned starting material (**31**:**32** = 76:24). [d] 96% returned starting material (**31**:**32** = 38:62). All of the ratios were determined by analytical HPLC.

(12) Newman, M. S.; Logue, M. W. *J. Org. Chem.* **1971**, *36*, 1398−1401.
(13) Klebe, J. F. In *Silylation in Organic Synthesis. Advances in Organic Chemistry*; Taylor, E. C., Ed.; Wiley-Interscience: New York, 1972; pp 119−135.
(14) The Nicolaou synthesis reduces **20** to the derived alcohol and selectively *O*-benzylates (*J. Am. Chem. Soc.* **2004**, *126*, 12888−12896, Scheme 6, p 12893). Neither NaHMDS nor LiHMDS worked in our hands; consequently, we examined maintaining the carboxylate oxidation level through the direct use of **21** and the formation of the trianion **21a**.
(15) For references to azaxylylene intermediates formed from 1,4-elimination, see: Ly, T.-M.; Laso, N. M.; Zard, S. Z. *Tetrahedron* **1998**, *54*, 4889−4898. Corey, E. J.; Steinhagen, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 1928−1931. Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 5068−5069. Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2005**, *7*, 677−680. Avemaria, F.; Vanderheiden, S.; Bräse, S. *Tetrahedron* **2003**, *59*, 6785−6796.

Scheme 6. Correlation with the First Nicolaou Synthesis of Diazonamide A



formation of only **33**.[16] Eventually, through a series of events that involved repeating all of this work and discovering a TLC solvent system that revealed that a mixture of **33** and **34** was being formed, we realized that the transformation of **31** and **32** was stereoselective in favor of **33**, but not stereoconvergent in that both **31** and **32** were not converted into the same stereoisomer **33**, but a mixture of both **33** and **34**, Scheme 5 and Table 1.

In the solid phase at −20 °C, both **31** and **32** are converted into **33** and **34** in ratios of 96:4 and 33:67, respectively. Even though we started with pure **31** and pure **32**, the recovered ethers consisted of a mixture of **31** and **32** in ratios of 78:22 and 20:80, respectively, entries 1 and 2. Carrying out the same reaction of **31** and **32** in the solid phase at 83 °C allowed complete conversion into **33** and **34** in ratios of 80:20 and 18:82, respectively, entries 3 and 4.

In solution at −20 °C in dichloromethane, **31** and **32** are partially converted into **33** and **34**, entries 5 and 6, whereas at 21 °C, complete conversion takes place within 7 days to give **33** and **34** in ratios of 82:18 and 55:45, respectively, entries 7 and 8. The above rearrangement in dichloromethane is complete in 5 days if a catalytic amount of acetic acid is present, entries 9 and 10, and gives **33** and **34** in almost exactly the same ratio as in the nonacid-catalyzed version.

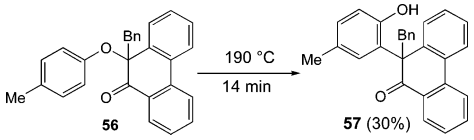
The most practical method of converting **31** and **32** into the correct stereoisomer **33** is heating the ethers in chloroform at reflux (61 °C) for 6 h, entries 11 and 12, which results in **33** and **34** in ratios of 84:16 and 56:44, respectively. This corresponds to a 70% yield of **33** and a 30% yield of **34**. In more polar solvents that would be expected to favor dissociation of the C−O bond, entries 14−21, the ratio of **33** to **34** varies from 49:51 to 67:33. Finally, exposure of **34** to a variety of reaction conditions (TFA/CH_2Cl_2, TFA/$(CF_3)_2CHOH$, etc.) that have the potential to convert **34** into **33** via *ipso*-protonation[17] did nothing.

The overall trends that are apparent from the data in Table 1 are that: (a) **31** produces more of **33** than does **32**; (b) **32** is less selective in the rearrangement than **31**, and as the temperature is increased from 21 to 61 °C the amount of **33** increases, and it becomes the major isomer; and (c) dissociating solvents tend to convert **31** and **32** to equal amounts of **33** and **34**.[18] The equilibration of **31** into **32** and vice versa must be slower than their conversion into **33** and **34**, respectively. Both **31** and **32** can convert into **33** and **34**, the difference being that **31** → **33** involves dissociation to a tight ion-pair (Scheme 9) and formation of the new carbon−carbon bond without bond rotation, whereas the conversion of **31** → **34** involves dissociation of the C−O bond, rotation, and recombination of the dissociated ions to give the inverted product **34**.

The assignment of the stereochemistry at C10 in **33** is based on its subsequent conversion into **37**, which is an advanced intermediate in Nicolaou's first synthesis of diazonamide A **1**, Scheme 6.[4a,c] The C10 stereochemistry in **34** is based on the comparison of its spectral data with **44** (Scheme 7) whose structure was established by X-ray crystallography. Therefore, from the principle of least motion[19] we can assign the C10 stereochemistry of **31** and **32** as shown in Scheme 5.

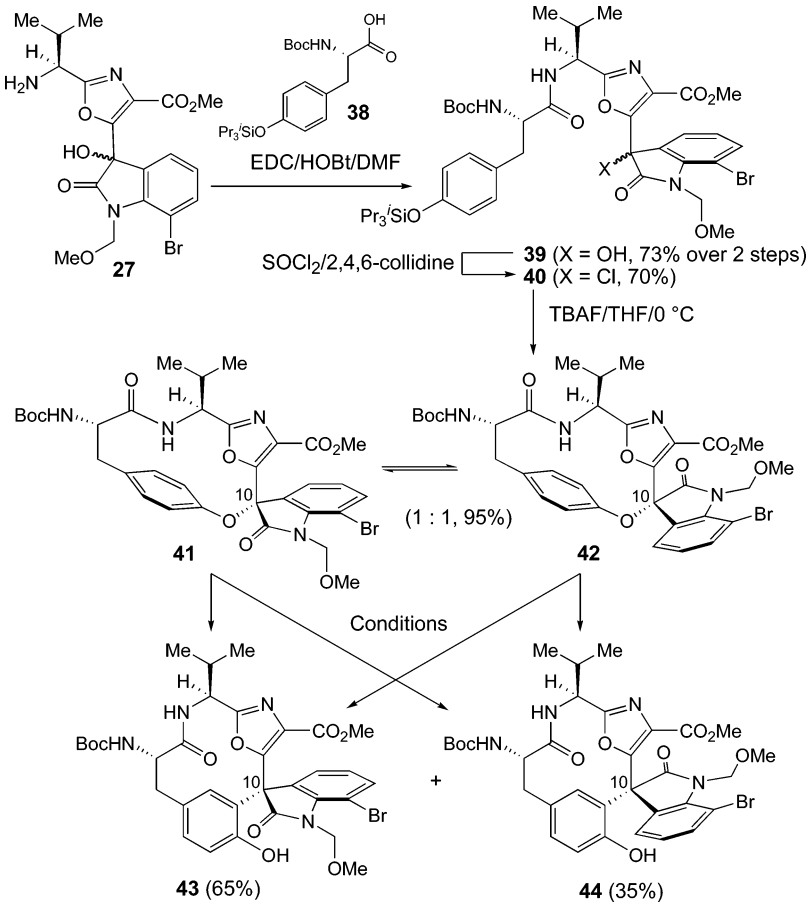
As alluded to above, we decided that the most expeditious way to confirm the structure of **33** was to convert **33** into a known compound that had been itself converted into diazona-

(16) Bould, L. Studies on the synthesis of tetracycline. Ph.D. Thesis; Imperial College, London, 1968; pp 91 and 153. In the above thesis, the conversion of **56** into **57** is described. The text (p 93) describes the yield of **57** as 20%. However, the experimental section (p 153) converts **56** (125 mg) into **57** (37 mg), corresponding to a 29.6% yield. In 1968, Magnus was a Ph.D. student working next to Bould, and as a consequence knew about the transformation of **56** into **57**. This information initiated the notion (36 years later!) that this type of reaction could be used for the construction of the C-10 quaternary center in diazonamide A.

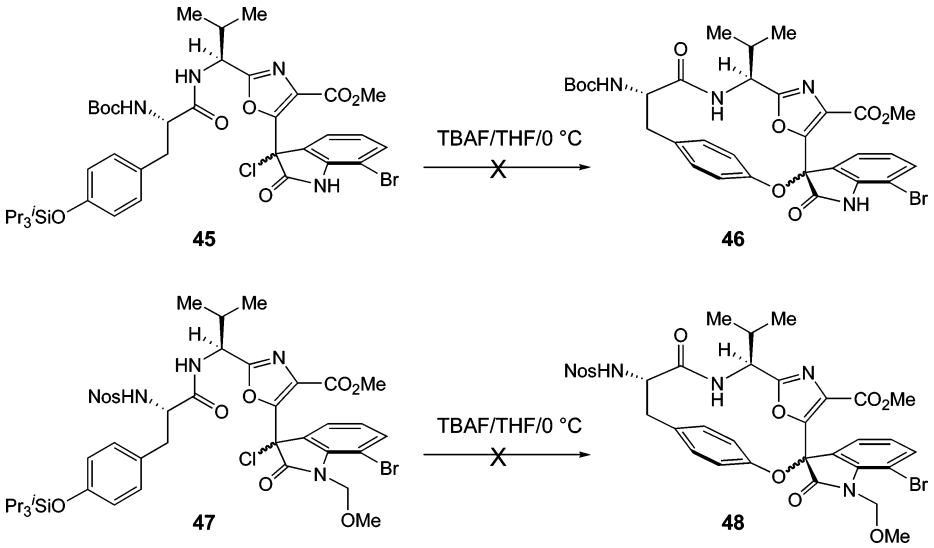


(17) Goldberg, F. W.; Magnus, P.; Turnbull, R. *Org. Lett.* **2005**, *7*, 4531−4534.
(18) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; VCH: New York, 1988.
(19) Rice, F. O.; Teller, E. *J. Chem. Phys.* **1938**, *6*, 489−496. Hine, J. *Adv. Phys. Org. Chem.* **1977**, *15*, 1−61. "A spontaneous reaction will yield a product which has a similar spatial arrangement of the atoms rather than a very different one even if energetically favorable." Isaacs, N. *Physical Organic Chemistry*; Longman Group Ltd.: Harlow, U.K., 1995; pp 123−124.

Scheme 7. Stereoselective *O*- to *C*-Rearrangement of **41** and **42** into **43** and **44**, Respectively



Scheme 8



mide A. The simplest way to achieve this structural correlation was to convert **33** into **37**, an advanced intermediate in Nicolaou's[4a,c] first synthesis of diazonamide A, Scheme 6. To establish the above proposed correlation, the phenolic hydroxyl group in **33** was converted into its derived methoxymethyl ether **35** by treatment with $MeOCH_2Cl/NPr_2^iEt$ in dichloromethane at 0 °C, Scheme 6. Reduction of the methyl ester functionality in **35** was achieved by exposure of **35** to $LiBH_4$/THF to give **36** (75%), which was converted into **37** by treatment with *n*-Bu_4NI/NaH/BnBr in DMF/THF at 0 °C (89%). Comparison of data for **37** (*J. Am. Chem. Soc*. **2004**, *126*, 12888−12896, Scheme 7, p 12893, compound **43**), ^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz), IR, HRMS, and optical rotation, lit.[4c] $[\alpha]^{20}_D$ −177.0 (c = 0.57, MeOH), $[\alpha]^{20}_D$ −180.7 (c = 0.7, MeOH) (within 2.1%) clearly established the structure of **37**, and thus the remarkable stereoselective conversion of **31** and **32** into **33**. Since **37** has been converted into diazonamide A **1** in Nicolaou's first synthesis,[4a,c] this constitutes a formal total synthesis of **1**.

While the work described so far has the tyrosine nitrogen atom protected as the benzyloxycarbonyl derivative (Cbz), we

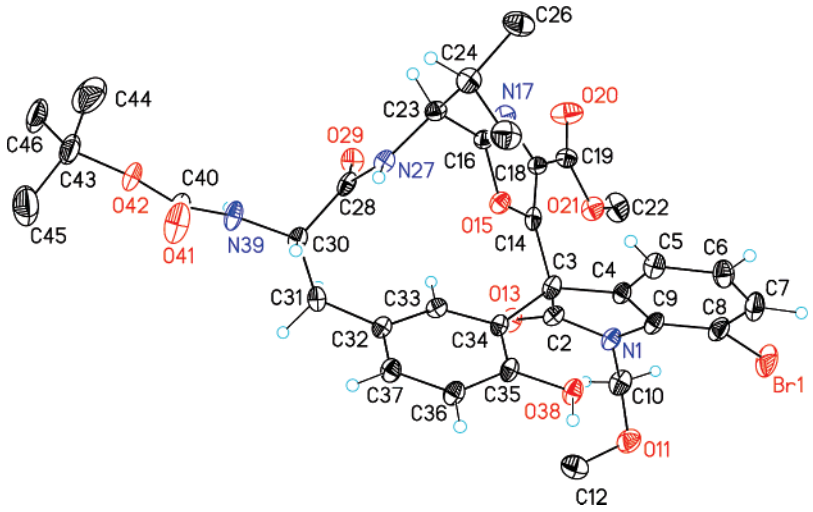


Figure 2. View of **44** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 30% probability level. The methyl hydrogen atoms have been removed for clarity.

Scheme 9. Mechanism of *O*-Ar to *C*-Ar Rearrangement

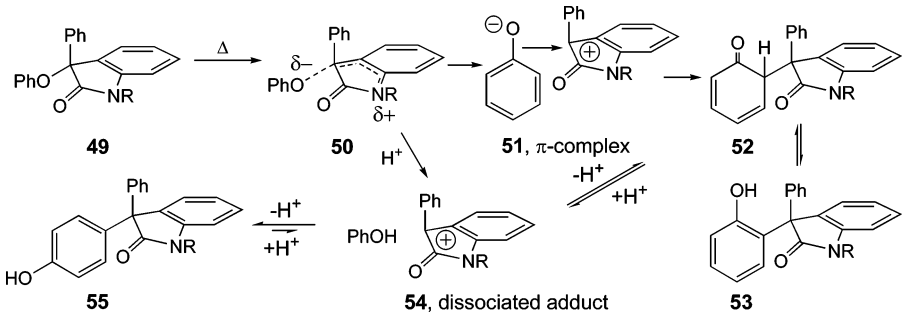


Table 2

entry, starting material	conditions	time	product (**43**:**44**)
1, **41**	solid, −20 °C	3 weeks	77:23 (18% conv.)[a]
2, **42**	solid, −20 °C	3 weeks	13:87 (48% conv.)[b]
3, **41**	CH_2Cl_2, −20 °C	3 weeks	46:54 (2% conv.)[c]
4, **42**	CH_2Cl_2, −20 °C	3 weeks	0% conv.[d]
5, **41**	CH_2Cl_2, 21 °C	7 days	62:38
6, **42**	CH_2Cl_2, 21 °C	7 days	66:34
7, **41**	CH_2Cl_2, AcOH, 21 °C	5 days	47:53
8, **42**	CH_2Cl_2, AcOH, 21 °C	5 days	58:42
9, **41** + **42**	$CHCl_3$, reflux	6 h	65:35

[a] 82% returned starting material (**41**:**42** = 84:16). [b] 52% returned starting material (**41**:**42** = 8:92). [c] 98% returned starting material (**41**:**42** = 90:10). [d] 100% returned starting material (**41**:**42** = 4:96). All of the ratios were determined by analytical HPLC.

also explored *t*-butoxycarbonyl (Boc) protection. Treatment of **27** with **38**[20] under standard amide coupling reaction conditions gave **39** (73% from **25**), Scheme 7. The derived chloride **40** on exposure to *n*-Bu_4NF (TBAF)/THF at 0 °C resulted in clean conversion into the phenolic ethers **41** and **42** (1:1, 95%). The separated ethers **41** and **42** were subjected to a number of reaction conditions, Table 2, to give **43** and **44**. The trends are similar to those seen for the Cbz series (Scheme 5, Table 1). The structure of **44** was unequivocally established by X-ray crystallography, Figure 2.

In the solid phase at −20 °C, both **41** and **42** are converted into **43** and **44** in ratios of 77:23 and 13:87, respectively. Even though we started with pure **41** and pure **42**, the recovered ethers consisted of a mixture of **41** and **42** in ratios of 84:16 and 8:92, respectively, entries 1 and 2.

In solution at −20 °C in dichloromethane, **41** is partially (2%) converted into **43** and **44** (46:54), entry 3, whereas under the same reaction conditions **42** remained unchanged, entry 4. At 21 °C in dichloromethane, **41** and **42** are completely converted within 7 days to give **43** and **44** in ratios of 62:38 and 66:34, respectively, entries 5 and 6. The above rearrangement in dichloromethane is complete in 5 days if a catalytic amount of acetic acid is present, entries 7 and 8, and gives **43** and **44** in ratios of 47:53 and 58:42.

The most practical method of converting **41** and **42** into the correct stereoisomer **43** is heating the ethers in chloroform at reflux (61 °C) for 6 h, entry 9, which results in **43** and **44** (6:35). Exposure of **44** to a variety of reaction conditions (TFA/CH_2Cl_2, TFA/$(CF_3)_2CHOH$, etc.) did not produce **43**.

It was also discovered that the formation of the 14-membered phenolic ether ring requires a protecting group on the tryptophan nitrogen atom. In contrast to the above results, the unprotected oxindole substrate **45** on exposure to TBAF/THF at 0 °C produced a complex mixture, and none of the desired phenolic ether **46** could be detected, Scheme 8. The nature of the protecting group on the tyrosine nitrogen atom was also crucial. As alluded to above, both the *N*-Cbz and the *N*-Boc derivatives **30** and **40** cyclized to give the phenolic ethers **31**/**32** (Scheme 4) and **41**/**42** (Scheme 7), respectively, whereas the *N*-Nos protected adduct **47** on exposure to TBAF/THF at 0 °C resulted in a complex mixture, and none of the desired phenolic ether

(20) Wasserman, H. H.; Zhang, R. *Tetrahedron* **2002**, *58*, 6277−6284.

48 was observed. Presumably, the pyramidal *N*-Nos prevents **47** from adopting a conformation that can result in **48**.

We have studied the mechanism of the *O*-aryl to *C*-aryl rearrangement on simple oxindoles and have made the following observations.[17] Heating **49** at 80 °C results in **53** (R = H), Scheme 8, whereas treatment of **49** with a catalytic amount of CF_3CO_2H in benzene at 25 °C gave **55** (R = H). Both the thermal and the acid-catalyzed rearrangment exhibit crossover when carried out in the presence of another phenol. Treatment of **53** with a catalytic amount of CF_3CO_2H in benzene at 25 °C cleanly converted it into the *p*-isomer **55**.

There appears to be two mechanisms operating. Under neutral thermal conditions, **49** (R = H) dissociates to **50** (R = H), which forms **51** (R = H) (π-complex or ion-pair) and converts into the *o*-cyclohexa-2,5-dienone **52** (R = H), which tautomerizes to give **53** (R = H). In the presence of acid, the partially dissociated adduct **50** (R = H) can completely ionize to give **54** (R = H), which gives the thermodynamically more stable product **55** (R = H). *ipso*-Protonation of **53** (R = H) leads to **52** (R = H) and eventually **55** (R = H), thus providing further evidence that acid catalysis promotes the formation of the more stable rearrangement product. In the NMe series, treatment of *N*-methyl-3-chloro-3-phenyloxindole with $PhOH/Cs_2CO_3/CH_2Cl_2$ at 25 °C gave **53** (R = Me) directly, presumably via **49** (R = Me). The rearrangement of **31**/**32** into **33** and likewise **41**/**42** into **43** most probably proceeds via the dissociative pathway through a π-complex analogous to **51**.

This fortuitous rearrangement has some analogy in the *O*-arylglycoside to *C*-arylglycoside conversion,[21] and the Lewis acid/Bronsted acid-catalyzed conversion of benzyl ethers into 2-hydroxydiphenylmethane derivatives.[22] Also, there is an unpublished thermal rearrangement of an *O*-cresyl ether into an *C*-cresol derivative, which, in fact, provided the motivation to pursue the rearrangement chemistry described in Scheme 5.[16]

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Supporting Information Available: Complete experimental details and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0744448

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