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A General Approach to Angucyclines: Synthesis of Hatomarubigin A, Rubiginone B2, Antibiotic X-1488E, 6-Hydroxytetrangulol, and Tetrangulol

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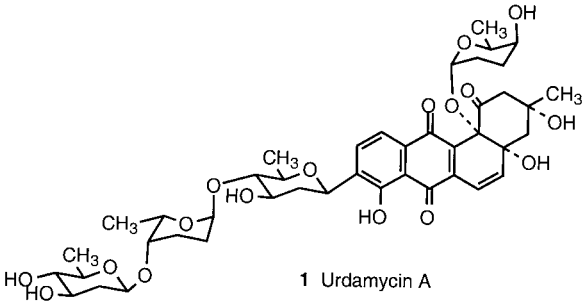
Abstract—Hatomarubigin A was prepared in 41% yield in a single procedure from acyl naphthoquinone **15** and 5-methylcyclohexane-1,3-dione (**16**). The net reaction consists of Michael addition to an acyl quinone followed by intramolecular aldol condensation. Hatomarubigin A then served as a common intermediate in syntheses of the angucyclinone antibiotics rubiginone B2, antibiotic X-1488E, 6-hydroxytetrangulol, and tetrangulol.

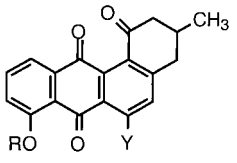
Introduction

The angucyclines and angucyclinones are natural products which have structures based on the benz(a)anthracene ring system.[1] All of the known angucyclines (structures which bear hydrolyzable sugars) and all of the known angucyclinones (which do not) are produced by *Actinomycetes*.[2] In general, the structurally elaborate angucyclines, for example the urdamycins (see urdamycin A, **1**),[2,3] show anticancer activity as well as general antibacterial activity. The simple angucyclinones show activity against Gram-positive bacteria. Members of both classes show other specific activities as well.



1 Urdamycin A

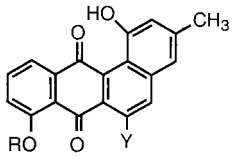
A comprehensive program for synthesis of the angucyclines and angucyclinones might be designed around an appropriately functionalized benz(a)anthracene derivative if such a compound were readily available. We considered Hatomarubigin A (**2**) to have the desired structural features of a common synthetic intermediate for numerous members of these classes. In addition, we realized that the closely related natural products **3**–**7** might be derived from Hatomarubigin A and that one or more of these might prove to be a useful intermediate for more functionally complex targets.



2 R = Me, Y = OH
Hatomarubigin A

3 R = Me, Y = H
Rubiginone B2

4 R = H, Y = H
Ochrimycinone



5 R = H, Y = OH
Dehydrorabelomycin
(6-Hydroxytetrangulol)

6 R = Me, Y = H
X-14881 E

7 R = H, Y = H
Tetrangulol

Previously reported syntheses of the angucyclinone natural products include schemes based on a relatively unexploited radical trapping procedure,[4] on Diels–Alder reactions,[5] on directed orthometallation,[6] on a biomimetic polyketide condensation,[7] and on acyl anion equivalent chemistry.[8] Like Kraus and Wu[9] who reported the synthesis of 3-deoxyrabelomycin, we recognized that the functionalized, angularly fused tetracyclic ring system might be available by manipulation of the condensation product of an acyl naphthoquinone and a 1,3-cyclohexanedione or its equivalent. Our experience (Scheme 1)[10] taught that the adducts of quinones and β-ketoesters (see **11**) were subject to dehydrative aromatization to benzofurans (see **10**) but that these seemingly stable compounds could be converted by Dieckmann condensation followed by oxidative cleavage to

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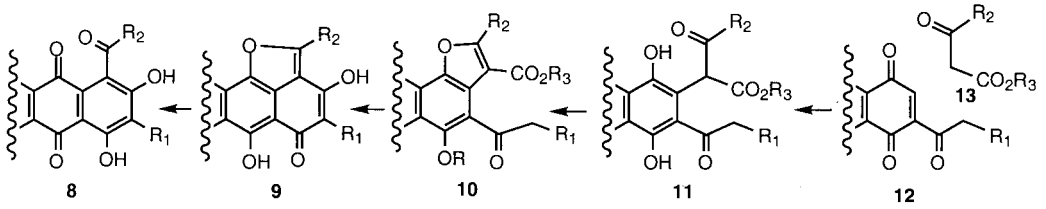
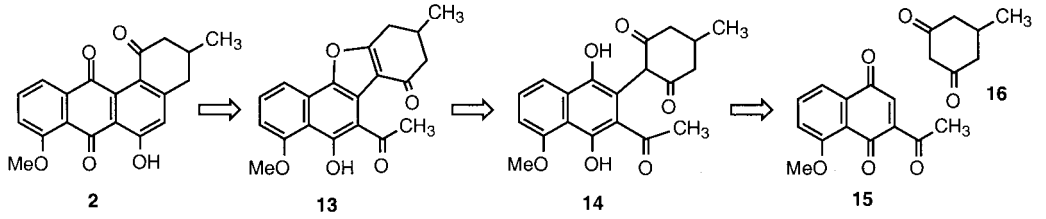


Scheme 1. Quinone annelation with β-keto esters.



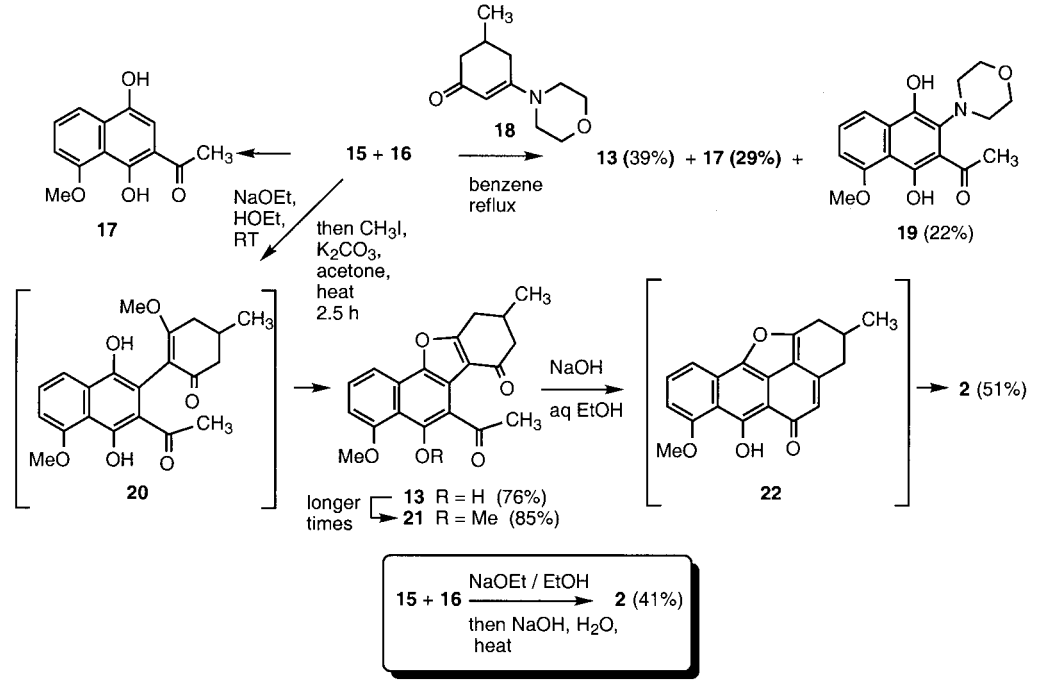
Scheme 2. Proposed strategy for hatamaubigin A synthesis.

acyl substituted, annelated quinone products (**10**→**9**→**8**). We imagined (Scheme 2) that the appropriate β-diketone/acyl naphthoquinone adduct might be converted, by similar chemistry, to Hatomarubigin A (see **2**⇒**13**⇒**14**⇒**15**+**16**).

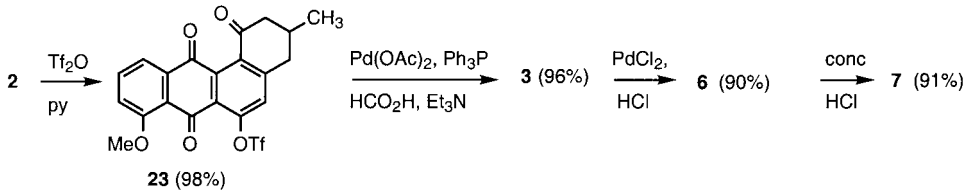
Exploration of this approach was rewarding in that a synthesis based on this original concept proceeded in good overall yield. Furthermore, we developed a one-pot synthesis of Hatomarubigin A from quinone **15** and dione **16**. Hatomarubigin A was then converted to Rubiginone B2 (**3**) and to dehydrorabelomycin (**5**). Finally, dehydrorabelomycin was converted to antibiotic X-14881 E (6-hydroxytetrangulol, **6**) and to Tetrangulol (**7**).

Results

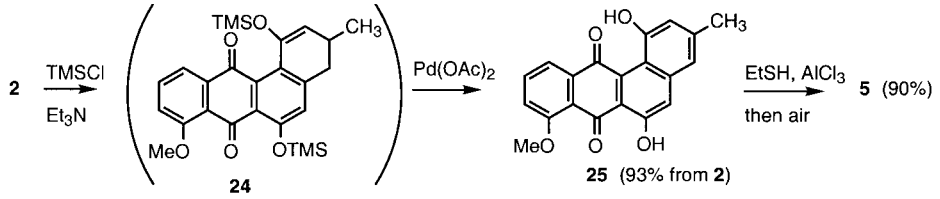
Successful addition of 1,3-cyclohexanedione **16** to the acyl naphthoquinone **15**[11] required some experimentation (see Scheme 3). Eugster had shown that 2-acetyl benzoquinone added cyclohexanediones upon mixing.[12] However, addition of dione **16** to naphthoquinone **15** provided the simple reduction product **17** as the only isolated material. Addition of enaminone **18** to quinone **15** gave naphthofuran **13** directly in 39% yield along with reduction product **17** (29%) and the morpholine adduct **19** (22%). A promising mixture was obtained from addition of diketone **16** to quinone **15** in ethanol containing some ethoxide. The



Scheme 3. Synthesis of hatamarubigin A (**2**).



Scheme 4. Synthesis of rubiginone (**3**), X-14881 E (**6**), and tetrangulol (**7**).



Scheme 5. Synthesis of dehydrorabelomycin (**5**).

crude product appeared to be the cyclic hemiketal but was not characterizable. Treatment of this material with methyl iodide and potassium carbonate in refluxing acetone for 2 1/2 h afforded the desired fused furan **13** in 76% yield. In this procedure, the methyl group from the methyl iodide is presumably incorporated in the vinylogous ester functionality of **20**, as shown by Kraus, and then lost in the cyclization step. The same procedure but with an extended reaction time in the second step provided the *O*-methylated naphthofuran **21**.

Naphthofuran **13**, on refluxing with excess sodium hydroxide in ethanol, gave hatomarubigin A (**2**). Although this direct conversion was unexpected, it is not totally surprising. We assume that the anticipated aldol condensation was followed by hydrolytic furan ring cleavage, an event which is implicit in reports that certain benzofurans rearrange to other heterocycles in base[13] and which would be relatively favorable in the presumed aldol product **22**.

It is interesting to note that the methylated acyl naphthofuran **21** is also converted to hatamarugin A on reflux in basic aqueous ethanol, albeit in only 15% yield. This transformation presumably involves nucleophilic attack by hydroxide on the carbon bearing the methoxyl group adjacent to the acetyl group.

Noting that the three steps which comprise the conversion of **15** and **16** to **2** were all effected by base, we examined the possibility that they might take place sequentially in a single operation. Indeed when the addition reaction of diketone **16** and naphthoquinone **15** (sodium ethoxide/ethanol) was quenched with aqueous sodium hydroxide followed by heating, hatomarubigin A could be obtained directly in 41% yield.

Hatomarubigin A was easily modified (Scheme 4) to supply samples of rubiginone B2 (**3**), dehydrorabelomycin (**5**, also known as 6-hydroxytetrangulol), antibiotic X-14881 E (**6**), and tetrangulol (**7**). Deoxygenation of hatomarubigin A was accomplished by preparation of the triflate **23** and palladium catalyzed formate reduction.[14] This two step procedure converted hatomarubigin A to rubiginone B2 (**3**) in 96% yield. Oxidative aromatization of the D-ring of rubiginone B2 was effected by palladium chloride in concentrated hydrochloric acid,[15] providing X-14881 E (**6**) in 90% yield. Exposure to the same conditions for longer periods of time led to the demethylated tetrangulol (**7**). The synthesis of rubiginone B2 is a formal total synthesis of ochrimycinone (**4**, also known as X 14881 C).[6a]

Hatomarubigin A (**2**) was also efficiently converted to dehydrorabelomycin (**5**, Scheme 5). Unlike rubiginone B2 (**3**), hatomarubigin A was not oxidatively aromatized by palladium chloride in concentrated hydrochloric acid. Likewise DDQ, and chloranil were ineffective. Suspecting that the conjugation of the 6-hydroxyl group with the C-1 carbonyl was responsible for the stability of ketone **3**, we devised a two step sequence based on the intermediacy of enol silyl ether **24**. Thus palladium acetate oxidation afforded **25**, the monomethyl ether of dehydrorabelomycin, and subsequent treatment with ethanethiol and aluminum chloride[16] followed by air oxidation gave the natural product **5**.

Conclusions

Hatomarubigin A (**2**) and the related angucyclinones (**3**–**7**) are now readily available by the Michael addition/Claisen condensation strategy demonstrated in this work. Consequently they are attractive starting materials for the synthesis of more complex angucylclinones and angucyclines.

Experimental

Melting points were taken on a Thomas–Hoover capillary apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 1600 series FT-IR. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker WM 250 or a Bruker AM 400 WB instrument. Ether refers to diethyl ether. All reactions were conducted under an atmosphere of N_2 unless otherwise indicated.

Naphthofuran 13. To a stirred suspension of 2-acetyl-8-methoxy naphthalenedione **15** (60 mg, 0.26 mmol) and

5-methyl 1,3-cyclohexanedione **16** (66 mg, 0.52 mmol) in 4 mL ethyl alcohol, sodium hydride (2 mg, 0.10 mmol) was added and the mixture was stirred at 0°C for 1 h. Ethyl alcohol was removed and the residue was dissolved in dry acetone. To the stirred solution, potassium carbonate (1.00 g) and methyl iodide (0.25 mL) were added and the mixture was stirred at reflux for 2.5 h. The mixture was cooled to room temperature and the solid was removed by filtration. The filtrate was concentrated to yield a yellow solid. Flash chromatography with 50% EtOAc/hexanes gave 67 mg (76%) of a light yellow solid: mp 167–169°C. IR ($CDCl_3$) 3394, 2962, 2930, 1702, 1675, 1584, 1457, 1400, 1369, 1245, 1186, 1041 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (d, 3H, J=6.4 Hz), 2.30–2.70 (m, 4H), 2.74 (s, 3H), 3.15 (dd, 1H, J=14, 6 Hz), 4.09 (s, 3H), 6.87 (d, 1H, J=7.4 Hz), 7.40 (t, 1H, J=8.0 Hz), 7.78 (d, 1H, J=8.4 Hz), 9.58 (s, H); ^{13}C NMR ($CDCl_3$) δ 20.9, 30.4, 31.9, 32.3, 46.2, 56.3, 105.0, 112.4, 113.5, 116.5, 117.0, 117.6, 122.7, 127.7, 144.1, 148.1, 156.8, 169.7, 192.7, 203.0; MS (*m*/*e*) 73 (100), 147 (64.7), 207 (28.7), 221 (19.8), 281 (15.0), 339 (25.2); HRMS calcd for $C_{20}H_{18}O_5$ 338.3635, found 338.3629.

***O*-Methyl ether 21**. The above procedure with extended reflux times provided a yellow solid (86%). IR ($CDCl_3$) 1705, 1678, 1630, 1576, 1519, 1460 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.23 (d, 3H, J=6.3 Hz), 2.30–2.88 (m, 4H), 2.74 (s, 3H), 3.10 (dd, 1H, J=14, 6 Hz), 3.83 (s, 3H), 4.05 (s, 3H), 6.97 (dd, 1H, J=0.6, 8.2 Hz), 7.51 (t, 1H, J=8.0 Hz), 7.83 (d, 1H, J=8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 21.0, 30.5, 31.9, 32.9, 46.2, 56.0, 64.4, 106.2, 112.7, 115.2, 117.0, 117.1, 123.5, 127.8, 128.0, 147.2, 149.5, 156.6, 169.9, 192.9, 203.0; HRMS calcd for $C_{21}H_{20}O_5$ 352.3906, found 352.3900.

Hatomarubigin A (2) from naphthofuran 13. To the stirred solution of naphthofuran **13** (20 mg, 0.06 mmol) in 3 mL of ethyl alcohol was added 2.5 mL of sodium hydroxide solution (prepared by dissolving 0.60 g of sodium hydroxide in a mixture of 1 mL of water and 5 mL ethyl alcohol). The mixture was purged with N_2, stirred at reflux for 5.5 h, and then cooled. The reaction was quenched with 10% hydrochloric acid and the resulting mixture was extracted with ether (3×7 mL). The combined extract was dried (Na_2SO_4) and concentrated. Flash chromatography (5% ether in CH_2C1_2) of the solid orange residue gave 10 mg (51%) of a pale orange solid, mp 237–238°C. IR (KBr) 3349, 1696, 1676, 1639 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (d, 3H, J=6.3 Hz), 2.30–2.70 (m, 3H), 2.80–3.0 (m, 2H), 4.04 (s, 3H), 6.95 (s, 1H), 7.25–7.33 (m, 1H), 7.69–7.76 (m, 2H), 13.05 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.3, 30.2, 38.6, 47.5, 56.6, 117.4, 117.7, 119.7, 119.9, 120.9, 128.1, 136.3, 137.4, 137.7, 158.2, 160.3, 163.6, 184.5, 188.4, 197.8; MS (*m*/*e*) 63 (7.6), 139 (21.3), 152 (21.1), 220 (16.3), 248 (11.9), 264 (9.3), 276 (9.3), 294 (100), 308 (39.8), 336 (58.7); HRMS calcd for $C_{20}H_{16}O_5$ 336.0998, found 336.1000.

Hatomarubigin A (2) from naphthoquinone 15 and diketone 16. To a stirred suspension of naphthofuran **15** (40 mg, 0.2 mmol) and diketone **16** (30 mg, 0.24 mmol) in 4 mL of ethyl alcohol, sodium hydride (3 mg. 0.12 mmol) was added and the mixture was stirred at 0°C for 1 h. Then a solution of sodium hydroxide (200 mg) in 1 mL water was added and the resulting mixture was stirred at reflux for 6 h. The reaction was quenched with 5% hydrochloric acid and the mixture was extracted with dichloromethane (3×10 mL). The combined organic extract was dried (Na_2SO_4) and concentrated to give an orange solid. Chromatography with 50% EtOAc/hexanes gave 28 mg (41%) of Hatomarubigin A.

Trifluoromethanesulfonate 23. To the stirred solution of Hatomarubigin A (**5**) (17 mg, 0.05 mmol) in dichloromethane (3 mL), triflic anhydride (17 mg, 0.06 mmol) and pyridine (0.03 mL) were added successively at 0°C. The mixture was warmed to room temperature and stirred for 100 min before being quenched by the addition of water (10 mL). The resulting mixture was extracted with dichloromethane (3×5 mL) and the combined organic solution was washed with 5% hydrochloric acid (2×10 mL) and water (2×10 mL), then dried (Na_2SO_4) and concentrated to yield 22 mg (91%) of a yellow solid. 1R ($CDCl_3$) 2964, 2931, 2843, 1706, 1683, 1595, 1473, 1435, 1314, 1262, 1218, 1141, 1028 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (d, 3H, J=6.3 Hz), 2.40–2.80 (m, 3H), 2.97–3.06 (m, 2H), 4.01 (s, 3H), 7.28–7.37 (m, 2H), 7.62–7.75 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.3, 30.7, 38.0, 47.2, 56.6, 117.1, 117.7, 118.9, 120.3, 121.7, 126.6, 127.1, 135.5, 136.4, 138.5, 148.0, 150.2, 159.7, 179.3, 183.8, 197.4; HRMS calcd for $C_{21}H_{15}F_3SO_7$ 468.4087, found 468.4068.

Rubiginone B_2 (3). Triflate **23** (15 mg, 0.03 mmol), palladium (II) acetate (2.3 mg, 0.002 mmol), triphenylphosphine (2.1 mg, 0.008 mmol), triethylamine (11 mg, 0.11 mmol) and formic acid (80%, 2.7 mL) were combined and the mixture was stirred at 50°C for 3 h and then diluted with dichloromethane (15 mL). The combined organic solution washed with 5% hydrochloric acid (2×10 mL) and with water (20 mL). Then it was dried (Na_2SO_4) and concentrated. The residual yellow solid was chromatographed with 50% EtOAc/hexanes to give 10 mg (98%) of a yellow solid, mp 235°C-dec. IR ($CDCl_3$) 1700, 1672, 1594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (d, 3H, J=6.4 Hz), 2.40–2.60 (m, 2H), 2.61–2.75 (m, 2H), 2.90–3.10 (m, 1H), 4.04 (s, 3H), 7.28 (d, 1H, J=8.0 Hz), 7.49 (d, 1H, J=8.0 Hz), 7.68 (t, 1H, J=8.0 Hz), 7.76 (d, 1H, J=8.0 Hz), 8.25 (d, 1H, J=8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 21.4, 30.8, 38.3, 50.2, 56.5, 108.2, 117.2, 119.7, 120.7, 129.6, 133.0, 135.0, 135.1, 135.3, 137.7, 149.1, 159.8, 181.6, 184.5, 198.8; MS (*m*/*e*) 63 (15.6), 82 (15.2), 151 (24.6), 163 (53.9), 176 (16.8), 189 (14.6), 221 (16.4), 249 (42.1), 261 (30.9), 278 (100), 293 (32), 305 (17.3), 320 (98.4); HRMS calcd for $C_{20}H_{16}O_4$ 320.1048, found 320.1042.

X-14881 E (6). Rubiginone B2 (**3**, 10 mg, 0.031 mmol), palladium (II) chloride (11 mg, 0.06 mmol), concentrated hydrochloric acid (2 mL) and *t*-butyl alcohol (2 mL) were combined and the mixture was stirred at reflux until TLC showed no starting material (40 min). The mixture was cooled and the reaction was quenched with 5% hydrochloric acid (10 mL). The resulting mixture was extracted with dichloromethane (3×5 mL) and the extract was dried (Na_2SO_4) and concentrated to yield a dark red solid. Chromatography with 33% EtOAc/hexanes yielded 9.8 mg (98%) of a dark orange solid. IR ($CDCl_3$) 1662, 1620, 1586 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.49 (s, 3H), 4.08 (s, 3H),

7.13 (d, 1H, J=1.7 Hz), 7.26 (d, 1H, J=1.7 Hz), 7.34 (d, 1H, J=7.8 Hz), 7.71 (t, 1H, J=7.8 Hz), 7.93 (dd, 1H, J=1.5, 7.7 Hz), 8.10 (d, 1H, J=8.7 Hz), 8.28 (d, 1H, J=8.7 Hz), 11.15 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.2, 56.6, 118.2, 119.1, 119.7, 119.9, 121.0, 121.1, 122.8, 130.7, 135.3, 136.7, 137.3, 137.6, 138.4, 141.2, 155.1, 159.6, 182.2, 190.8; MS (*m*/*e*) 101 (24.3), 189 (24.6), 203 (20), 215 (11.2), 244 (15.9), 272 (12), 301 (11.7), 318 (100); HRMS calcd for $C_{20}H_{14}O_4$ 318.0888, found 318.0868.

Tetrangulol (7). Palladium (II) chloride (11 mg, 0.06 mmol) was dissolved in 2 mL of conc. hydrochloric acid and the mixture was concentrated to about 1 mL. To the stirred solution, was added 7 mg (0.022 mmol) of X-14881 E (**6**) and the mixture was stirred at reflux for 4 h. The reaction was quenched with 5% hydrochloric acid (8 mL) and the mixture was extracted with dichloromethane (3×5 mL). The combined organic solution was dried (Na_2SO_4) and concentrated to give 6.2 mg (93%) of a green solid: mp 197–200°C; IR ($CDCl_3$) 1636, 1618 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H), 7.16 (s, 1H), 7.27 (s, 1H), 7.31 (d, 1H, J=8.5 Hz), 7.69 (t, 1H, J=8.5 Hz), 7.85 (d, J=8.5 Hz), 8.13 (d, 1H, J=8.6 Hz), 8.32 (d, 1H, J=8.6 Hz), 11.27 (s, 1H), 12.26 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.3, 112.7, 114.7, 120.1, 120.2, 121.2, 121.3, 121.9, 124.8, 132.4, 134.8, 136.9, 137.7, 139.1, 142.0, 155.3, 161.7, 187.9, 189.7; HRMS calcd for $C_{19}H_{12}O_4$ 304.0736, found 304.0738.

Dehydrorableomycin methyl ether 25. Hatomarubigin A **5** (10 mg, 0.03 mmol), TMSCI (10 mg, 0.12 mmol) and triethylamine (24 mg, 0.24 mmol) were dissolved in DMF (3 mL) and the resulting solution was stirred in a sealed tube for 12 h at 120°C. After the tube was cooled to room temperature, the reaction was quenched with saturated $NaHCO_3$ solution. Then the mixture was extracted with dichloromethane (3×4 mL) and the combined organic solution was washed with saturated $NaHCO_3$ (2×10 mL) and water (10 mL) and then dried and concentrated. The proton NMR of this residue showed the presence of the characteristic vinyl proton at δ 5.2. Without purification, this crude material was dissolved in 3 mL acetonitrile and palladium (II) acetate (8 mg, 0.04 mmol) was added. The mixture was stirred at room temperature for 12 h and then concentrated. The residue was partitioned between 5% hydrochloric acid (5 mL) and dichloromethane (3×5 mL). The combined organic solution was dried (Na_2SO_4) and concentrated to give a green solid. Flash chromatography with 33% EtOAc/hexanes gave 9.3 mg (93%). IR ($CDCl_3$) 3683, 3601, 1643, 1620, 1578 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H), 4.10 (s, 3H), 6.94 (d, H, J=1.6 Hz), 7.09 (d, H, J= 1.6 Hz), 7.36 (d, 1H, J=8.7 Hz), 7.65 (s, 1H), 7.77 (t, 1H, J=8.7 Hz), 7.90 (d, 1H, J=8.7 Hz), 10.12 (s, 1H), 12.71 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.3, 56.7, 112.6, 116.9, 117.9, 118.4, 119.5, 121.0 (2C), 123.8, 131.5, 136.2, 137.3, 140.7, 142.0, 154.1, 156.6, 160.1, 188.9, 190.5; HRMS calcd for $C_{20}H_{14}O_5$ 334.0837, found 334.0838.

Dehydrorableomycin (5). To the stirred solution of 5 mg (0.015 mmol) of dehydrorableomycin methyl ether **25** in ethanethiol (1.5 mL), was added 12 mg (0.09 mmol) of aluminum chloride. The reaction mixture was stirred at room temperature for 2 h and then quenched with 5% hydrochloric acid and exposed to air overnight. The original yellow solution turned green during this period. The green solution was extracted with dichloromethane (3×5 mL), dried (Na_2SO_4) and concentrated to give 4.3 mg (90%) of a dark green solid.[11] IR ($CDCl_3$) 3050, 2926, 1634, 1609, 1458, 1312, 1266; ^{1}H NMR δ 2.42 (s, 3H), 6.91 (s, 1H), 7.05 (s, 1H), 7.31 (d, 1H, J=8.5 Hz), 7.61 (s, 1H), 7.69 (dd, 1H, J=8.4 Hz, 7.6 Hz), 7.82 (d, 1H, J=7.5 Hz), 10.31 (s, 1H), 11.74 (s, 1H), 12.09 (s, 1H). HRMS calcd for $C_{19}H_{12}O_5$ 320.0685, found 320.0682.

Acknowledgements

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