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Rapid Access to Complex Molecular Architectures via *o*-Azaquinones**

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

We have recently reported a number of new synthetic technologies[1] based on the use of the hypervalent iodine reagent DMP and its precursor IBX (for abbreviations of reagents, see legends to schemes). Despite their similar structures and ability to oxidize alcohols to carbonyl compounds, IBX and DMP exhibit distinctly different reactivity profiles towards a multitude of organic substrates. The facile generation of *o*-azaquinone-type structures from anilides and DMP, and their demonstrated ability to undergo inter- and intramolecular Diels–Alder reactions as heterodienes (Scheme 1, path a)[1a,f] or to undergo further oxidation to *p*-quinones[1f] (Scheme 1, path b) prompted us to investigate
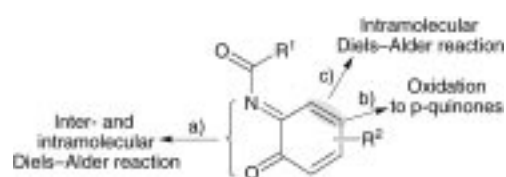

Scheme 1. Reactivity of *o*-azaquinones as versatile chemical entities. a) Participation in inter- and intramolecular Diels–Alder reactions (ref. [1a,f]), b) oxidation to *p*-quinones (ref. [1f]), and c) proposed intramolecular Diels–Alder reactions.

them further. Close inspection revealed the potential of utilizing these quinones to construct rapidly complex mimics of known natural products and potential protein ligands. Herein we report a new mode of reactivity of these under-explored molecular entities in which the double bond adjacent to the imide moiety (Scheme 1, path c) is richly exploited by means of cascade reactions. Initiated by DMP, this pathway proceeds through an intramolecular Diels–Alder reaction of the generated *o*-azaquinone–diene constructs and leads, via ketohydroxyamides, to a multitude of molecules (e.g. **1**, **2a**, and **3a**, Scheme 2), which resemble the pseudopterosin natural products.[2] Alternatively, further

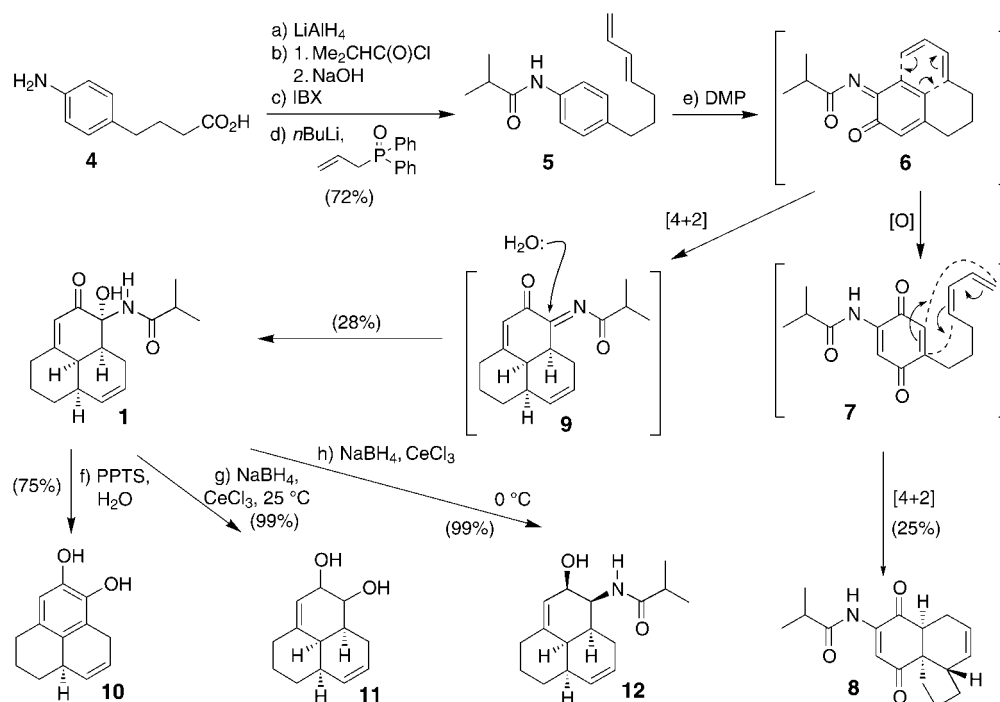[*] Prof. Dr. K. C. Nicolaou, Dr. Y.-L. Zhong, P. S. Baran, Dr. K. Sugita
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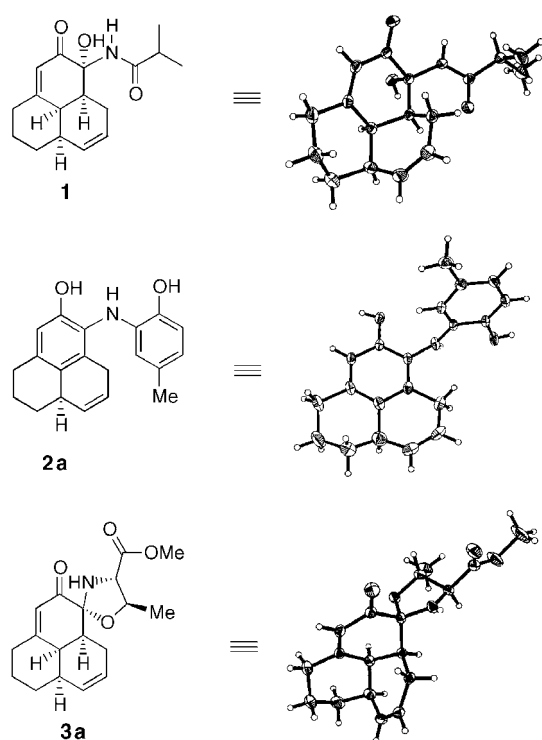
Scheme 2. ORTEP diagrams of complex, natural product like compounds obtained from chemical synthesis.[7]

oxidation to *p*-quinones and intramolecular Diels – Alder fusion leads to the full carbon skeleton of the elisabethin type of natural products.[3]

To investigate the reactivity of the olefin adjacent to the imide group in *o*-azaquinones (Scheme 1, path c), the diene **5** (Scheme 3) was designed and targeted for synthesis. Anilide **5** was prepared efficiently from the commercially available amino acid **4** in 72% overall yield by means of the sequence summarized in Scheme 3. Exposure of **5** to DMP (4.0 equiv)/H$_2$O (2.0 equiv) led to ketohydroxyamide **1** (Scheme 2, Table 5) and quinone **8** (Scheme 3, Table 5). The former presumably arises from the hydration of the initially formed intramolecular Diels – Alder product **9**. To the best of our knowledge, the intramolecular Diels – Alder reaction of *o*-azaquinones (acting as a dienophile) has not been explored. More importantly, ketohydroxyamide **1** closely resembles the pseudopserin natural products. The quinone **8**, which embodies the full carbon skeleton of the naturally occurring elisabethin A,[3] was undoubtedly formed by means of an intramolecular Diels – Alder fusion of the intermediate *p*-quinone **7**, which was generated from **6** by the oxidative action of DMP.[1f]

The easy access to ketohydroxyamides such as **1** coupled with their scarcely investigated chemistry[4] offered us the opportunity to explore their reactivity and synthetic potential (Scheme 3). We were able to access compounds **11** (99% yield) and **12** (99% yield) under reductive conditions (NaBH$_4$) simply by altering the temperature of the reaction. On the other hand, compound **1** was cleanly converted into diphenol **10** by the catalytic action of PPTS (75% yield).

We reasoned that a dicarbonyl compound was a fleeting intermediate in the conversion of ketohydroxyamide **1** into diphenol **10** (Scheme 3) and sought to trap this reactive

Scheme 3. Rapid entry into complex pseudopterosin and elisabethin analogues from anilides and DMP. Reagents and conditions: a) LiAlH$_4$ (5.0 equiv), THF, 0 →25 °C, 2 h, 96%; b) 1. Me$_2$CHC(O)Cl (3.0 equiv), Et$_3$N (4.0 equiv), CH$_2$Cl$_2$, 0 →25 °C, 1 h, 2. NaOH (1 N, 3.0 equiv), MeOH, 50 °C, 2 h, 95% for two steps; c) IBX (2.0 equiv), DMSO, 25 °C, 6 h, 95%; d) Ph$_2$P(O)CH$_2$CH=CH$_2$ (3.0 equiv), *n*BuLi (2.5 equiv), HMPA (6.0 equiv), THF, −78 °C, 20 min; then add aldehyde, −78 →25 °C, 14 h, 83%; e) DMP (4.0 equiv), H$_2$O (2.0 equiv), CH$_2$Cl$_2$, 25 °C, 3 h, 28% (**1**), 25% (**8**); f) PPTS (0.2 equiv), H$_2$O, 50 °C, 30 min, 75%; g) NaBH$_4$ (5.0 equiv), CeCl$_3$ (10.0 equiv), THF, 25 °C, 99%; h) NaBH$_4$ (5.0 equiv), CeCl$_3$ (1.1 equiv), THF, 0 °C, 99%. IBX = *o*-iodoxybenzoic acid, DMP = Dess – Martin periodinane, HMPA = hexamethyl phosphoramide, PPTS = pyridinium 4-toluenesulfonate.

species with an array of nucleophiles as a means of expanding the accessible molecular complexity. Thus, in the presence of catalytic amounts of PPTS, anilines were treated with compound **1** at 90 °C to afford polycyclic amines (**2a–d**, [Eq. (1)],
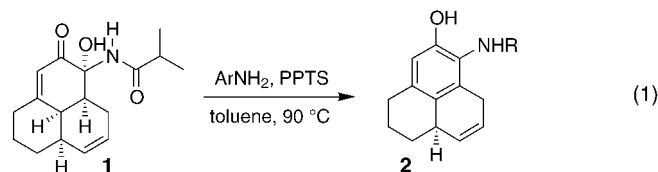

$$(1)$$

Table 1. Synthesis of polycyclic anilines from ketohydroxyamide **1**.[a]

RNH₂	Product	Yield [%]
	2a	84
	2b	71
	2c	45[b]
	2d	89

[a] Reagents and conditions: ArNH₂ (5.0 equiv), PPTS (0.2 equiv), toluene, 90 °C, 3–24 h. [b] Accompanied with 20 % of **10**.

Table 1, Table 5). As this reaction was highly efficient, we treated **1** with C-protected amino acids and discovered an interesting cascade heterocyclic annulation. Under similar conditions as those used for the amines, ketohydroxyamide **1** was easily converted into the complex polycyclic scaffolds **14a–g** ([Eq. (2)], Table 2). A postulated mechanism for this


$$(2)$$
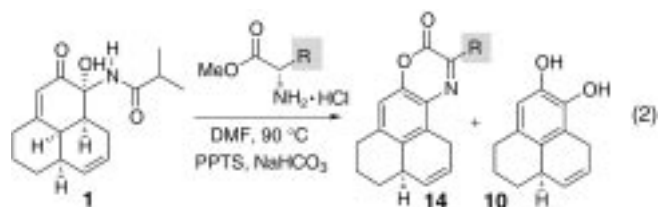
cascade reaction begins with the conversion of **1** into the corresponding diketone **15** after the expulsion of isobutyramide. This is followed either by the formation of diphenol **10** (after aromatization), or by addition of the amino group of the amino acid derivative to form intermediate **16**. Dehydration

Table 2. Synthesis of complex polycyclic systems from ketohydroxyamide **1** and C-protected amino acid derivatives.[a]

Protected amino acid	Product (yield [%])	Bis-phenol **10** (yield [%])
	14a (51)	23
	14b (49)	20
	14c (80)	5
	14d (53)	15
	14e (72)	10
	14f (66)	10
	14g (39)	31

[a] Reagents and conditions: C-protected amino acid (3.0 equiv), PPTS (0.2 equiv), NaHCO₃ (3.0 equiv), DMF, 90 °C, 6–24 h.

of **16** followed by aromatization may then furnish, via **17**, intermediate **18**, which rapidly cyclizes and undergoes oxidation by air to give the observed product **14** (Scheme 4).
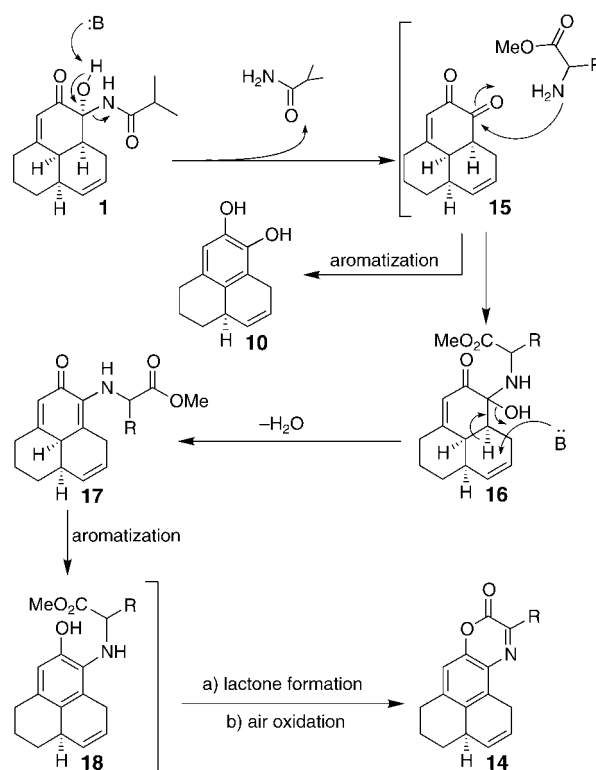
Scheme 4. Postulated mechanism for the cascade reactions that lead to polycyclic systems **14** from ketohydroxyamide **1** and amino acid derivatives.

Given the importance of N-heterocycles in medicinal chemistry,[5] we then turned our attention to the synthesis of pyrazines. The combination of ketohydroxyamide **1** with a number of 1,2-diamines led smoothly to complex polycyclic pyrazines ([Eq. (3)], Table 3, **19a – e**) in a highly efficient
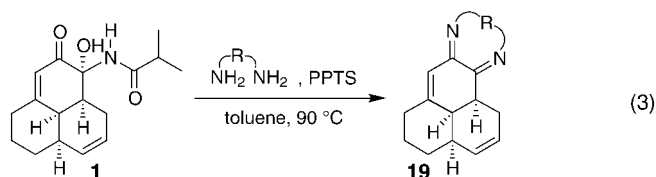
(3)

Table 3. Synthesis of polycyclic pyrazines from ketohydroxyamide **1**.[a]

Diamine	Product	Yield [%]
H₂N—CH₂CH₂—NH₂	**19a**	85
Ph / H₂N—CH(Ph)CH(Ph)—NH₂	**19b**	73
o-C₆H₄(NH₂)₂	**19c**	94
	19d	90
	19e	88

[a] Reagents and conditions: diamine (5 – 10 equiv), PPTS (0.2 equiv), toluene, 90 °C, 3 – 8 h.

manner (73 – 94 % yield). Additionally, by enlisting 1,2-amino alcohols in this reaction we were able to effect a unique heterocyclic spiroannulation reaction and obtain yet another series of novel heterocycles ([Eq. (4)]; Table 4, **3a – d**, **20a – d**; Table 5).
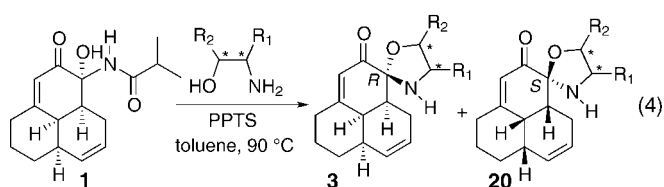
(4)

Table 4. Synthesis of complex spiroheterocycles from ketohydroxyamide **1** and 1,2-hydroxyamines.[a]

Amino alcohol	Products (Yield)	
MeO₂C—CH(S)—CH(R)(OH)—Me, NH₂	**3a**: (32%)	**20a**: (31%)
	3a': (12%)	**20a'**: (12%)
Ph—CH(R)(OH)—CH₂—NH₂	**3b**: (34%)	**20b**: (32%)
(S)-tBu—CH(NH₂)—CH₂OH	**3c**	**20c** (85%) (1:1)
indane amino alcohol	**3d**	**20d** (87%) (1:1)

[a] Reagents and conditions: Amino alcohol (3.0 equiv), PPTS (0.2 equiv), toluene, 90 °C, 6 – 24 h.

Finally, amino acid- and diamine-derived polycycles ([Eq. (2)], Table 2 and [Eq. (3), Table 3, respectively) could easily be dehydrogenated by heating in air at 100 °C in *N,N*-dimethylformamide or toluene (48 h), to furnish unusual polyaromatic systems such as **14d'** (95 % yield) and **19c'**.

In conclusion, we have demonstrated a new and highly productive mode of reaction of *o*-azaquinones, which can be derived from anilides and DMP, and explored its scope and generality. Through a series of cascade reactions that involve two previously unexplored chemical species (*o*-azaquinones and ketohydroxyamides), a number of complex natural

Table 5. Data for selected compounds: **1**, **2a**, **3a**, and **8**.

1: Colorless needles; m.p. 112 – 113 °C (hexane/Et$_2$O 2/1); R_f = 0.35 (silica gel, hexane/EtOAc 1:1); IR (film): $\tilde{v}_{max}$ = 3378, 2967, 2931, 2867, 1664, 1506, 1463, 1427, 1399, 1239, 1180, 1081, 1055, 754 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ = 7.20 (br s, D$_2$O exchangeable, 1H), 5.85 (t, J = 2.2 Hz, 1H), 5.66 – 5.61 (m, 1H), 5.46 (ddd, J_1 = 9.9 Hz, J_2 = 4.1 Hz, J_3 = 1.2 Hz, 1H), 4.82 (br s, D$_2$O exchangeable, 1H), 3.26 (ddd, J_1 = 11.0 Hz, J_2 = 7.0 Hz, J_3 = 4.0 Hz, 1H), 3.23 – 3.18 (m, 1H), 2.73 – 2.66 (m, 1H), 2.50 – 2.30 (m, 1H), 2.45 (sep, J = 7.0 Hz, 1H), 2.35 – 2.36 (m, 1H), 1.95 – 1.82 (m, 2H), 1.75 – 1.61 (m, 2H), 1.57 – 1.48 (m, 1H), 1.44 – 1.31 (m, 1H), 1.18 (d, J = 7.0 Hz, 3H), 1.17 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 191.8, 179.5, 167.9, 131.2, 126.3, 121.1, 84.0, 40.4, 36.7, 35.9, 34.7 (2 C), 30.5, 23.2, 20.4, 19.7, 19.0; HR-MS (MALDI-FTMS) calcd for C$_{17}$H$_{23}$NO$_3$Na [M+Na$^+$]: 312.1570, found: 312.1573

2a: Colorless plates; m.p. 206 – 208 °C (hexane/CH$_2$Cl$_2$); R_f = 0.29 (silica gel, hexane/EtOAc 1/1); IR (film): $\tilde{v}_{max}$ = 3347, 2919, 2847, 1655, 1592, 1519, 1477, 1452, 1384, 1332, 1241, 1159, 1123, 1093, 1027, 787 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 6.77 (s, 1H), 6.67 (bd, J = 7.9 Hz, 1H), 6.47 (bd, J = 7.9 Hz, 1H), 6.15 (br s, 1H), 6.09 (br s, D$_2$O exchangeable, 1H), 5.82 – 5.75 (m, 2H), 5.24 (br s, D$_2$O exchangeable, 1H), 4.70 (br s, D$_2$O exchangeable, 1H), 3.21 (dt, J_1 = 20.2 Hz, J_2 = 4.4 Hz, 1H), 3.10 – 3.00 (m, 1H), 2.96 (dd, J_1 = 20.2 Hz, J_2 = 8.3 Hz, 1H), 2.87 – 2.75 (m, 2H), 2.19 – 2.11 (m, 1H), 2.10 (s, 3H), 2.00 – 1.82 (m, 2H), 1.51 – 1.40 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 152.7, 141.7, 137.1, 135.5, 133.9, 132.4, 132.2, 129.0, 124.6, 123.2, 120.2, 115.3, 114.9, 112.8, 35.2, 30.4, 29.5, 26.6, 22.9, 21.0; HR-MS (MALDI-FTMS) calcd for C$_{20}$H$_{21}$NO$_2$ 308.1645 [M+H$^+$], found: 308.1646

3a: colorless cubes; m.p. 142 – 143 °C (hexanes/Et$_2$O); R_f = 0.49 (silica gel, hexane/EtOAc 1/1); [α]$_D$ = +139.7° (0.35, CHCl$_3$); IR (film) $\tilde{v}_{max}$ = 3283, 3017, 2929, 2862, 1740, 1678, 1437, 1374, 1239, 1202, 1147, 1086, 786 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.88 (t, J = 2.3 Hz, 1H), 5.71 – 5.63 (m, 1H), 5.46 (dq, J_1 = 10.0 Hz, J_2 = 2.0 Hz, 1H), 4.11 (br s, D$_2$O exchangeable, 1H), 3.77 (s, 3H), 3.58 (d, J = 8.6 Hz, 1H), 3.23 (br s, D$_2$O exchangeable, 1H), 3.80 (s, 3H), 3.74 – 3.63 (m, 1H), 3.46 (d, J = 9.0 Hz, 1H), 3.15 – 3.08 (m, 1H), 2.73 – 2.64 (m, 1H), 2.47 (bd, J = 15.5 Hz, 1H), 2.38 – 2.11 (m, 2H), 2.20 – 2.10 (m, 1H), 1.84 (dt, J = 13.2, 2.2 Hz, 1H), 1.75 – 1.53 (m, 5H), 1.46 – 1.36 (m, 1H), 1.35 (d, J = 5.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 194.2, 171.3, 167.8, 131.7, 127.6, 123.1, 96.8, 76.9, 66.5, 52.8, 42.6, 36.8, 34.9 (2 C), 30.7, 23.4, 20.5, 18.5; HR-MS (MALDI-FTMS) calcd for C$_{18}$H$_{23}$NO$_4$ [M+H$^+$]: 318.1700, found: 318.1698

8: Yellow oil; R_f = 0.51 (silica gel, hexane/EtOAc 2/1); IR (film): $\tilde{v}_{max}$ = 3330, 3028, 2969, 2932, 2873, 1688, 1668, 1613, 1504, 1467, 1385, 1318, 1157, 1099, 1026, 944, 884 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.89 (br s, D$_2$O exchangeable, 1H), 7.39 (s, 1H), 6.02 (dq, J_1 = 9.9 Hz, J_2 = 2.0 Hz, 1H), 5.47 (dq, J_1 = 9.9 Hz, J_2 = 3.2 Hz, 1H), 3.08 (dd, J_1 = 9.8 Hz, J_2 = 8.3 Hz, 1H), 2.60 – 2.49 (m, 2H), 2.25 – 2.13 (m, 3H), 2.00 (dd, J_1 = 12.9 Hz, J_2 = 8.5 Hz, 1H), 1.88 – 1.59 (m, 4H), 1.22 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 202.2, 198.3, 177.5, 138.3, 131.0, 124.0, 118.5, 59.7, 53.4, 45.7, 37.1, 35.8, 30.0, 26.0, 21.5, 19.4, 19.3; HR-MS (MALDI-FTMS) calcd. for C$_{17}$H$_{21}$NO$_3$ [M+H$^+$]: 288.1594, found: 288.1589

14d'   **19c'**
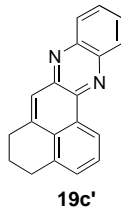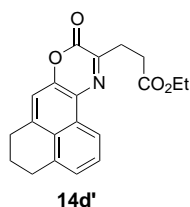
product like compounds are now readily accessible. A solid-phase version that uses ketohydroxyamides in a "heterocycle release" strategy[6] may expand the scope of the reported chemistry. Biological screening of the synthesized and projected compound libraries is expected to facilitate chemical biology studies and pharmaceutical research.

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Separation of Spliceosome Assembly from Catalysis with Caged pre-mRNA Substrates**

Steven G. Chaulk and Andrew M. MacMillan*

Pre-messenger RNAs (pre-mRNAs) in eukaryotes are characterized by a split-gene structure in which coding exon sequences are separated by noncoding intron sequences.[1] The process by which the introns are excised from the pre-mRNA and the exons are joined together is known as pre-mRNA splicing and is catalyzed by the spliceosome—a biochemical machine that contains both protein and RNA components.[2] The spliceosome includes the U1, U2, and U4/

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