

3222.32(8) Å³, $\rho_{\text{calcd}} = 1.29 \text{ g cm}^{-3}$, $2\theta_{\text{max}} = 52.3^\circ$, MoK α radiation ($\lambda = 0.71069 \text{ Å}$), ω scans, $T = -115^\circ\text{C}$, of 15644 measured reflections, 10891 were unique, and 8247 were observed (with $I > 3.00\sigma(I)$), data corrected for Lorentz and polarization effects, analyzed for agreement and absorption using XPREP with an empirical absorption correction using SADABS ($T_{\text{max}} = 0.78$, $T_{\text{min}} = 0.71$). The structure was solved by direct methods (SIR92) and developed by least-squares refinement against $|F|$. No. of parameters, 739; H atoms were calculated but not refined; $R = 0.032$, $R_w = 0.039$, GOF = 1.61.

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-153030 (3), CCDC-153031 (4), and CCDC-153749 ([Cp₂Zr(bpy)]). 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).

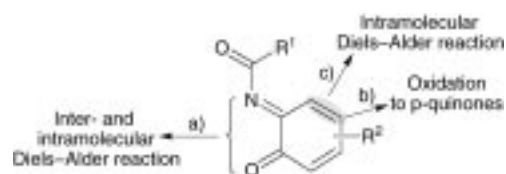
Received: January 12, 2001 [Z16411]

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

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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

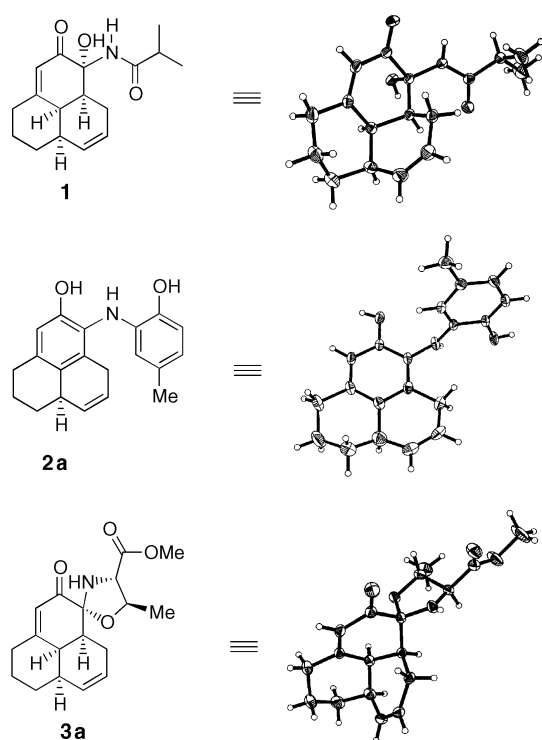


Scheme 1. Reactivity of *o*-azaquinones as versatile chemical entities. a) Participation in inter- and intramolecular Diels–Alder reactions (ref. [1a,f]), b) oxidation to *p*-quinones (ref. [1f]), and c) proposed intramolecular Diels–Alder reactions.

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 underexplored 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

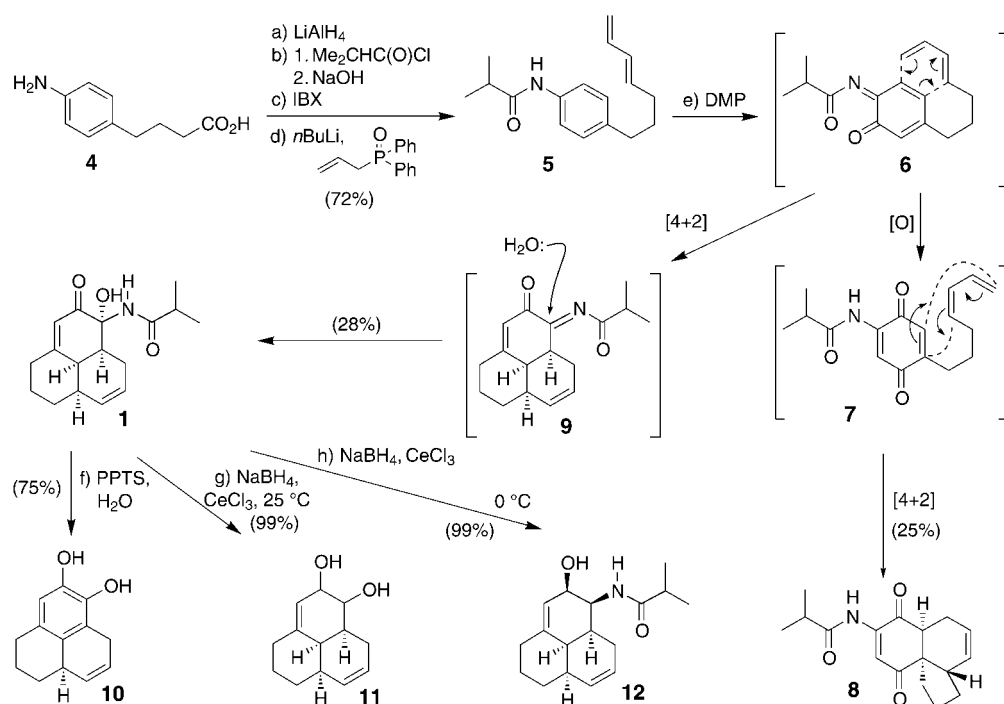
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[**] We thank Dr. D. H. Huang, G. Siuzdak, and Dr. R. Chadha for NMR spectroscopic, mass spectrometric, and X-ray crystallographic assistance, respectively. This work was supported financially by The Skaggs Institute for Chemical Biology, the National Institutes of Health (USA), a predoctoral fellowship from the National Science Foundation (P.S.B.), and grants from ArrayBiopharma, Pfizer, Glaxo, Merck, Schering Plough, Hoffmann–La Roche, Boehringer Ingelheim, Dupont, and Abbott Laboratories.



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]



Scheme 3. Rapid entry into complex pseudopterisins and elisabethin analogues from anilides and DMP. Reagents and conditions: a) LiAlH_4 (5.0 equiv), THF, $0 \rightarrow 25^\circ\text{C}$, 2 h, 96%; b) 1. $\text{Me}_2\text{CHC}(\text{O})\text{Cl}$ (3.0 equiv), Et_3N (4.0 equiv), CH_2Cl_2 , $0 \rightarrow 25^\circ\text{C}$, 1 h, 2. NaOH (1N, 3.0 equiv), MeOH , 50°C , 2 h, 95% for two steps; c) IBX (2.0 equiv), DMSO, 25°C , 6 h, 95%; d) $\text{Ph}_2\text{P}(\text{O})\text{CH}_2\text{CH}=\text{CH}_2$ (3.0 equiv), $n\text{BuLi}$ (2.5 equiv), HMPA (6.0 equiv), THF, -78°C , 20 min; then add aldehyde, $-78 \rightarrow 25^\circ\text{C}$, 14 h, 83%; e) DMP (4.0 equiv), H_2O (2.0 equiv), CH_2Cl_2 , 25°C , 3 h, 28% (**1**), 25% (**8**); f) PPTS (0.2 equiv), H_2O , 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.

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_2O (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 pseudoserin 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

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)]),

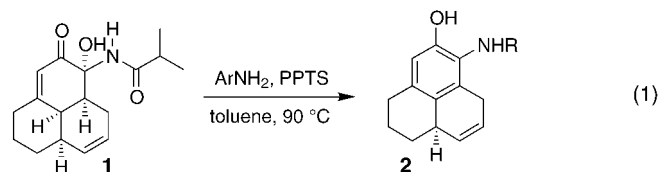
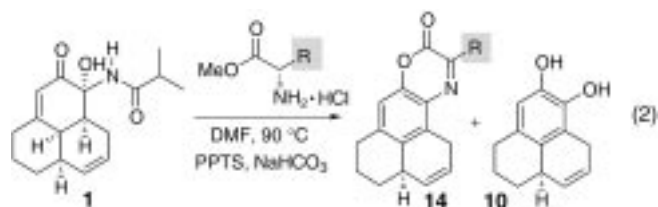


Table 1. Synthesis of polycyclic anilines from ketohydroxyamide **1**.^[a]

RNH ₂	Product	Yield [%]
		84
		71
		45 ^[b]
		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



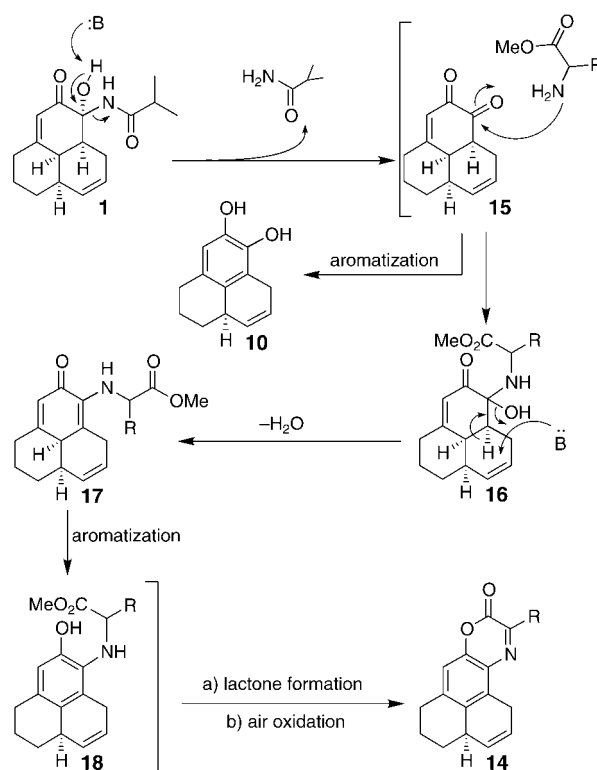
cascade reaction begins with the conversion of **1** into the corresponding diketone **15** after the expulsion of isobutyramide. This is followed either by the formation of diphenol **10** (after aromatization), or by addition of the amino group of the amino acid derivative to form intermediate **16**.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

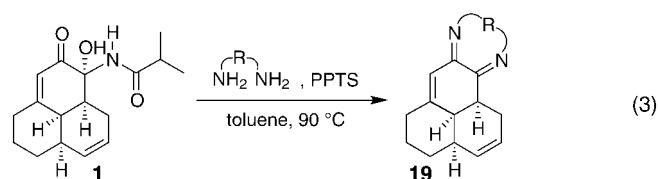


Table 3. Synthesis of polycyclic pyrazines from ketohydroxyamide **1**.^[a]

Diamine	Product	Yield [%]
		85
		73
		94
		90
		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).

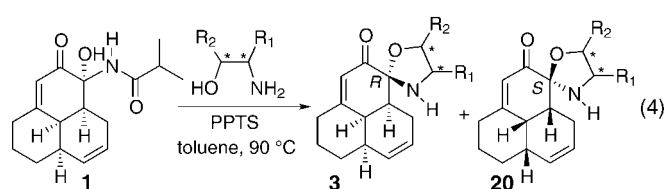


Table 4. Synthesis of complex spiroheterocycles from ketohydroxyamide **1** and 1,2-hydroxyamines.^[a]

Amino alcohol	Products (Yield)	

[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

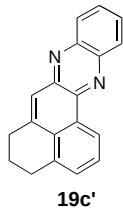
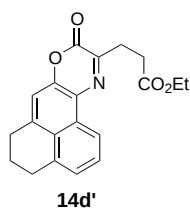
Table 5. Data for selected compounds: **1**, **2a**, **3a**, and **8**.

1: Colorless needles; m.p. 112–113 °C (hexane/Et₂O 2/1); R_f = 0.35 (silica gel, hexane/EtOAc 1:1); IR (film): $\tilde{\nu}_{\max}$ = 3378, 2967, 2931, 2867, 1664, 1506, 1463, 1427, 1399, 1239, 1180, 1081, 1055, 754 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 7.20 (br s, D₂O 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, D₂O 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); ¹³C NMR (125 MHz, CDCl₃): 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 C₁₇H₂₃NO₃Na [M +Na⁺]: 312.1570, found: 312.1573

2a: Colorless plates; m.p. 206–208 °C (hexane/CH₂Cl₂); R_f = 0.29 (silica gel, hexane/EtOAc 1/1); IR (film): $\tilde{\nu}_{\max}$ = 3347, 2919, 2847, 1655, 1592, 1519, 1477, 1452, 1384, 1332, 1241, 1159, 1123, 1093, 1027, 787 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): 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, D₂O exchangeable, 1H), 5.82–5.75 (m, 2H), 5.24 (br s, D₂O exchangeable, 1H), 4.70 (br s, D₂O 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₂₀H₂₁NO₂ 308.1645 [M +H⁺], found: 308.1646

3a: colorless cubes; m.p. 142–143 °C (hexanes/Et₂O); R_f = 0.49 (silica gel, hexane/EtOAc 1/1); [α]_D = +139.7° (0.35, CHCl₃); IR (film) $\tilde{\nu}_{\max}$ = 3283, 3017, 2929, 2862, 1740, 1678, 1437, 1374, 1239, 1202, 1147, 1086, 786 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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, D₂O exchangeable, 1H), 3.77 (s, 3H), 3.58 (d, J = 8.6 Hz, 1H), 3.23 (br s, D₂O 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₁₈H₂₃NO₄ [M +H⁺]: 318.1700, found: 318.1698

8: Yellow oil; R_f = 0.51 (silica gel, hexane/EtOAc 2/1); IR (film): $\tilde{\nu}_{\max}$ = 3330, 3028, 2969, 2932, 2873, 1688, 1668, 1613, 1504, 1467, 1385, 1318, 1157, 1099, 1026, 944, 884 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.89 (br s, D₂O 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₁₇H₂₁NO₃ [M +H⁺]: 288.1594, found: 288.1589



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.

Received: February 28, 2001 [Z16702]

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- To the best of our knowledge, there have been no reported synthetic studies of α,β -unsaturated ketohydroxyamides such as **1**, except for a brief study of the related 3-bromo-2-hydroxy-2-acetamidocyclohexanone, see: K. M. Ermolaev, V. I. Maimind, *Biol. Aktiv. Soedin.* **1968**, 142–146.
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- Crystallographic data (excluding structure factors) for the structures **1**, **2a**, and **3a** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-159145–159147. 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).

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

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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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[**] A.M.M. acknowledges support from the Natural Sciences and Engineering Research Council of Canada and the Alberta Heritage Foundation for Medical Research.