Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 2136–2138
Tetrahedron Letters

Synthesis of the pentacyclic core of lihouidine

Ken S. Feldman *, Adiel Coca

Chemistry Department, The Pennsylvania State University, University Park, PA 16802, USA

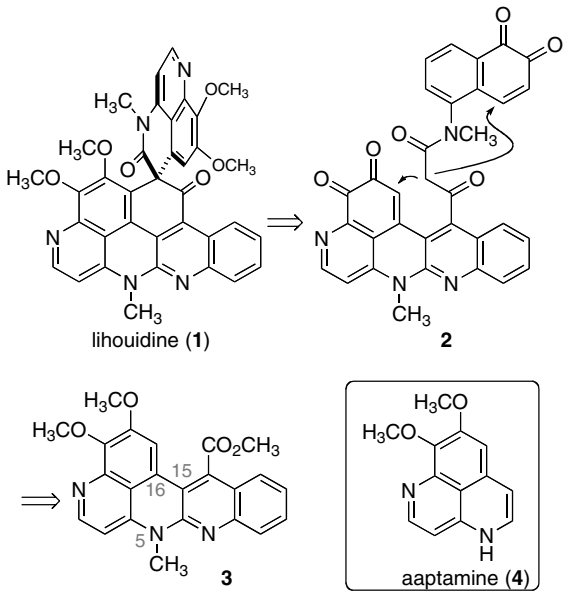
Received 6 December 2007; revised 16 January 2008; accepted 24 January 2008
Available online 1 February 2008

Abstract

The pentacyclic base of the sponge-derived alkaloid lihouidine has been assembled from two quinoline fragments. The key step is a nitration-promoted cyclization to form the C–C bond between the two quinoline units.

The bright red *Suberea* sponge metabolite lihouidine (**1**) possesses a stereogenic center but was isolated as a racemate.[1] A biosynthetic hypothesis, based on speculation by Bowden et al.,[1] that accounts for this unusual observation is illustrated in **2**, where spontaneous, successive Michael-type additions of the β-dicarbonyl's (deprotonated) nucleophilic methylene carbon into the adjacent electrophilic orthoquinone moieties may occur outside of a chiral environment. A reduced (catecholic) version of **2** might be traced back to two molecules of aaptamine (**4**). We have initiated a synthesis project to test this premise. Our route passes through the pentacyclic platform **3**, and the concise synthesis of this key intermediate is described in Scheme 1.

The synthesis strategy for **3** was predicated on intramolecularly forging the key C(15)–C(16) bond uniting the two quinoline units from a precursor bearing quinolines already linked through N(5). To implement this strategy, assembly of quinoline building blocks **10** and **13** was achieved as described in Scheme 2. Chloride **9** is a known compound, prepared from **6** and methyl propiolate,[2] but substitution of the Meldrum's acid derivative **7**[3] for the alkyne electrophile led to isolated yields of **9** that were superior to those achieved with the earlier chemistry. Heating **9** and methylamine in a sealed tube effected nucleophilic aromatic substitution of $NH(CH_3)$ for Cl much more efficiently than



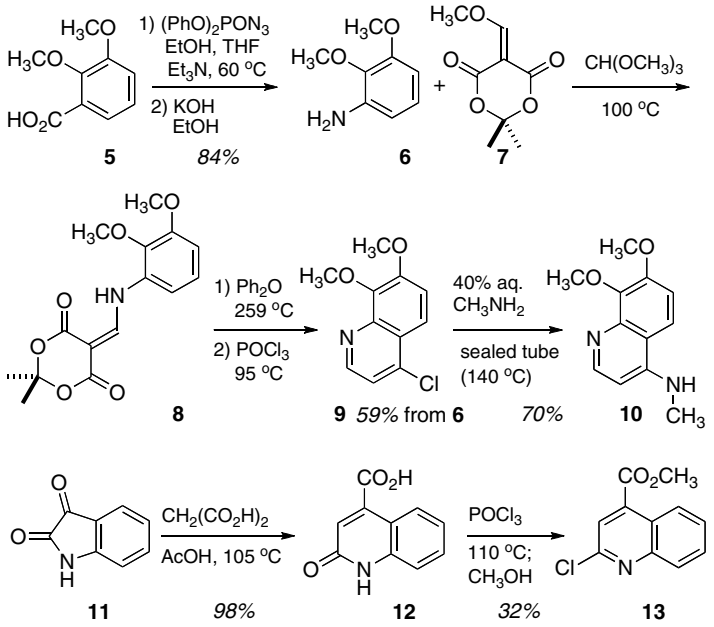
Scheme 1. Lihouidine biomimetic retrosynthesis.

with either lower temperature conditions or with microwave irradiation. With quinoline **10** in hand, synthesis of the second quinoline coupling partner, **13**, from isatin (**11**) was accomplished by modification of the method reported by Vargas.[4]

A Buchwald–Hartwig-type coupling[5] between amine **10** and chloride **13** proceeded after much optimization to furnish the desired *bis* quinoline cyclization substrate **14**

* Corresponding author. Tel.: +1 814 863 4654; fax: +1 814 863 5319.
E-mail address: ksf@chem.psu.edu (K. S. Feldman).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.01.118



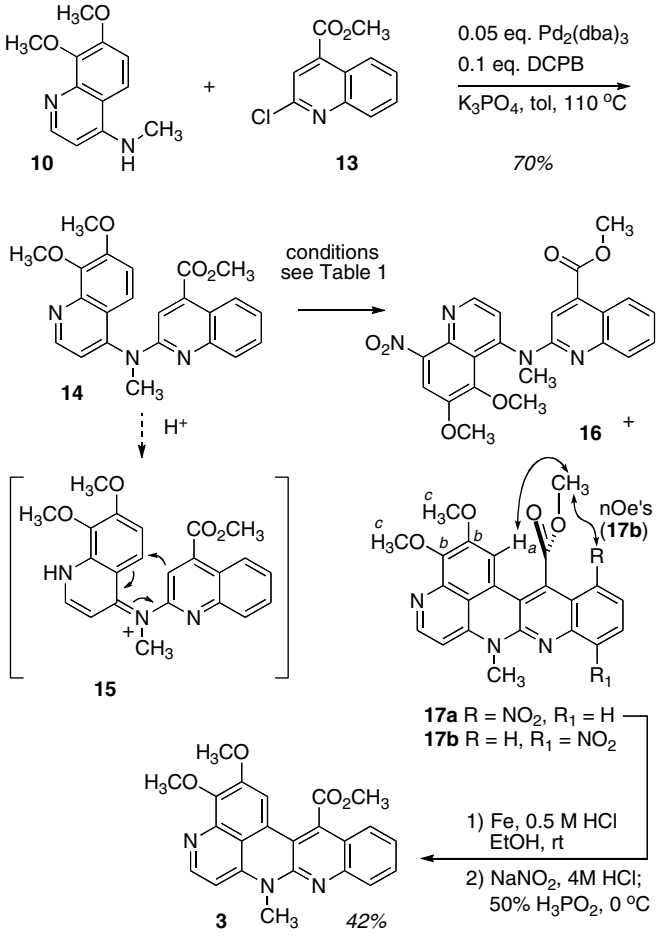
Scheme 2. Preparation of the two quinoline building blocks.

in good yield. The original plan for inducing oxidative cyclization within **14** involved protonation of the 'DMAP'-type moiety to generate, at least transiently, a cationic system **15** that might participate in a 6π electrocyclization followed by rearomatization via air oxidation. However, exhaustively screening acids in search of this reactivity was not rewarded–no evidence of C–C bond formation was detected under either thermal or photochemical conditions. These trials were met with either recovery of intact **14**, or substrate destruction without the formation of any characterizable products. In the course of these experiments, an attempt at substrate nitration with the classic reagent combination HNO_3/H_2SO_4 led to a singular result; formation of discrete products upon consumption of **14** (Table 1, entry 1). Separation of three compounds from this reaction mixture and subsequent spectroscopic characterization[6] led to the assignments **16**, **17a**, and **17b**. A diagnostic proton signal H_a in the ^1H NMR spectrum of **17a** occurred as a *singlet* at δ 7.54 ppm. This proton's assignment was confirmed by an HMBC correlation to the carbons labeled *b* in **17**, which in turn were identified by their HMBC correlations to the protons *c* of the methoxy units. The regiochemical assignment of the nitro group position in **17b** was based upon the NOE's shown in Scheme 3. The regiochemistry of **17a** nitration then was assigned by default as the other

Table 1
Results of the nitration of *bis* quinoline **14**

Entry	Conditions	**16** (%)	**17a** (%)	**17b** (%)
1	HNO_3, H_2SO_4, 0 °C	10	31	9
2	KNO_3, H_2SO_4, 0 °C	8	14	5
3	Bu_4NNO_3, $(F_3CCO)_2O$, 0 °C→rt	71	—	—
4	NO_2BF_4, sulfolane, rt	—	—	—
5	Fuming HNO_3, CH_3SO_3H, rt	—	22	5
6	Fuming HNO_3, 0 °C	12	52	—

All yields reported are for chromatographically pure material.



Scheme 3. Completion of pentacycle **3** synthesis.

possible isomer. Nitration of one of the quinoline rings occurred in each product, but for the first time, products featuring the key C(15)–C(16) bond were detected. Optimization studies (Table 1) led to the conclusion that the best yield of the cyclized material **17** could be achieved by treatment with undiluted fuming nitric acid (entry 6). The mechanistic course of this transformation remains a matter of speculation, as the central question of whether nitration precedes or follows C(15)–C(16) bond formation is unknown. The role of an electrocyclization (cf. **15**) in this C–C bond formation cannot be ascertained at present.

The desired pentacyclic target **3** could be derived from **17a**, or equally efficiently, from **17a**/**17b** mixtures, by two simple operations. Initial reduction of the nitro function with Fe metal led to an intermediate amine that was not isolated. This compound(s) immediately was converted to an intermediate diazonium product(s) en route to the parent hydrocarbon via H_3PO_2-mediated reductive cleavage of nitrogen. Thus, compound **3** was available in 10 steps from the commercially available **5**. Studies to convert **3** into a β-ketoamide precursor to *bis* orthoquinone **2**, and thence to lihouidine, are ongoing.

Acknowledgment

Support from the National Institutes of Health, General Medical Sciences Division (GM37681), is gratefully acknowledged.

References and notes

1. Bowden, B. F.; McCool, B. J.; Willis, R. H. *J. Org. Chem.* **2004**, *69*, 7791–7793.
2. Kelly, T. R.; Maguire, M. P. *Tetrahedron* **1985**, *41*, 3033–3036.
3. Walz, A. J.; Sundberg, R. J. *J. Org. Chem.* **2000**, *65*, 8001–8010.
4. Torres, J. C.; Pilli, R. A.; Vargas, M. D.; Violante, F. A.; Garden, S. J.; Pinto, A. C. *Tetrahedron* **2002**, *58*, 4487–4492.
5. (a) Guram, A.; Rennels, R.; Buchwald, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348–1350; (b) Louie, J.; Hartwig, J. *Tetrahedron Lett.* **1995**, *36*, 3609–3612.
6. Compound **14**: orange solid. Mp 116–118 °C; IR (CH_2Cl_2) 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.01 (d, $J = 4.6$ Hz, 1H), 8.42 (dd, $J = 8.5$, 0.9 Hz, 1H), 7.91 (d, $J = 8.1$ Hz, 1H), 7.66 (ddd, $J = 8.3$, 7.0, 1.3 Hz, 1H), 7.61 (d, $J = 9.3$ Hz, 1H), 7.38 (ddd, $J = 8.3$, 7.0, 1.2 Hz, 1H), 7.32 (d, $J = 9.3$ Hz, 1H), 7.23 (d, $J = 4.6$ Hz, 1H), 6.92 (s, 1H), 4.22 (s, 3H), 4.05 (s, 3H), 3.82 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 156.7, 152.9, 152.4, 151.8, 149.3, 146.5, 144.4, 137.2, 130.8, 128.2, 126.1, 124.9, 122.4, 120.9, 119.7, 118.3, 116.5, 114.2, 62.6, 57.5, 53.2, 39.8; ESCI *m*/*z* (relative intensity) 404.2 (M+H, 100%), 426.1 (M+Na, 12%); HRMS calcd for $C_{23}H_{21}N_3O_4$ (M+H) 404.1610, found 404.1596.
Compound **16**: Mp 161–164 °C; IR (thin film) 1727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.04 (d, $J = 4.6$ Hz, 1H), 8.50 (d, $J = 8.2$ Hz, 1H), 7.79 (d, $J = 8.3$ Hz, 1H), 7.61 (t, $J = 7.7$ Hz, 1H), 7.58 (s, 1H), 7.37 (t, $J = 7.7$ Hz, 1H), 7.30 (d, $J = 4.6$ Hz, 1H), 7.16 (s, 1H), 4.25 (s, 3H), 4.02 (s, 3H), 3.88 (s, 3H), 3.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 154.8, 152.5, 150.0, 149.9, 148.1, 146.3, 145.3, 142.3, 136.4, 129.8, 127.7, 125.3, 124.5, 120.7, 120.6, 114.8, 113.4, 112.1, 62.2, 57.1, 52.4, 39.2; ESCI *m*/*z* (relative intensity) 449.2 (M+H, 100%), 471.2 (M+Na, 12%); HRMS calcd for $C_{23}H_{19}N_3O_4$ (M+H) 449.1461, found 449.1440.
Compound **17a**: Mp 68–70 °C. IR (CH_2Cl_2) 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.47 (d, $J = 2.5$ Hz, 1H), 9.03 (d, $J = 4.5$ Hz, 1H), 8.31 (dd, $J = 9.2$, 2.5 Hz, 1H), 7.76 (d, $J = 8.9$ Hz, 1H), 7.54 (s, 1H), 7.28 (d, $J = 4.5$ Hz, 1H), 4.22 (s, 3H), 3.95 (s, 3H), 3.85 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 157.0, 152.7, 151.3, 150.3, 148.4, 146.7, 145.4, 143.8, 142.0, 137.5, 128.8, 123.9, 123.1, 121.2, 119.3, 114.9, 114.4, 112.6, 62.5, 57.3, 53.0, 39.4; ESI *m*/*z* (relative intensity) 447.1 (M+H, 100%), 404.2 (M−CO_2, 34%); HRMS calcd for $C_{23}H_{18}N_4O_6$ (M+H) 447.1305, found 447.1291.
Compound **17b**: Mp 162 °C (dec); IR (thin film)1726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.72 (d, $J = 5.2$ Hz, 1H), 8.52 (d, $J = 2.4$ Hz, 1H), 8.41 (dd, $J = 9.2$, 2.4 Hz, 1H), 7.90 (d, $J = 9.2$ Hz, 1H), 7.58 (s, 1H), 6.69 (d, $J = 5.3$ Hz, 1H), 4.19 (s, 3H), 4.18 (s, 3H), 4.04 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 152.5, 151.1, 148.9, 144.5, 144.3, 135.9, 130.0, 128.8, 127.7, 124.3, 121.5, 121.2, 121.1, 116.9, 115.5, 113.8, 109.8, 100.8, 61.7, 57.0, 53.7, 31.4; ESCI *m*/*z* (relative intensity) 447.1 (M+H, 100%); HRMS calcd for $C_{23}H_{18}N_4O_6$ (M+H) 447.1305, found 447.1308.
Compound **3**: IR (CH_2Cl_2) 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, $J = 5.3$ Hz, 1H), 7.86 (d, $J = 8.4$ Hz, 1H), 7.66 (ddd, $J = 8.2$, 6.9, 1.2 Hz, 1H), 7.59 (d, $J = 8.3$ Hz, 1H), 7.56 (s, 1H), 7.41 (ddd, $J = 8.1$, 7.0, 1.1 Hz, 1H), 6.59 (d, $J = 5.3$ Hz, 1H), 4.14 (s, 3H), 4.13 (s, 3H), 4.03 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 152.3, 152.0, 148.5, 146.3, 146.2, 143.7, 143.4, 135.1, 130.6, 127.7, 125.6, 124.3, 122.4, 122.3, 115.4, 114.7, 108.4, 99.8, 61.5, 56.9, 53.2, 31.0; ESCI *m*/*z* (relative intensity) 402.1 (M+H, 100%); HRMS calcd for $C_{23}H_{19}N_3O_4$ (M+H) 402.1454, found 402.1477.