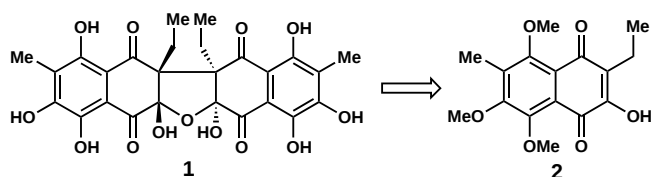


Total Synthesis of Hybocarpone**

K. C. Nicolaou* and David Gray

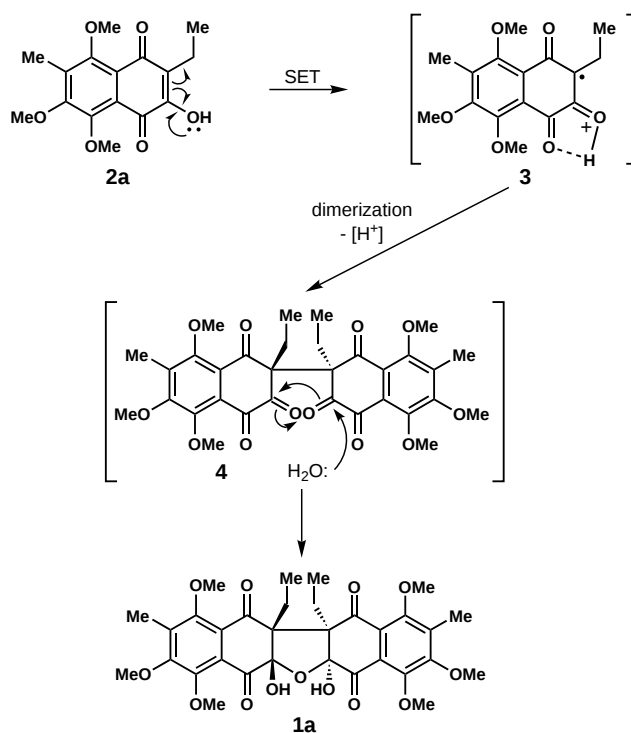
A recent report^[1] disclosed the isolation and structural elucidation of a novel naphthazarin-related natural product with a unique and unprecedented molecular architecture containing a dinaphtho[2,3-*b*:2,3-*d*]furan–tetraone skeleton. Termed hybocarpone (**1**, Scheme 1), this naturally occurring



Scheme 1. Structures of hybocarpone (**1**) and its postulated precursor, naphthazarin **2**.

substance was produced by mycobiont cultures derived from the lichen *Lecanora hybocarpa* and exhibited potent cytotoxic properties against the murine mastocytoma P815 cell line (IC_{50} value 0.15 mg mL^{-1}).^[1] Intrigued by the unique molecular structure and important biological activity of hybocarpone (**1**), we initiated a program directed towards its chemical synthesis. Herein we describe a short total synthesis of racemic **1** based on a dimerization–hydration cascade strategy that may bear resemblance to its biogenetic origins.

The C_2 -symmetric structure of hybocarpone (**1**) renders itself to an aesthetically pleasing retro dimerization disconnection, whereby naphthazarin **2** (Scheme 1) becomes a possible precursor. Crucial to the success of a synthetic strategy based on this premise are: 1) the construction of the highly hindered central carbon–carbon bond and 2) the setting of the relative configuration of the four stereogenic centers of **1** during the assembly process. A viable scenario for the dimerization of **2a** to **1a**, the hexamethylated derivative of **1**, is shown in Scheme 2. Thus, it was postulated that activation of a protected form of **2** (compound **2a**) via a single-electron transfer (SET) process could lead to the highly reactive cation radical species **3**, which may suffer dimerization and proton loss to afford the bridged system **4**. Spontaneous and selective hydration of the hexaketone intermediate **4**, as shown in



Scheme 2. Postulated dimerization–hydration cascade of naphthazarin **2a** to hybocarpone hexamethyl ether (**1a**) initiated by single-electron transfer (SET).

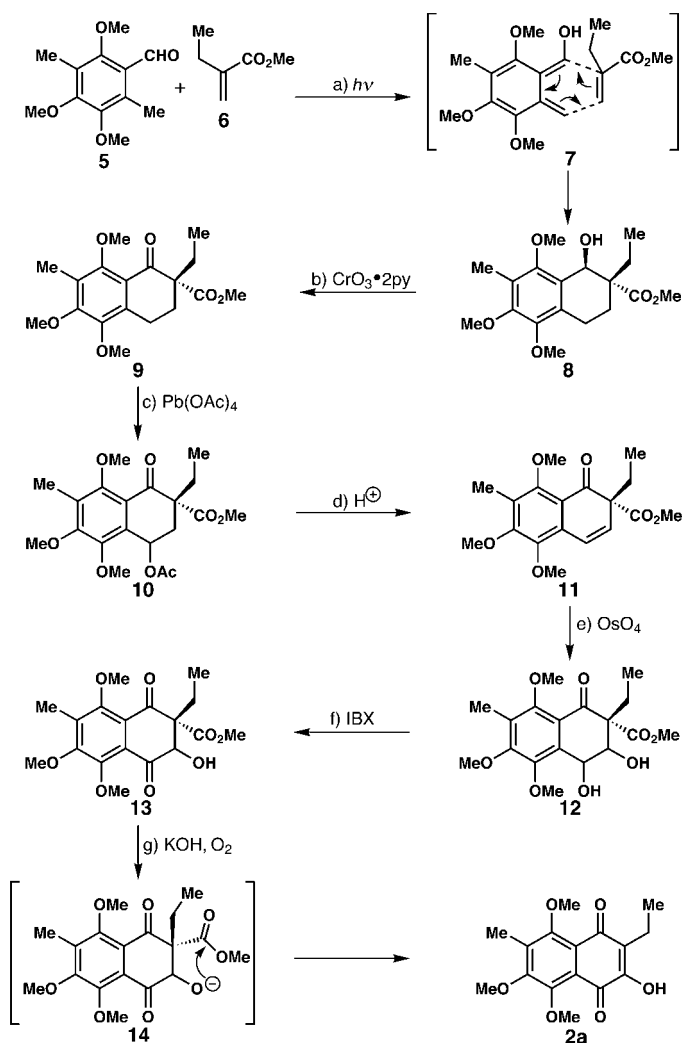
Scheme 2, could then furnish the desired hybocarpone framework **1a**. Only demethylation separates the latter compound from hybocarpone (**1**). The attractiveness of this simple and potentially economical strategy prompted a swift attempt at its laboratory execution.

In pursuing the total synthesis of **1** according to the above dimerization strategy, our first goal was defined as the construction of naphthazarin **2a** (Scheme 2), a monomeric species resembling previously isolated natural products.^[2] Scheme 3 summarizes the synthesis of **2a**. Thus, the known aromatic aldehyde **5**^[3] was irradiated with UV light in toluene in the presence of methyl 2-ethylacrylate (**6**),^[4] furnishing the fused bicyclic system **8** (via the presumed intermediacy of the orthoquinodimethane **7**) in 82% yield.^[5] Oxidation of the hydroxy group of **8** with $\text{CrO}_3 \cdot 2\text{py}$ in methylene chloride afforded ketone **9** (86% yield), which underwent selective acetoxylation with $\text{Pb}(\text{OAc})_4$ under UV light irradiation, leading to acetate **10** in 71% yield. Exposure of **10** to HCl in AcOH at 70°C gave olefin **11** in 72% yield, which was subjected to dihydroxylation with NMO/OsO_4 to afford the *vic*-diol **12** (92% yield, ca. 10:1 ratio of diastereomers, unassigned configuration). IBX oxidation of **12** led, chemoselectively, to hydroxyketone **13** (92% yield) which was treated with KOH in aqueous THF in the presence of air to afford, through a decarboxylation–oxidation sequence, the desired naphthazarin **2a** in 87% yield. The unusual rapidity of the last reaction suggests neighboring group participation in the ester hydrolysis step as indicated in structure **14**.

With naphthazarin **2a** at hand, we proceeded to investigate its dimerization through the proposed (Scheme 2) radical-

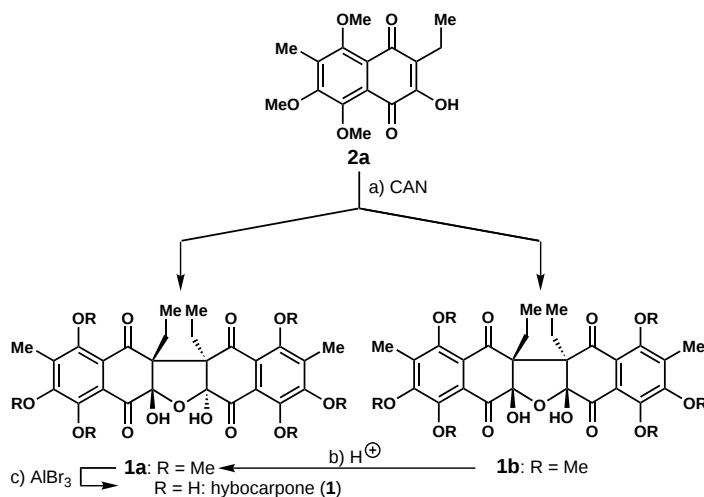
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Scheme 3. Synthesis of naphthazarin **2a**. Reagents and conditions: a) **6** (4.0 equiv), $h\nu$, toluene, 2 h, 82%; b) $\text{CrO}_3 \cdot 2\text{py}$ (8.0 equiv), CH_2Cl_2 , 0 $\rightarrow$ 25 $^\circ\text{C}$, 1 h, 86%; c) $\text{Pb}(\text{OAc})_4$ (1.4 equiv), $h\nu$, AcOH, 2 h, 71%; d) aqueous HCl, AcOH, 70 $^\circ\text{C}$, 30 min, 72%; e) OsO_4 (0.1 equiv), NMO (3.0 equiv), THF/*t*-BuOH/ H_2O /py (20:20:4:1), 12 h, 92%; f) IBX (3.0 equiv), DMSO, 20 $^\circ\text{C}$, 1 h, 92%; g) 1M KOH, H_2O /THF (3:1), air, 1 h, 87%. IBX = 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide, NMO = *N*-methylmorpholine *N*-oxide.

based mechanism. A search for suitable SET reagents led to the identification of CAN as an inducer of the desired coupling reaction, leading directly to a mixture of two isomeric hybocarpone derivatives **1a** and **1b** (ca. 3:2 ratio, 36% combined yield based on 60% recovered starting material; Scheme 4), which were chromatographically separated and spectroscopically characterized (see Table 1). Interestingly, the more complex ^1H NMR spectrum (CDCl_3 , 500 MHz) of the minor product **1b** was observed to undergo simplification as this apparently unfavorable isomer was transformed to the thermodynamically more stable isomer **1a**. The same transformation was observed when **1b** was exposed to AcOH in CHCl_3 (**1b** $\rightarrow$ **1a**, >95%). This acid-catalyzed transformation also confirmed the *trans* relationship of the two ethyl groups at the junction joining the two monomeric units of both isomers, an outcome predictable on the basis of severe steric congestion within the *cis* isomer.



Scheme 4. Final steps of the total synthesis of hybocarpone (**1**). Reagents and conditions: a) CAN (1.0 equiv), degassed acetonitrile, then **2** in acetonitrile, $-35 \rightarrow 0$ $^\circ\text{C}$, 3 min; then 5M aqueous KOH, 0 $\rightarrow$ 25 $^\circ\text{C}$, 10 min, 36% based on 60% recovered starting material, **1a:1b** (ca. 3:2); b) CDCl_3 , 48 h; or AcOH, 10 min, >95%; c) AlBr_3 (1M in CH_2Br_2 , 28 equiv), EtSH/ CH_2Cl_2 (1:1.5), 0 $^\circ\text{C}$, 1 h, 60%. CAN = ceric ammonium nitrate.

Table 1. Selected data for compounds **2a**, **1a**, and **1**.

2a : yellow solid; R_f = 0.3 (silica gel, hexane/EtOAc 2:1 with 1% AcOH); m.p. 106–108 $^\circ\text{C}$ (CH_2Cl_2); IR (film) $\tilde{\nu}_{\text{max}}$ = 3351, 2928, 1646, 1460, 1402, 1351, 1285, 1127 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ = 7.39 (s, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.83 (s, 3H), 2.57 (q, J = 7.7 Hz, 2H), 2.28 (s, 3H), 1.13 (t, J = 7.7 Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ = 184.1, 180.8, 157.5, 156.6, 152.0, 151.1, 137.3, 125.6, 121.9, 121.6, 61.6, 61.5, 61.2, 17.2, 13.0, 10.4; HR-MS (MALDI): calcd for $\text{C}_{16}\text{H}_{19}\text{O}_6^+$ [$M+H^+$] 307.1176, found 307.1181
1a : colorless solid; R_f = 0.15 (silica gel, hexane/EtOAc 2:1); m.p. 210–212 $^\circ\text{C}$ (CH_2Cl_2); IR (film) $\tilde{\nu}_{\text{max}}$ = 3388, 2938, 1690, 1559, 1462, 1322, 1117, 1036 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz): δ = 5.11 (s, 2H), 3.95 (s, 6H), 3.92 (s, 6H), 3.81 (s, 6H), 2.36 (dq, J = 12.8, 7.4 Hz, 2H), 2.31 (s, 6H), 1.88 (dq, J = 12.8, 7.4 Hz, 2H), 0.59 (t, J = 7.4 Hz, 6H); ^{13}C NMR (CDCl_3 , 150 MHz): δ = 192.9, 192.0, 157.8, 155.9, 149.4, 136.6, 128.1, 123.8, 101.84, 70.0, 62.7, 62.1, 61.6, 26.5, 11.1, 10.5; HR-MS (MALDI): calcd for $\text{C}_{32}\text{H}_{36}\text{O}_{13}$ [$M+Na^+$] 651.2048, found 651.2041
1 : orange prisms; m.p. 169–170 $^\circ\text{C}$ (EtOH/ H_2O) (ref. [1]); m.p. 167–168 $^\circ\text{C}$; HPLC: t_{ret} = 23.3 min (0 $\rightarrow$ 100% acetonitrile in water (1% trifluoroacetic acid) over 30 min, 3.5 mL min $^{-1}$, VYDAC C18-reverse-phase column); IR (KBr) $\tilde{\nu}_{\text{max}}$ = 3442, 2965, 1650, 1634, 1595, 1460, 1440, 1362, 1282, 1207, 1134, 1074, 1040, 1012 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz): δ = 13.13 (s, 2H), 10.96 (s, 2H), 6.43 (brs, 2H), 4.79 (s, 2H), 2.63 (dq, J = 14.9, 7.3 Hz, 2H), 2.33 (dq, J = 14.9, 7.3 Hz, 2H), 2.28 (s, 6H), 0.68 (t, J = 7.3 Hz, 6H); ^{13}C NMR (CDCl_3 , 125 MHz): δ = 198.5, 193.4, 157.8, 150.2, 143.5, 123.3, 108.6, 107.7, 99.5, 67.3, 25.2, 10.5, 8.9; HR-MS (MALDI): calcd for $\text{C}_{26}\text{H}_{25}\text{O}_{13}^-$ [$M-H^-$] 543.1144, found 543.1154

Molecular mechanics calculations on all six possible diastereomers of the hybocarpone skeleton revealed that, indeed, **1a** was the thermodynamically most stable (in terms of strain energy) isomer. The generation of hybocarpone (**1**) from its hexamethylated derivative **1a** was effected by exposure to $\text{AlBr}_3/\text{EtSH}$ in methylene chloride at 0 $^\circ\text{C}$ (60% yield). Synthetic **1** exhibited identical spectral data (^1H and ^{13}C NMR) to those reported for natural hybocarpone.^[1, 6]

In conclusion, an expedient strategy for the construction of the hybocarpone (**1**) molecular architecture has been devised and executed, producing the title compound in racemic form. This radical-based dimerization approach, or a closely related

variant of it, may not be too dissimilar to the pathway adopted by nature in the biosynthesis of this natural product. Studies to further elucidate the mechanism of the postulated oxidative dimerization process and the application of the developed chemistry to the construction and biological evaluation of hybocarpone libraries are in progress.

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 [6] Our attempts to obtain an authentic sample of **1** have so far been unsuccessful.

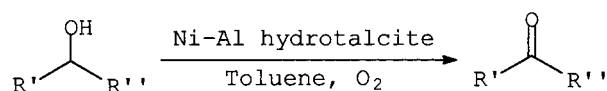
The First Example of Activation of Molecular Oxygen by Nickel in Ni-Al Hydrotalcite: A Novel Protocol for the Selective Oxidation of Alcohols**

B. M. Choudary,* M. Lakshmi Kantam, Ateeq Rahman, Ch. Venkat Reddy, and K. Koteswara Rao

The oxidation of α -ketols as well as allylic and benzylic alcohols to a carbonyl functionality is the foundation of many important current industrial and fine-chemical processes. Several methods are available to effect this conversion and continuous attention is drawn to newer and selective methods of oxidation.^[1] Catalytic oxidation with molecular oxygen is particularly attractive from an economical and environmental point of view.^[2] The oxidation of alcohols employing molec-

ular oxygen requires co-oxidants such as aldehydes, *N*-hydroxyphthalimide, diethyl azodicarboxylate, hydroquinone, or nitrosonium ions to accomplish the catalytic cycle with catalysts based on Ru and Co,^[3] Cu,^[4] and Zr,^[5] while molecular oxygen as the sole oxidant is sufficient when catalysts based on Pt,^[6] Rh,^[7] Pd,^[8] Ru,^[9] Co,^[10] V,^[11] and Os^[12] are used. To the best of our knowledge no report is available in the literature in regard to the activation of molecular oxygen by a nickel catalyst.

The use of heterogeneous catalysts in the liquid phase offers several advantages over homogeneous ones, such as ease of recovery and recycling, atom utility, and enhanced stability in the oxidation of alcohols. Layered double hydroxides (LDHs) or hydrotalcite-like compounds (HTLCs) have recently received much attention as basic catalysts.^[11] We report herein the first direct activation of molecular oxygen by nickel in Ni-Al hydrotalcite as demonstrated by the selective oxidation of various kinds of α -ketols as well as benzylic and allylic alcohols (Scheme 1) at atmospheric pressure. Incidentally, this is also the first report of the selective oxidation of α -ketols by a solid oxidant catalyst.



Scheme 1. Oxidation of allylic and benzylic alcohols in the presence of molecular oxygen.

In order to identify and develop the best Ni catalyst for the activation of molecular oxygen, a study on various hydrotalcite catalysts of different Ni:Al ratios (prepared^[12] by different coprecipitation agents) and Ni: γ -Al₂O₃ in the oxidation of 4-nitrobenzyl alcohol with molecular oxygen was undertaken (Table 1). A series of hydrotalcites containing different ratios of Ni:Al, such as 2:1, 2.5:1, and 3:1, were screened and cat. **A** (Ni:Al 2:1) was found to be the most active. The calcined and rehydrated forms of the hydrotalcite cat. **A** were further evaluated in the oxidation reactions. The activity of the calcined catalyst was considerably reduced, whereas the activity was slightly lowered on rehydration. Hydrotalcite cat. **B** (Ni:Al 2:1) was prepared by an ammonia

Table 1. Oxidation of 4-nitrobenzyl alcohol by different nickel catalysts using molecular oxygen.^[a]

Entry	Catalyst	Time [h]	Yield [%] ^[b]	Specific activity [mmol g ⁻¹ h ⁻¹] ^[c]
1	Ni-Al HTLC (2:1, cat. A)	6	98	0.65
2	Ni-Al HTLC (2:1, rehydrated)	6	80	0.53
3	Ni-Al HTLC (2.5:1)	6	78	0.51
4	Ni-Al HTLC (3:1)	6	37	0.24
5	Ni-Al HTLC (2:1, calcined)	21	58	0.11
6	Ni-Al (cat. B)	20	47	0.09
7	Ni: γ -Al ₂ O ₃ (2 %)	20	no reaction	–
8	Ni: γ -Al ₂ O ₃ (5 %)	20	no reaction	–
9	Ni: γ -Al ₂ O ₃ (10 %)	20	no reaction	–

[a] All reactions were performed with 2 mmol of substrate in 10 mL of toluene using 0.5 g of catalyst under oxygen at 90 °C in the specified time. [b] Yields after column chromatography. [c] Specific activity: mmol of product obtained per gram of catalyst per hour.

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