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Photo-Fries rearrangement for the synthesis of the diazonamide macrocycle

Philip Magnus* and Cyrille Lescop

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, TX 78712, USA

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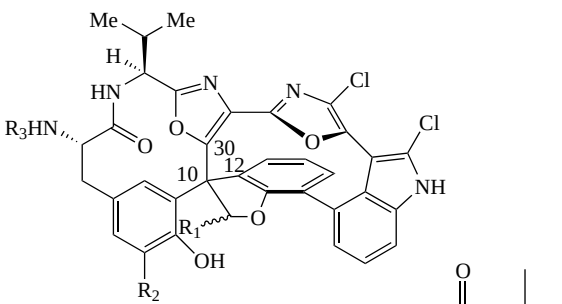
Abstract—Irradiation of the macrolactam **15** results in a photo-Fries rearrangement to give the complete diazonamide core skeleton **16** in good yield. © 2001 Published by Elsevier Science Ltd.

In 1991 Fenical and Clardy reported the structure of diazonamide A, **1** and diazonamide B, **2** (Scheme 1).[1] The structures of these unusual alkaloids was inferred from the X-ray determination of the acetal **3**, which was formed by treatment of **2** with *p*-BrC_6H_4COCl/pyridine. The diazonamides were isolated from the colonial ascidian *Diazona chinensis*, collected from the ceilings of caves along the northwest coast of Siquijor Island in the Philippines. It was reported that **1** has potent in vitro activity against HCT-116 human colon carcinoma and B-16 murine melanoma cancer cells (IC_{50} <15 ng/mL). The diazonamides have generated some considerable synthetic interest,[2] and the synthesis of oxazoles and bis-oxazoles has undergone renewed interest.[3–5] In this letter we report the synthesis of the macrocyclic core structure that incorporates the CDE-FGI rings through the use of an extremely efficient photo-Fries rearrangement (Scheme 2).[6]



1, Diazonamide A, R_1 = OH, R_2 = H, R_3 =

2, Diazonamide B, R_1 = OH, R_2 = Br, R_3 = H.

3, R_1 = O2 (acetal), R_2 = Br, R_3 = COC_6H_4Br-*p*.

Scheme 1. Structures of diazonamides.

The overall retrosynthetic analysis we have pursued is based upon the formation of **4** through a transannular cyclization of **5**, which can, in principle, be accomplished via a benzylic cation or radical. The precursor to **5**, namely **6**, should be available from the photo-Fries rearrangement of **7**. In order to test the validity of the photo-Fries rearrangement in such a complicated environment we elected to first study a simpler substrate as outlined in Scheme 3.[7a–d]

Hydrogenolysis of **8**[7a] gave **9**, which was treated with 2-methoxybenzoyl chloride/pyridine/4-*N*,*N*-dimethylaminopyridine (DMAP) to give **10** (100%) (Scheme 3). Irradiation of **10** in benzene (0.001 M) with a medium pressure mercury vapor lamp at 23°C gave **11** (39%) along with about 20% of the *p*-isomer **11a**. The characteristic hydrogen-bonded phenolic hydroxyl group gave rise to a singlet at 12.4 ppm in the ^{1}H NMR spectrum, which is diagnostic for the *o*-isomer **11**.

The next key test of the viability of the photo-Fries rearrangement was in the context of a macrocyclic lactam–lactone such as compound **15** (Scheme 4). Treatment of **8** with trifluoroacetic acid in dichloromethane provided the amine **12**, which was coupled to the acid **14d**[8] to give the amide **13** (80%) (Scheme 4). Hydrogenolysis of **13** removed both benzyl protecting groups, and the product was exposed to the Keck[9] modification of the Steglich[10] esterification conditions to give **15** (66% on a 1 gram scale) as a mixture of atropisomers (1.5:1 rt) (see Fig. 1 for the X-ray structure of one of the atropisomers).[11] Photolysis of a solution of **15** (0.001 M) in benzene resulted in formation of **16** (76%) as the main product (two atropiso-

Keywords: diazonamide; photo-Fries rearrangement; macrolactam.

* Corresponding author.

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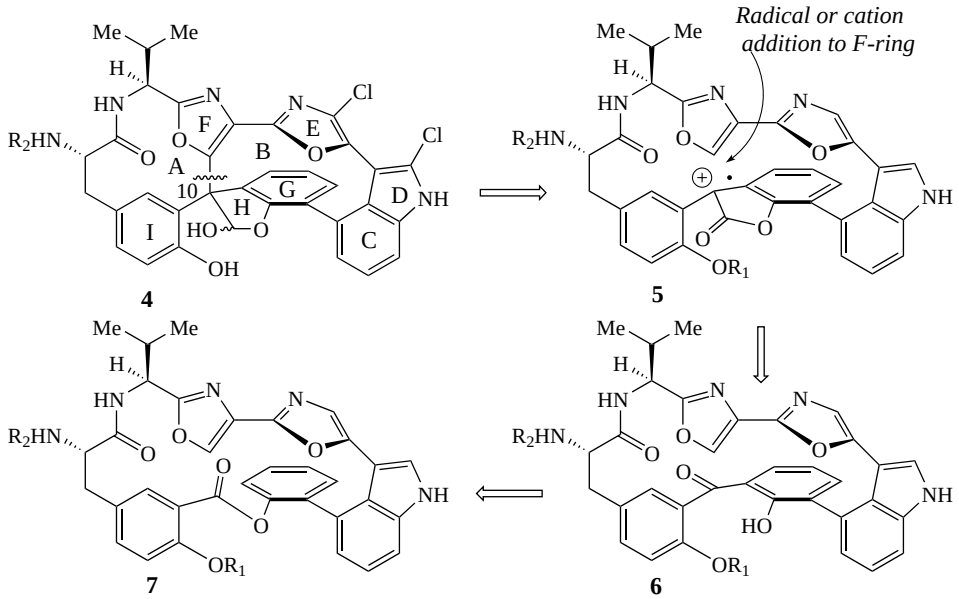
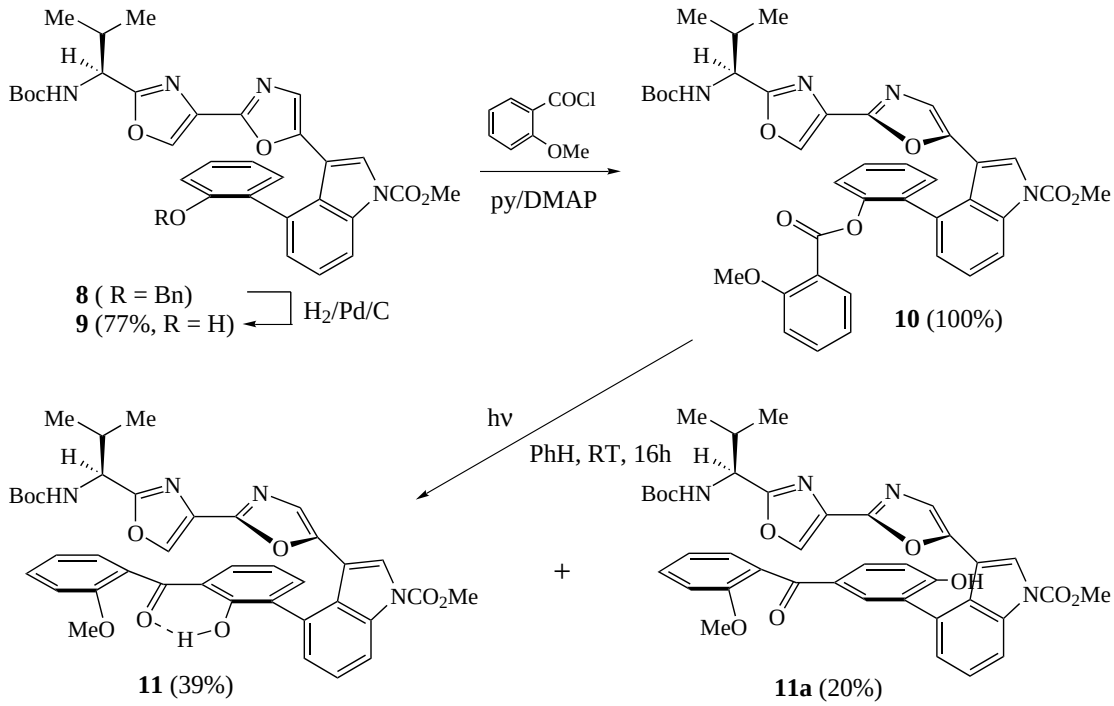


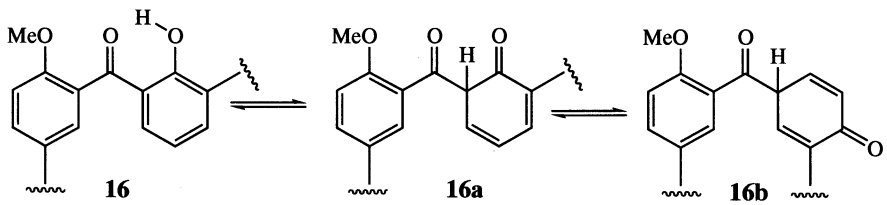
Scheme 2. Retrosynthetic analysis of the diazonamides.



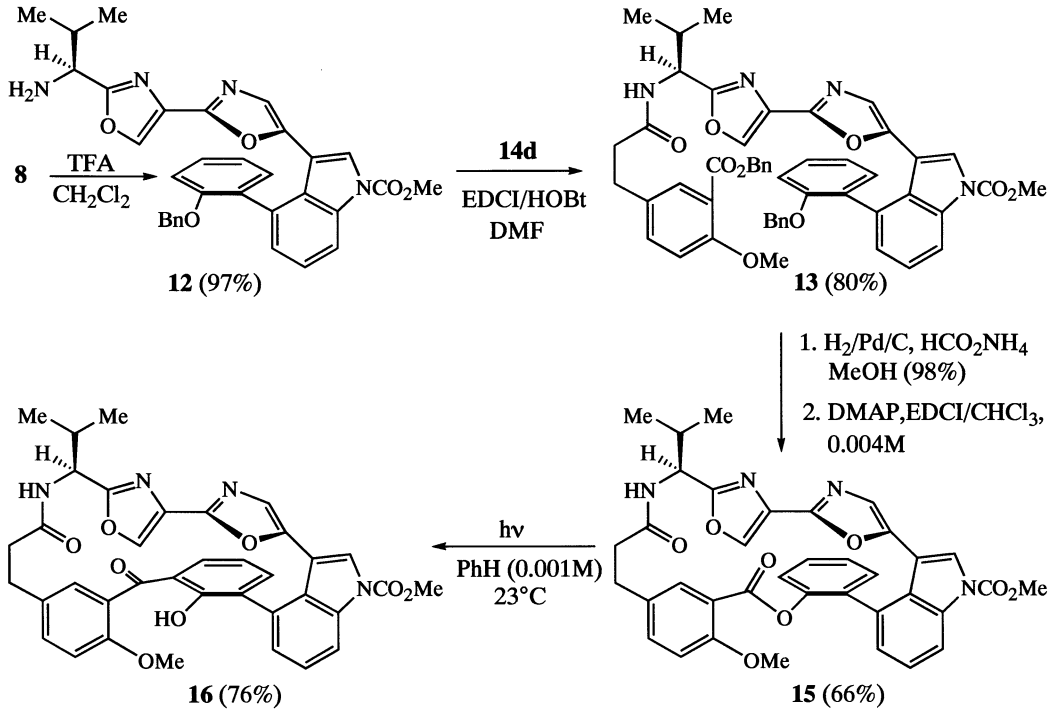
Scheme 3.

mers, 2:1) and a small amount of the *p*-isomer (<10%) **16a** (see Fig. 2 for X-ray structure).[12] Interestingly, photolysis of pure **16**, under the same conditions as above, gave about 5–8% conversion into the *p*-isomer.[13]

The conversion of **16** into its *p*-isomer presumably proceeds via the cyclohexa-2,4-dienone tautomer **16a** which can undergo 1,3-acyl shift to give **16b** (Eq. (1)).



(1)



Scheme 4.

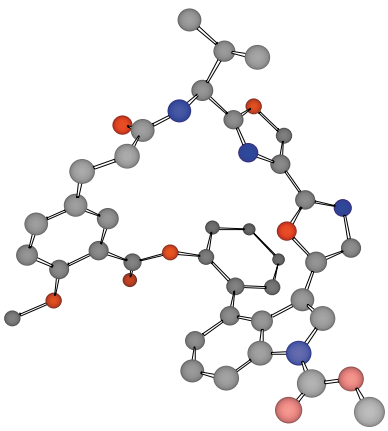


Figure 1. Chem 3D representation of **15** from the X-ray crystallographic coordinates.

The combination of macrolactonization to give **15**, followed by photo-Fries rearrangement to **16** provides a simple and direct route to the diazonamide skeleton.

Acknowledgements

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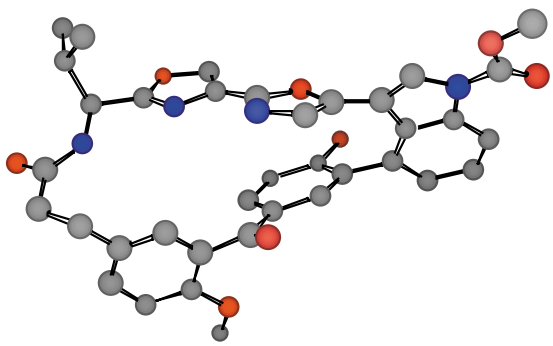
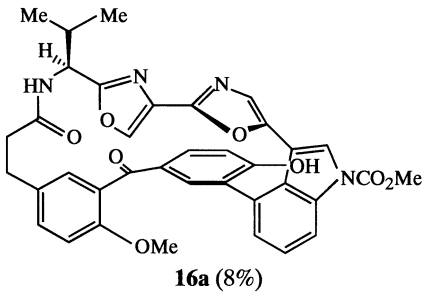
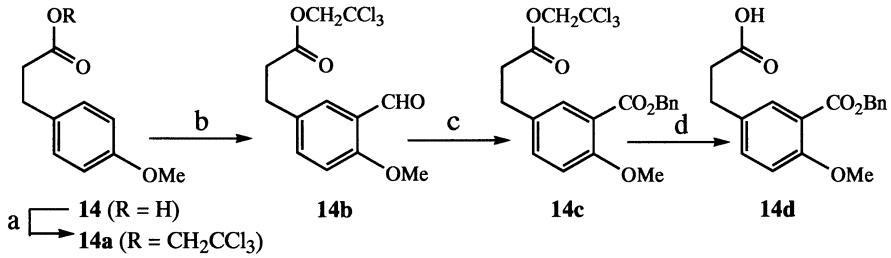




16a (8%)

Figure 2. Chem 3D representation of **16a** from the X-ray crystallographic coordinates.



Scheme 5. (a) $HOCH_2CCl_3$ (1.2 equiv.)/DCC (1.2 equiv.)/DMAP (0.5 equiv.)/CH_2Cl_2, 23°C, 21 h, **14a** (94%); (b) $MeOCHCl_2$ (1.3 equiv.)/$SnCl_4$ (2.0 equiv.)/CH_2Cl_2, −7°C to reflux, 2 h, **14b** (100%, crude); (c) $KMnO_4$ (2.5 equiv.)/acetone/H_2O, 50°C, 5 h, followed by BnBr (3.0 equiv.)/n-Bu_4NI (0.5 equiv.)/$NaHCO_3$ (5.0 equiv.)/DMF, 60°C, 16 h, **14c** (78%); (d) Zn (15 equiv.)/90% AcOH, 0–23°C, 6 h, **14d** (82%). The reaction sequence was conducted on a scale that gave 4 g of **14d**.

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8. The acid **14d** was synthesized as shown in Scheme 5.
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11. Crystals of **15** were grown from dichloromethane/isooctane (Dr. Jon Clardy is thanked for his advice concerning appropriate crystallization solvents).
12. Spectral data for **16**: IR (neat): 3418, 2925, 1747, 1644, 1615; ^1H NMR ($CDCl_3$): two atropisomers, δ 0.84–1.00 (m, 6H major and 6H minor, CH_3), 2.00–2.23 (m, 1H, CH major), 2.25–2.32 (m, 1H, CH minor), 2.62–3.01 (m, 3H major and 3H minor, CH_2), 3.10–3.19 (m, 1H major and 1H minor, CH_2), 3.62 (s, 3H, CH_3O, major), 3.66 (s, 3H, CH_3O, minor), 4.08 (s, 3H major and 3H minor, CH_3CO_2), 4.97 (dd, 1H, CH major, $J=8.8$, 6.4 Hz), 5.04 (dd, 1H, CH minor, $J=9.2$, 6.8 Hz), 6.24 (d, 1H, NH minor, $J=9.2$ Hz), 6.50 (brs, 1H, NH major), 6.57–7.45 (m, 9H major and 9H minor, CH), 7.47–7.54 (m, 1H major and 1H minor, CH), 7.81 (s, 1H, CH, minor), 7.84 (s, 1H, CH major), 8.30–8.36 (m, 1H major and 1H minor, CH), 12.2 (s, 1H, OH major), 12.4 (s, 1H, OH minor); ^{13}C NMR ($CDCl_3$): two atropisomers, δ 18.1, 18.3, 18.6, 19.0, 30.5, 30.9, 31.6, 32.7, 36.5, 37.8, 52.0, 52.5, 54.2, 55.5, 55.6, 109.3, 109.7, 111.4, 111.6, 114.8, 114.9, 117.9, 118.3, 119.4, 119.5, 125.3, 125.5, 125.6, 125.8, 126.3, 126.6, 126.9, 127.1, 127.2, 127.3, 128.2, 128.6, 129.1, 129.6, 130.4, 130.6, 131.2, 131.5, 131.7, 132.0, 133.2, 135.5, 135.6, 136.6, 136.7, 137.8, 138.0, 144.1, 145.1, 150.9, 154.4, 154.5, 155.0, 159.4, 159.7, 164.7, 164.9, 171.3, 171.4, 201.9, 202.6. HRMS (CI) calcd for $C_{37}H_{32}N_4O_8$ $(M+H)^+$ 661.2298. Found: 661.2300.
13. Transient cyclohexa-2,4-dienones have been observed in photo-Fries rearrangement. See: Jiménez, M. C.; Miranda, M. A.; Scaiano, J. C.; Tormos, R. *Chem. Commun.* **1997**, 1487.