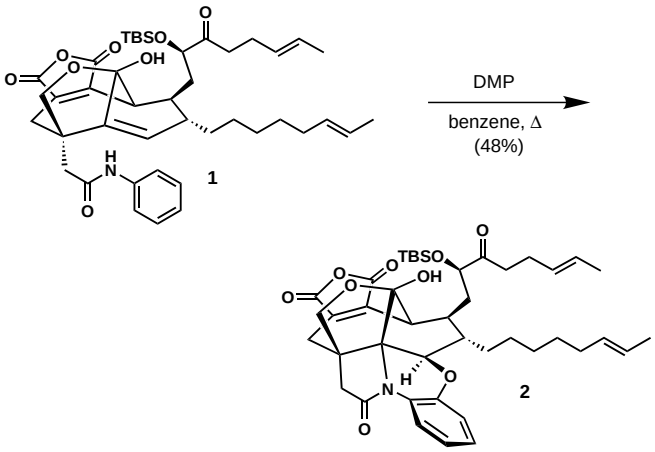
New Synthetic Technology for the Rapid Construction of Novel Heterocycles—Part 1: The Reaction of Dess–Martin Periodinane with Anilides and Related Compounds**

K. C. Nicolaou,* Yong-Li Zhong, and Phil S. Baran

Contemporary organic synthesis is faced with the challenge of developing simple methods for the rapid construction of complex, biologically relevant compounds which rival the complexity and diversity of natural products for combinatorial chemistry, biological screening, and chemical biology studies. Total synthesis endeavors provide novel forums and opportunities for exploration and for the discovery and development of new chemistry to address this formidable task. During the course of our recent total synthesis of the CP molecules[1] we observed the unexpected conversion of **1** into **2** (Scheme 1), brought about by exposure of **1** to DMP[2] in



Scheme 1. Serendipitous observation leading to the present methodologies. DMP = Dess–Martin periodinane, TBS = *tert*-butyldimethylsilyl.

refluxing benzene. This serendipitous discovery directly led to the development of a number of new chemical processes for the construction of molecular diversity, while unearthing a new paradigm for periodinane-mediated reactions with ani-

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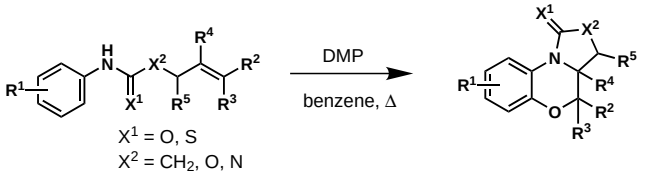
Table 1. DMP-mediated construction of novel polycycles.

Entry	Substrate	Product	Yield [%]
1	**3a:** R = F	**3b:** R = F	15
2	**4a:** R = NO_2	**4b:** R = NO_2	10
3	**5a**	**5b** [ca. 1:1]	11
4	**6a**	**6b** [ca. 2:1]	49
5	**7a**	**7b**	40
6	**8a**	**8b**	52
7	**9a**	**9b**	36
8	**10a**	**10b**	38
9	**11a**	**11b** [ca. 2:1] (other regioisomer (–Br))	42
10	**12a**	**12b**	37

lides and related substrates (Scheme 2). Herein we report an unprecedented cascade reaction for the elaboration of complex natural product-like heterocycles from simple building blocks in only two synthetic operations.



Scheme 2. General construction of complex, natural product-like polycycles from a DMP-mediated cascade reaction.

Our first attempts to establish the generality of this new transformation were disappointing. As seen in entries 1–3 in Table 1[3], the reactions of very simple anilides bearing a terminal alkene led to low yields of the desired products, presumably due to an excess of conformational freedom enjoyed by these substrates. We then reasoned that embedding a ring into the olefinic segment of the starting material might solve this problem. Indeed, as can be seen from entries 4–10 in Table 1, the chemical yields were considerably improved with this modification to provide a variety of complex polycycles. Notable is the capacity of this process to rapidly generate three stereocenters in a diastereocontrolled manner from simple achiral starting materials. The substrates shown in Table 1 were all easily prepared by the EDC-mediated dehydration of a substituted aniline with the appropriate carboxylic acid. The structure of one of these polycyclic products, compound **7b**, was verified by X-ray crystallographic analysis (Figure 1).[4]

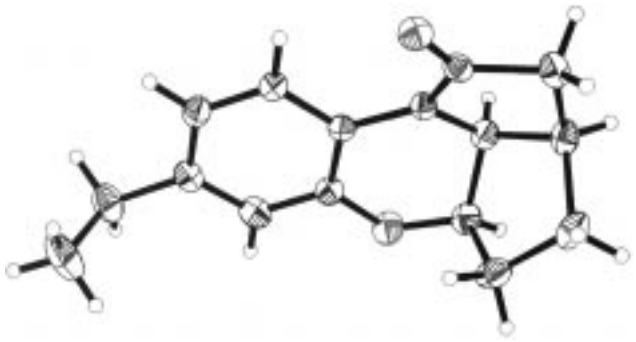
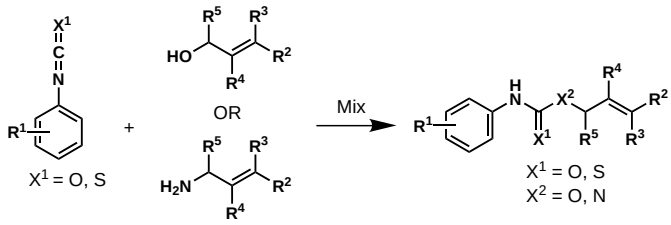


Figure 1. X-ray crystal structure of **7b**.

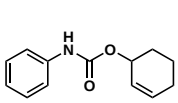
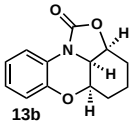
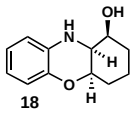
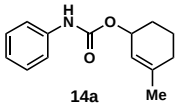
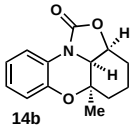
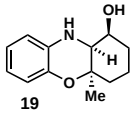
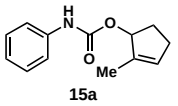
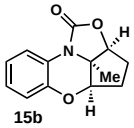
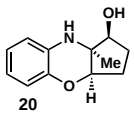
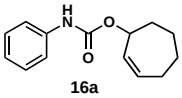
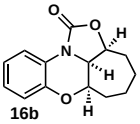
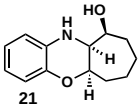
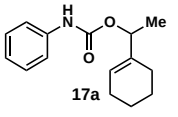
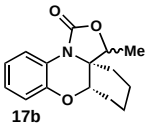
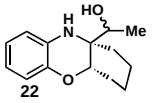
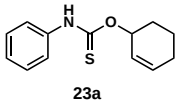
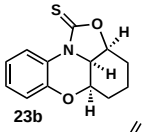
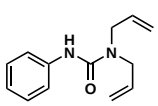
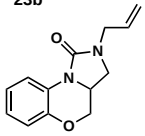
Recognizing that the scope and versatility of the reaction could be considerably enhanced if the library of starting materials was expanded to other effortlessly available compounds, we considered the nucleophilic attack of allylic alcohols or allylic amines on phenyl isocyanates or phenyl iso(thio)cyanates (Scheme 3).[5] The resulting substrates would lead to rigid scaffolds capable of projecting a manifold of functional groups in defined, three-dimensional space and they would be available in one step from readily accessible sources. Implementation of this strategy led to the results demonstrated in Table 2. To our delight, carbamates **13a**–**17a**, thiocarbamate **23a**, and urea **24a** afforded



Scheme 3. Preparation of reaction substrates from phenyl isocyanates or phenyl iso(thio)cyanates and allylic alcohols or allylic amines.

the corresponding polycycles in moderate to good yields (36–56%, Table 2). Given that hypervalent iodine reagents readily interact with sulfur-containing molecules,[6] the ease with which the reaction occurs with the thiocarbamate is admirable. In the case of urea **24a** the presumption that restriction of conformational freedom should enhance reactivity (vide supra) is accurately reflected, since simple amides lacking the rigidity incurred by the added nitrogen (see Table 1, entry 1) led to only low yields of polycyclic products. In the carbamate entries of Table 2, the formed products can be easily hydrolyzed (NaOH/EtOH) to provide the corresponding benzomorpholines **18**–**22** in excellent yields (90–96%). This DMP-

Table 2. DMP-mediated construction of novel polycycles from carbamates, thiocarbamates, and ureas, and the synthesis of benzomorpholines.

Entry	Substrate	Product	Yield [%]	Benzomorpholine	Yield [%]
1	 **13a**	 **13b**	50	 **18**	95
2	 **14a**	 **14b**	42	 **19**	95
3	 **15a**	 **15b**	40	 **20**	96
4	 **16a**	 **16b**	38	 **21**	95
5	 **17a**	 **17b**	36[a]	 **22**	90
6	 **23a**	 **23b**	42	—	
7	 **24a**	 **24b**	56	—	

[a] Ratio of diastereoisomers was about 1.5:1.

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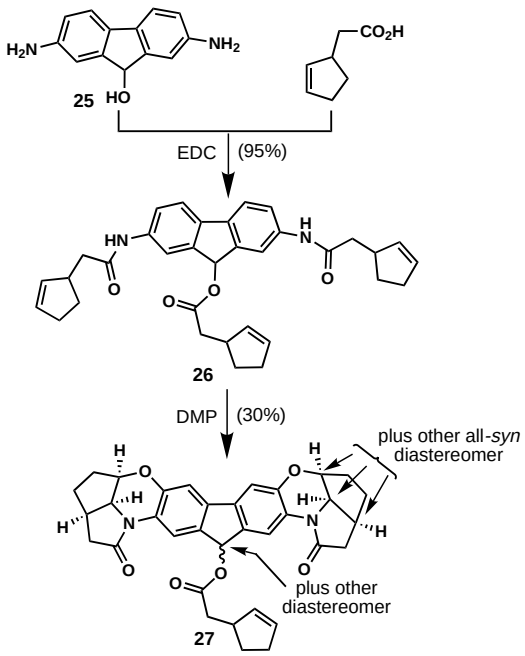
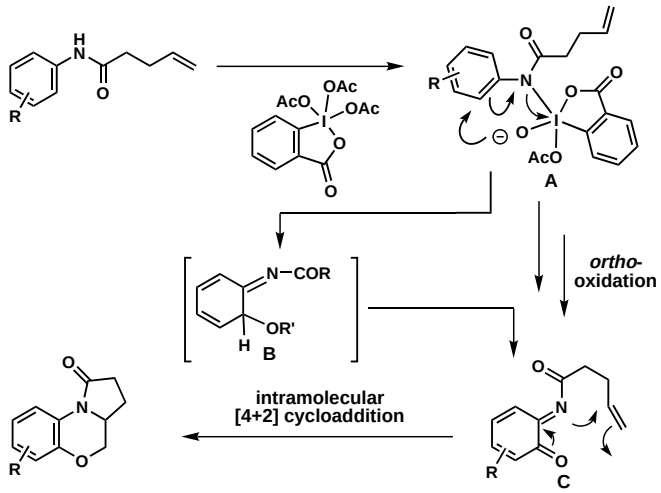
initiated cascade reaction also adds to the armory of reactions which generate quaternary centers in a stereoselective fashion (see Table 1, entries 9 and 10; Table 2, entries 2, 3, and 6). As a further test of the power of this process to deliver complex molecular diversity, we enlisted the diamide **26**, derived from bis-aniline **25**, as a potential substrate (Scheme 4). The reaction furnished the complicated polycycle **27**, harboring no less than ten rings and seven stereocenters (30% yield, mixture of four diastereoisomers).



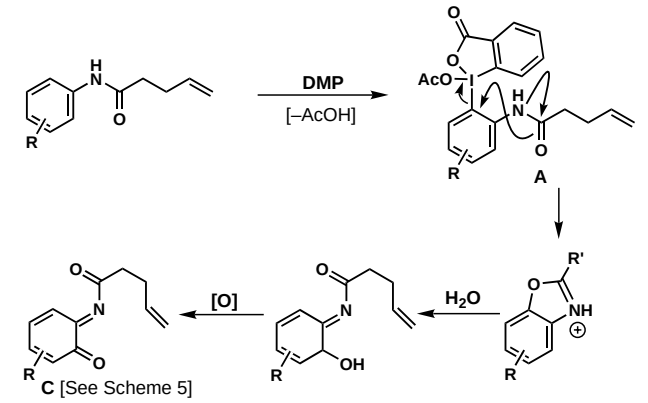
Scheme 4. Facile generation of complex polycycle **27** from simple bis-aniline **25** (mixture of four diastereoisomers). EDC = 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide.

Operationally, the reactions are as simple as the DMP-mediated oxidation of alcohols; they can be performed in benzene or benzotrifluoride (BTF)[7] under an aerobic atmosphere and are usually complete within 1 h at 80 °C. Standard workup, followed by chromatography, furnishes the products in generally moderate to good yields, which are satisfying due to the high level of complexity attained rapidly in a single step.

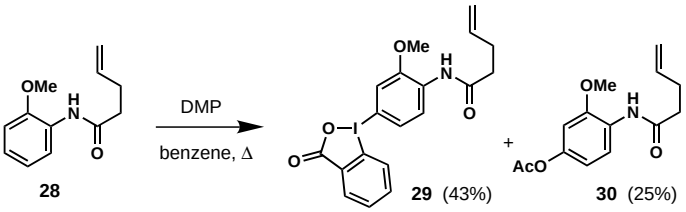
We propose the following tentative mechanism to account for the products arising from this remarkable cascade reaction (Scheme 5). The anilide nitrogen rapidly engages the electrophilic DMP reagent[8] to provide an intermediate of type **A**. *ortho*-Oxidation then occurs leading to the novel diene **C**,[9] presumably by a further oxidation of the intermediate **B**. An intramolecular hetero Diels–Alder reaction of **C** completes the tandem sequence. An alternative mechanism which converges at intermediate **C** could also be envisaged (Scheme 6). The isolation of compounds **29** and **30** from the reaction of substrate **28** with DMP (Scheme 8) provides credence for certain facets of the proposed mechanism in Scheme 5. In addition, we found that the interactions of periodinane species with amides is, so far, limited to anilides.[10] This is also reflected by the ease with which



Scheme 5. Tentative mechanistic proposal for the DMP-mediated cascade reaction of aryl carbamoyl alkenes.



Scheme 6. An alternative mechanistic pathway to explain the formation of intermediate **C**.



Scheme 7. Informative by-products in the reaction of **28** with DMP.

unsymmetricalureas (Table 2, entry 7) reacted. This result coupled with the isolation of aryl acetate **30** and aryl periodinane **29** (Scheme 6) implies that both the amide nitrogen and the phenyl ring are active participants in the reaction.

Notwithstanding the development of a highly useful protocol for the construction of complex, diverse heterocycles, which are relevant to chemical biology and medicinal chemistry, in two synthetic operations from ubiquitous and commercially available materials, we believe that we have uncovered a new class of chemical processes. The following communication[10] serves to demonstrate that the present reaction is perhaps only a glimpse of the rich heterocyclic chemistry attainable with periodinane-type reagents.

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Experimental Section

DMP (2.0 equiv) was added in one portion to a solution of **7a** (0.1 mmol) in benzene (4 mL) or BTF.[6] The solution was heated at reflux (or at 80–85 °C for the reactions in BTF) for about 30 min at which point TLC indicated complete consumption of starting material. Dilution with EtOAc followed by washing with 5% aq. $NaHCO_3$ (2 ×) and brine, drying over $MgSO_4$, and concentration led to crude **7b**. Pure **7b** was isolated in 40% yield after column chromatography (silica gel, EtOAc:hexane 1:2) (see Table 3 for selected physical properties).

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Table 3. Data for selected compounds.

7b: colorless needles, m.p. 135–136 °C (methanol); $R_f = 0.37$ [silica, EtOAc:hexane 1:2]; IR (film): $\tilde{\nu}_{max} = 2965, 2922, 1694, 1576, 1512, 1437, 1383, 1302, 1260, 1227, 1163, 1115, 866, 814\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.96$ (d, $J = 3.5$ Hz, 1H), 6.80–6.71 (m, 2H), 4.77–4.70 (m, 1H), 3.87 (dd, $J = 5.5$, 1.2 Hz, 1H), 2.96 (dd, $J = 17.2$, 8.6 Hz, 1H), 2.83–2.73 (m, 1H), 2.58 (q, $J = 7.6$ Hz, 2H), 2.24 (d, $J = 17.3$ Hz, 1H), 2.13–1.97 (m, 2H), 1.70–1.50 (m, 2H), 1.95 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 172.6, 144.0, 142.0, 128.0, 120.5, 121.1, 115.7, 78.6, 57.6, 39.7, 32.4, 29.0, 28.5, 15.5$; HRMS (MALDI-FTMS), calcd for $C_{15}H_{18}NO_2$ [$(M+H)^+$]: 244.1338, found 244.1332

24b: $R_f = 0.65$ [silica, EtOAc:hexane 1:1]; IR (film): $\tilde{\nu}_{max} = 2919, 2850, 1709, 1501, 1437, 1260, 753\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.95$ (dd, $J = 7.0$, 2.6 Hz, 1H), 7.00–6.94 (m, 2H), 6.89 (dd, $J = 7.4$, 2.2 Hz, 1H), 5.83–5.72 (m, 1H), 5.23 (dd, $J = 18.3$, 1.1 Hz, 1H), 5.22 (d, $J = 9.2$ Hz, 1H), 4.34 (dd, $J = 10.5$, 3.3 Hz, 1H), 4.10–4.02 (m, 1H), 3.94–3.88 (m, 2H), 3.79 (t, $J = 10.5$ Hz, 1H), 3.61 (t, $J = 9.4$ Hz, 1H), 3.11 (dd, $J = 9.4$, 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.8, 144.4, 132.6, 127.8, 123.4, 121.5, 120.6, 118.4, 116.6, 66.9, 47.8, 46.4, 43.6$; HRMS (MALDI-FTMS), calcd for $C_{13}H_{15}N_2O_2$ [$(M+H)^+$]: 231.1133, found 231.1128

29: colorless needles, m.p. 108–109 °C (hexane:diethyl ether 2:1); $R_f = 0.18$ [silica, EtOAc:hexane 1:4]; IR (film): $\tilde{\nu}_{max} = 3296, 3084, 2920, 2850, 1761, 1731, 1679, 1649, 1526, 1461, 1408, 1267, 1238, 1179, 1144, 1079, 1032, 1008, 908, 885\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.44$ (d, $J = 8.8$ Hz, 1H), 8.06 (d, $J = 7.9$ Hz, 1H), 8.02 (dd, $J = 7.9$, 1.5 Hz, 1H), 7.73 (br s, 1H), 7.47(t, $J = 7.9$ Hz, 1H), 7.22 (dt, $J = 7.9$, 1.5 Hz, 1H), 6.84 (dd, $J = 8.8$, 2.5 Hz, 1H), 6.81 (d, $J = 1.5$ Hz, 1H), 5.92–5.82 (m, 1H), 5.12 (d, $J = 16.9$ Hz, 1H), 5.04 (d, $J = 10.2$, 1H), 3.89 (s, 3H), 2.50 (br s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.7, 165.4, 148.7, 146.8, 142.1, 137.2, 134.5, 133.7, 132.0, 128.5, 126.2, 120.5, 116.3, 114.0, 104.7, 95.1, 56.4, 37.5, 29.9$; HRMS (MALDI-FTMS), calcd for $C_{19}H_{18}INO_4Na$ [$M+Na^+$]: 474.0178, found 474.0178

30: colorless needles, m.p. 63–64 °C (hexane:diethyl ether 2:1); $R_f = 0.10$ [silica, 1:4 ethyl acetate:hexane]; IR (film): $\tilde{\nu}_{max} = 3355, 3073, 2979, 2920, 2850, 1761, 1679, ,1602, 1526, 1491, 1408, 1367, 1267, 1202, 1185, 1150, 1114, 1032, 956, 897\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.37$ (d, $J = 8.8$ Hz, 1H), 7.69 (br s, 1H), 6.67 (dd, $J = 8.8$, 2.4 Hz, 1H), 6.63 (d, $J = 2.4$ Hz, 1H), 5.91–5.78 (m, 1H), 5.11 (d, $J = 17.6$ Hz, 1H), 5.04 (d, $J = 10.3$ Hz, 1H), 3.85 (s, 3H), 2.48 (br s, 4H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 170.3, 169.7, 148.2, 146.4, 136.8, 125.5, 120.0, 115.8, 113.5, 104.3, 55.8, 37.1, 29.4, 21.1; HRMS (FAB), calcd for $C_{14}H_{17}NO_4Na$ [$M+Na^+$]: 286.1055, found 286.1050

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[3] Compounds **3b** and **4b** are formed as single regioisomers, whereas **5b** and **6b** are mixtures. Efforts to understand this peculiar finding are underway.

[4] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-133866. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[8] Studies to determine whether DMP, its hydrolysis product,[2c] or both are the active oxidants in this reaction are underway.

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New Synthetic Technology for the Rapid Construction of Novel Heterocycles—Part 2. The Reaction of IBX with Anilides and Related Compounds**

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In the preceding communication[1] we disclosed a new cascade reaction for the preparation of novel heterocycles. The present discovery arose while optimizing that process, namely, the reaction of Dess–Martin periodinane (DMP) with anilides. When we attempted to access the polycycles reported[1] using IBX[2] we observed astoundingly efficient cyclization to *N*-phenyl γ-lactams. Herein, we report that the reaction of IBX with anilides leads not only to γ-lactams, but also to a variety of other heterocycles including oxazolidinones, thiooxazolidinones, and cyclic ureas in high yields (Scheme 1).

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