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Meroditerpenoids from the Brown Alga *Sargassum siliquastrum*

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Eleven new meroditerpenoids (**7–11**, **14–17**, **19**, **20**) and nine known compounds (**1–6**, **12**, **13**, **18**) were isolated from the brown alga *Sargassum siliquastrum*. Combined chemical and spectroscopic analyses revealed a common tetraprenyl hydroquinone structure; these compounds belonged to the nahocol, isonahocol, and sargahydroquinoic acid classes. The dihydroquinone moiety of **20** was unique and unprecedented in a brown alga. Stereochemical assignments were made for several of the known compounds based on their chemical reactivity. These compounds exhibited moderate to significant radical-scavenging activity as well as weak inhibitory activities against sortase A and isocitrate lyase.

Meroterpenoids consisting of a quinone or hydroquinone moiety and polyprenyl side chains are ubiquitous in animals, plants, and microorganisms.¹ In the marine environment, these metabolites are particularly abundant in brown algae (division Phaeophyta) of the genera *Cystoseira* and *Sargassum*.² These compounds exhibit varying degrees of bioactivity and may act as antioxidants, antimicrobial agents, cytotoxins, and neuronal and skin protectants.^{2–9} Recently, we isolated several meroterpenoids of the chromene class (sargachromenals A–P) from the brown alga *Sargassum siliquastrum* off the coast of Korea.¹⁰ These compounds contained diverse side chains and exhibited significant antioxidant activity and inhibitory activity against butylcholine esterase. On the other hand, specimens of *S. sagamianum* collected from the same area produced a series of monoglycerides exhibiting inhibitory activities against the enzymes PLA₂ and COX-2.¹¹

In our continuing search for bioactive metabolites from marine algae, we re-encountered *S. siliquastrum* from Jeju Island, Korea. However, the ¹H NMR spectra of the crude extract from this specimen differed significantly from those of previous collections, prompting further investigation. Here, we report the isolation and chemical structure determination of 10 new meroditerpenoids and related metabolites of the nahocol and isonahocol classes.¹² A novel meroterpenoid with a modified dihydroquinone moiety is also described. Stereochemistry was assigned on the basis of the results of concise chemical reactions. These compounds exhibited moderate to significant radical-scavenging activity as well as weak inhibitory activity against sortase A and isocitrate lyase.

Results and Discussion

The fresh collection was lyophilized, macerated, and repeatedly extracted with CH₂Cl₂ and MeOH. The combined extracts were separated with solvent partitioning followed by reversed-phase vacuum flash chromatography. Based on the results of bioassay and ¹H NMR analysis, the moderately polar fractions were separated by reversed-phase and silica HPLC, thereby affording 20 compounds as colorless gums.

Compounds **1–4** were readily identified by spectroscopic analyses as nahocols A, A₁, D₂, and D₁, respectively, plastoquinones from the Japanese brown alga *Sargassum autumnale*. The spectroscopic data for these compounds were in good agreement with those reported in the primary literature.¹² Similarly, compounds **5**

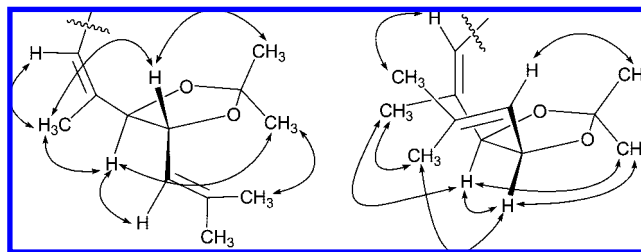


Figure 1. Selected NOESY correlations for **3** (left) and **4**, **12**, and **13** (right).

and **6** were identified as synthetic analogues of **1**. These nahocol compounds have hydroxyl groups on their prenyl chains with unknown stereochemistry. Stereochemical configurations were assigned by implementing well-known chemical modification techniques, such as the Mosher method. In this way, the absolute configurations at C-13' of **1** and **2** were assigned as *S* and *R*, respectively. The relative configurations of the diol portions were assigned as 12'*R**, 13'*R** and 12'*R**, 13'*S** for **3** and **4**, respectively, based on the formation of a cyclic ketal and subsequent NOESY experiments (Figure 1). Similarly, the hydroxyl component of **5** was assigned as 12'*R* using the Mosher method. Although the chemical modification producing **6** from **1** suggested the 12'*S* configuration, limited amounts of isolated material prohibited unambiguous assignment of stereochemistry using the Mosher method.

The ¹³C NMR data of compound **7** (C₂₉H₄₀O₆) showed signals characteristic of nahocols: a single ester carbonyl at δ 172.4, 14 olefinic signals including a terminal vinyl group at δ 150 and 110, a methoxy group at δ 51.9, and upfield methyl carbon atoms at δ 26–11 ppm (Table 1). The peak corresponding to a carbonyl carbon at δ 201.0, coupled with the IR absorption at 1695 cm⁻¹ and UV maximum at 217 nm, was indicative of an α,β-unsaturated ketone in the tetraprenyl chain. The significant downfield shift of H-13' to δ 5.29 (dd, *J* = 9.9, 5.8 Hz) indicated a carbonyl group at C-12'. This was confirmed by combined 2-D NMR analyses, which showed long-range correlations of the carbonyl carbon with H-10', H-13', H-14', and H-19' in the gHMBC data. The 13'*S* absolute stereochemical configuration was assigned using the Mosher method. Thus, the structure of **7** was that of a 10',11'-didehydro derivative of nahocol A (**1**).

The spectroscopic data of compounds **8** and **9** (C₂₉H₄₀O₆) were very similar. A combination of ¹H COSY, TOCSY, gHSQC, and gHMBC experiments revealed identical planar structures indicative of the 10',11'-didehydro derivative of the synthetic nahocol analogue

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Chart 1

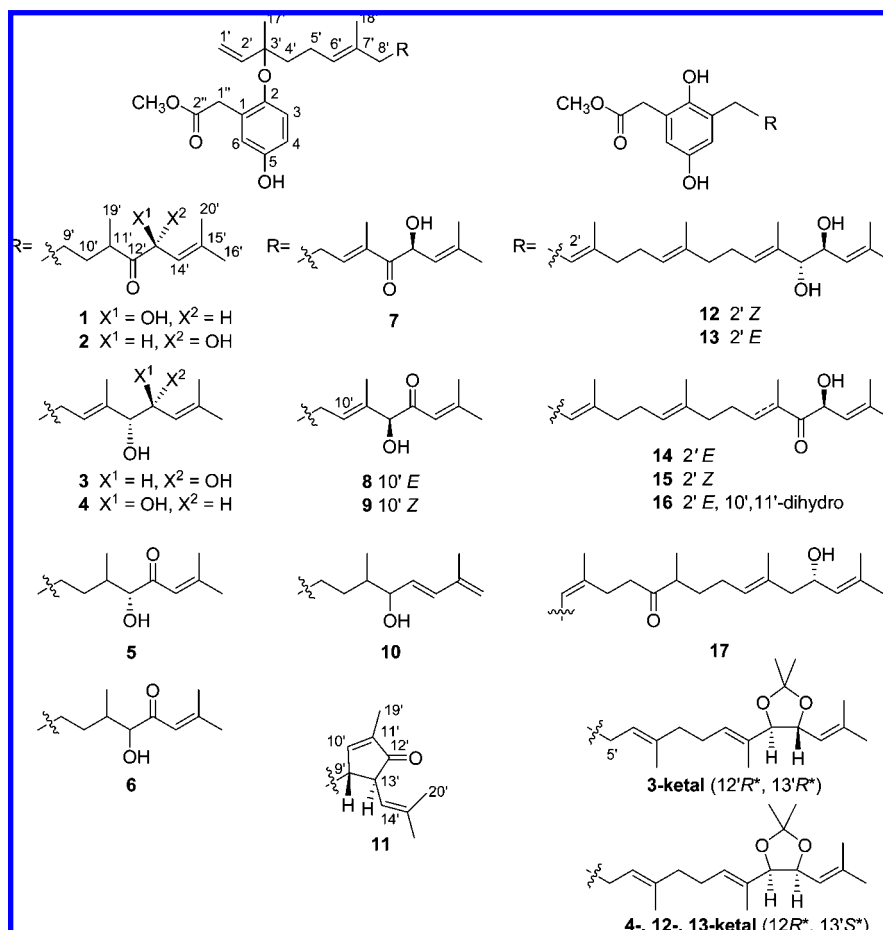


Table 1. ^{13}C NMR Assignments for Compounds **7–11**, **14–17**, **19**, and **20** in CDCl_3

| position | 7 | 8 | 9 | 10 | 11 | 14 | 15 | 16 | 17 | 19 | 20 |
|----------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| 1 | 127.0 | 127.2 | 127.2 | 127.1 | 127.2 | 121.7 | 121.7 | 121.9 | 121.7 | 127.3 | 139.9 |
| 2 | 147.7 | 148.1 | 148.2 | 148.1 | 148.2 | 146.9 | 146.8 | 146.8 | 146.8 | 145.9 | 201.1 |
| 3 | 119.6 | 119.7 | 119.6 | 119.5 | 119.7 | 130.7 | 131.0 | 130.7 | 130.9 | 121.2 | 50.3 |
| 4 | 114.1 | 114.0 | 114.0 | 114.0 | 114.0 | 115.9 | 115.9 | 115.9 | 115.9 | 112.6 | 46.5 |
| 5 | 150.0 | 149.6 | 149.6 | 149.3 | 149.6 | 149.0 | 149.2 | 149.2 | 149.2 | 147.8 | 197.7 |
| 6 | 117.7 | 117.7 | 117.7 | 117.6 | 117.7 | 115.1 | 115.1 | 115.1 | 115.1 | 115.7 | 140.8 |
| 1' | 114.3 | 114.3 | 114.3 | 114.3 | 114.4 | 29.1 | 28.9 | 29.1 | 29.1 | 22.4 | 38.2 |
| 2' | 143.5 | 143.6 | 143.6 | 143.6 | 143.6 | 121.9 | 122.6 | 121.7 | 122.6 | 31.4 | 116.9 |
| 3' | 81.5 | 81.7 | 81.7 | 81.7 | 81.6 | 137.2 | 137.1 | 137.3 | 137.4 | 75.1 | 141.2 |
| 4' | 41.8 | 42.0 | 42.0 | 42.1 | 42.0 | 39.5 | 31.9 | 39.6 | 31.9 | 39.5 | 39.7 |
| 5' | 22.3 | 22.3 | 22.3 | 22.3 | 22.4 | 26.4 | 26.5 | 26.2 | 26.3 | 22.1 | 26.1 |
| 6' | 125.2 | 124.5 | 124.7 | 123.9 | 126.7 | 125.2 | 125.5 | 124.5 | 214.8 | 125.6 | 124.2 |
| 7' | 133.8 | 134.8 | 134.6 | 135.4 | 133.0 | 133.7 | 133.7 | 134.5 | 41.3 | 133.6 | 135.0 |
| 8' | 38.0 | 39.0 | 39.6 | 39.7 | 44.6 | 38.0 | 38.0 | 39.4 | 33.5 | 38.0 | 39.1 |
| 9' | 27.4 | 26.6 | 26.6 | 25.5 | 45.4 | 27.4 | 27.2 | 25.3 | 25.2 | 27.4 | 25.9 |
| 10' | 145.4 | 132.5 | 131.3 | 32.2 | 160.2 | 145.4 | 145.5 | 33.6 | 124.5 | 145.3 | 129.8 |
| 11' | 133.7 | 132.8 | 132.0 | 38.9 | 140.2 | 133.7 | 133.7 | 41.3 | 134.7 | 133.8 | 133.5 |
| 12' | 201.0 | 83.4 | 75.2 | 76.7 | 210.0 | 201.4 | 201.3 | 214.8 | 39.4 | 201.3 | 80.3 |
| 13' | 69.7 | 199.3 | 199.0 | 131.1 | 52.3 | 69.8 | 69.7 | 74.3 | 74.2 | 69.8 | 68.9 |
| 14' | 123.3 | 118.8 | 118.7 | 123.8 | 121.4 | 123.4 | 123.3 | 121.0 | 120.9 | 123.5 | 123.4 |
| 15' | 137.9 | 159.8 | 160.1 | 141.4 | 136.1 | 137.9 | 138.0 | 140.0 | 140.1 | 137.8 | 139.5 |
| 16' | 25.8 | 28.1 | 28.1 | 116.6 | 25.9 | 25.9 | 25.9 | 25.9 | 25.9 | 25.9 | 26.1 |
| 17' | 22.4 | 22.5 | 22.5 | 22.3 | 22.4 | 16.2 | 23.4 | 16.2 | 23.4 | 24.0 | 16.3 |
| 18' | 15.8 | 15.8 | 15.9 | 15.8 | 15.9 | 16.0 | 15.8 | 15.8 | 16.1 | 15.8 | 15.9 |
| 19' | 11.7 | 10.8 | 17.6 | 14.6 | 10.4 | 11.8 | 11.7 | 16.1 | 15.8 | 11.7 | 11.6 |
| 20' | 18.3 | 21.3 | 21.4 | 18.6 | 18.4 | 18.3 | 18.3 | 18.6 | 18.6 | 18.2 | 18.7 |
| 1'' | 36.4 | 36.3 | 36.4 | 36.4 | 36.3 | 37.4 | 37.6 | 37.3 | 37.5 | 16.0 | 40.2 |
| 2'' | 172.4 | 172.2 | 172.2 | 172.1 | 172.1 | 173.9 | 174.1 | 173.9 | 173.9 | | 171.8 |
| OMe | 51.9 | 51.8 | 51.8 | 51.9 | 51.8 | 52.6 | 52.7 | 52.6 | 52.6 | | 51.9 |

5. However, detailed examination of the ^1H and ^{13}C NMR data showed noticeable shifts of both proton and carbon signals at and near the C-10' double bond (Tables 1 and 2). In particular, the chemical shifts of the H-12' oxymethine protons and the C-19' vinyl

methyl carbon differ significantly between **8** and **9**: δ_{H} 4.44 and 4.96 for H-12', δ_{C} 10.8 and 17.6 for C-19', respectively. These results suggest that **8** and **9** are geometric isomers about C-10' with 10'*E* and 10'*Z* stereochemical configurations, respectively, which

Table 2. ^1H NMR Assignments for Compounds **7–11** in CDCl_3

| position | 7 | 8 | 9 | 10 | 11 |
|----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| 3 | 6.89, d (8.8) | 6.92, d (8.8) | 6.93, d (8.8) | 6.93, d (8.8) | 6.93, d (8.8) |
| 4 | 6.57, dd (8.8, 3.0) | 6.58, dd (8.8, 3.0) | 6.59, dd (8.8, 3.1) | 6.58, dd (8.8, 3.1) | 6.59, dd (8.8, 3.1) |
| 6 | 6.66, d (3.0) | 6.69, d (3.0) | 6.69, d (3.1) | 6.69, d (3.1) | 6.69, d (3.1) |
| 1' | 5.18, d (11.0) | 5.18, d (11.0) | 5.18, d (11.1) | 5.18, d (10.9) | 5.20, d (10.7) |
| | 5.16, d (17.9) | 5.17, d (17.6) | 5.17, d (17.6) | 5.17, d (17.7) | 5.19, d (17.4) |
| 2' | 6.03, dd (17.9, 11.0) | 6.05, dd (17.6, 11.0) | 6.05, dd (17.6, 11.1) | 6.05, dd (17.7, 10.9) | 6.05, dd (17.4, 10.7) |
| 4' | 1.70, m | 1.76, m | 1.75, m | 1.74, m | 1.74, m |
| 5' | 2.04, m | 2.08, m | 2.08, m | 2.08, m | 2.10, m |
| 6' | 5.11, t (6.6) | 5.15, t (6.1) | 5.16, t (6.2) | 5.11, t (6.9) | 5.19, t (6.8) |
| 8' | 2.08, t (7.7) | 2.05, m | 2.10, m | 2.07, m; 1.96, m | 2.14, m |
| 9' | 2.34, dt (7.7, 7.2) | 2.17, m | 2.32, m | 1.41, m; 1.34, m | 2.65, m |
| 10' | 6.55, d (7.2) | 5.61, t (6.9) | 5.49, t (7.1) | 1.45, m; 1.06, m | 7.18, br s |
| 11' | | | | 1.58, m | |
| 12' | | 4.44, d (4.3) | 4.96, d (4.2) | 4.05, dd (6.8, 6.1) | |
| 13' | 5.29, dd (9.9, 5.8) | | | 5.66, dd (15.8, 6.8) | 2.83, dd (9.5, 2.2) |
| 14' | 4.98, d (9.9) | 6.14, br s | 6.03, br s | 6.30, d (15.8) | 4.89, d (9.5) |
| 16' | 1.72, s | 1.93, s | 1.93, s | 4.98, br s | 1.75, s |
| 17' | 1.35, s | 1.37, s | 1.37, s | 1.37, s | 1.37, s |
| 18' | 1.58, s | 1.60, s | 1.61, s | 1.57, s | 1.59, s |
| 19' | 1.80, s | 1.43, s | 1.49, s | 0.91, d (6.8) | 1.76, s |
| 20' | 1.82, s | 2.22, s | 2.23, s | 1.85, s | 1.69, s |
| 1'' | 3.57, AB | 3.61, AB | 3.61, AB | 3.59, AB | 3.61, AB |
| OMe | 3.67, s | 3.69, s | 3.67, s | 3.68, s | 3.68, s |
| OH | 4.08, d (5.8) | 4.17, d (4.3) | 4.13, d (4.2) | ND ^a | |

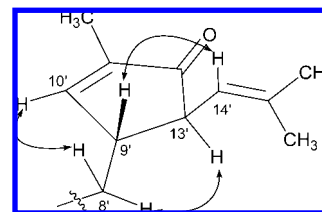
^a ND undetected.

was confirmed by key NOESY cross-peaks H-9'/H-19' and H-10'/H-12' for **8** and H-9'/H-12' for **9**. This interpretation was further supported by application of the Mosher method, which led to a 12'*S* assignment, opposite of the 12'*R* configuration of **5**, for both compounds.

A minor constituent, compound **10** ($\text{C}_{29}\text{H}_{42}\text{O}_5$), exhibited a shift in the position of the terminal double bond from C-14' to C-15' of other nahocol, as evidenced from the ^1H and ^{13}C NMR spectra. Peaks corresponding to the vinyl methyl group in the previously discussed compounds were replaced by peaks at δ_{H} 4.98 (2 H, br s) and δ_{C} 116.6 (Tables 1 and 2). Tracing the proton–proton and carbon–proton correlations of these peaks using 2-D NMR techniques revealed the presence of an α -hydroxy-diene moiety at the terminus of the side chain. However, due to the limited amounts of isolated material, the stereochemistry at the C-12' asymmetric center could not be assigned definitively.

Although the meroterpenoid nature of compound **11** ($\text{C}_{29}\text{H}_{38}\text{O}_5$) was evident from the spectroscopic data, preliminary examination of the ^{13}C NMR and DEPT data revealed significant differences in carbon signals from the two terminal isoprene units. These differences, in conjunction with 11 degrees of unsaturation inherent to the molecular formula, suggested the presence of an additional ring structure in the prenyl component. The structural difference was hypothesized to be associated with ^{13}C NMR signals from the carbonyl and trisubstituted double bond at δ 210.0 (C), 160.2 (CH), and 140.2 (C), respectively (Table 1). A corresponding ^1H NMR signal at δ 7.18 (1 H, br s), in addition to an IR absorption band at 1691 cm^{-1} and UV absorption maximum at 223 nm, represented evidence of a cyclic α,β -unsaturated ketone.

A combination of ^1H COSY and TOCSY experiments revealed that the hydroquinone moiety and its surrounding structure (C-1'–C-8') were intact in compound **11**. The methylene signals at δ 2.14 ppm in the ^1H NMR spectra were traced to a proton spin system including methine protons at δ 2.65, 2.83, and 4.89 in a linear array (Table 2). A small but consistent coupling (J_{vs}) was also uncovered between the methine and olefinic protons at δ 2.65 and 7.18, respectively. Long-range coupling of the olefinic proton with carbon signals at δ_{C} 52.3 (CH), 45.4 (CH), and 44.6 (CH_2) bearing protons at δ_{H} 2.83, 2.65, and 2.14, and the carbonyl and olefinic carbons at δ_{C} 210.0 and 140.2, respectively, provided evidence for a cyclopentenone moiety. The presence of a vinyl methyl group at C-19' was apparent by long-range coupling of the methyl proton

**Figure 2.** Selected NOE correlations for the compound **11**.

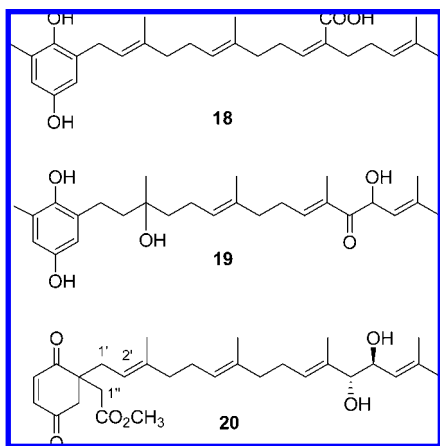
at δ 1.76 with both the carbonyl and olefinic carbons. Similarly, an isobutylene group at C-13' was evidenced by long-range correlations between the protons and carbon atoms of the isobutylene group with neighboring components.

The cyclopentenone moiety possessed two asymmetric centers at C-9' and C-13'. NOESY cross-peaks H-8'/H-10', H-8'/H-13', and H-9'/H-14' indicated *anti* orientations for H-9' and H-13' on the cyclopentenone ring and, thus, 9'*R**, 13'*S** stereochemical configurations for the asymmetric centers (Figure 2). Therefore, the structure of compound **11** is a meroterpenoid containing a cyclized tetraprenyl moiety. Meroterpenoids derived from brown algae possess polyprenyl components with a diversity of carbon skeleton arrangements. However, to our knowledge, the cyclization pattern in compound **11** is preceded only by sargachromenol P, a chromene meroterpenoid found in *S. siliquastrum*.¹⁰

In addition to the nahocol-based compounds, another series of metabolites were also isolated from *S. siliquastrum* as colorless gums. The most conspicuous structural feature of this series that is not found in the nahocols is the *ortho*-hydroxy attachment of the tetraprenyl side chain at the hydroquinone moiety. Compounds **12** and **13** were identified as isonahocols D₁ and D₂, respectively, based on combined NMR analyses and comparison of spectroscopic data with those in the literature.¹² The previously unassigned stereochemistry at the diol-attached centers was 12'*R**, 13'*S** for both compounds, as determined through ketal formation and NOESY experiments.

Compounds **14** and **15** ($\text{C}_{29}\text{H}_{40}\text{O}_6$) contained hydroquinone and side chain moieties identical to those of **12** and **7**, respectively, based on 2-D NMR analyses and comparison of spectroscopic data with those of the other metabolites (Tables 1 and 3). The chemical shifts of NMR signals at the C-2' double bond and neighboring atoms indicated *E* and *Z* stereochemical configurations for **14** and

Chart 2



15, respectively (Tables 1 and 3). This interpretation was supported by NOESY experiments in which cross-peaks were observed at H-1'/H-17' and H-2'/H-4' for **14**, while the opposite ones at H-2'/H-17' and H-1'/H-4' were observed for **15**, respectively. The 13'S configuration in both compounds was assigned by the Mosher method. By similar means, the structure of compound **16** (C₂₉H₄₂O₆), a related metabolite, was determined to be that of a 10',11'-dihydro derivative of **14**.

The ¹H and ¹³C NMR data of compound **17** (C₂₉H₄₂O₆) showed characteristic signals of an isonahocol meroterpenoid possessing a side chain with both ketone and hydroxyl groups. In contrast to the other nahocols and isonahocols, combined 2-D NMR data indicated a ketone group at C-6'. This assignment was further evidenced by long-range correlations of the ketone carbon with H-4', H-7', and H-18' in the gHMBC data. The same data were used to assign the hydroxyl group to C-13' and an *S* configuration was determined with the Mosher method. The stereochemical configurations of the double bonds in the side chain of this compound were assigned as 2'Z and 10'E based on ¹³C and ¹H NMR chemical shifts of the vinyl group, which was confirmed by NOESY cross-peaks at H-1'/H-4', H-2'/H-17', H-9'/H-19', and H-10'/H-12'.

In addition to nahocols and isonahocols, three additional meroterpenoids were isolated. Compound **18** was identified as sargahydroquinic acid, an antioxidant found in the brown algae *Sargassum sagamianum* var. *yezoense* and *S. thunbergii*, by spectroscopic analyses and comparison of NMR data with those reported previously.^{7,13} The NMR data of compound **19** (C₂₇H₄₀O₅) were similar to those of **18**, implying a similar meroterpenoid nature. Combined 2-D NMR indicated the presence of a ketone and hydroxyl groups at C-12' and C-13' of the side chain, respectively. These findings were supported by the long-range correlations of these carbons with neighboring protons (Tables 1 and 3). Correlations of an oxygen-bearing quaternary carbon atom at δ 75.1 with neighboring protons, including the methyl protons at δ 1.26, indicated a tertiary hydroxyl group at C-3'. The structure of **19** was therefore a derivative of sargahydroquinic acid bearing a ketone and two hydroxyl groups in the side chain. However, due to the limited amount of material available, the stereochemistry at C-13' could not be assigned.

A related metabolite, compound **20** (C₂₉H₄₂O₆), showed characteristics of a meroterpenoid. However, detailed examination of the ¹³C NMR data showed significant changes in the hydroquinone moiety: two carbonyl carbons at δ 201.1 and 197.7, two olefinic carbons at δ 140.8 and 139.9, and a quaternary carbon at δ 50.3 (Table 1). Corresponding differences were observed in the ¹H NMR spectra with new signals appearing at δ 6.74 (1 H, d, *J* = 10.6 Hz), 6.71 (1 H, d, *J* = 10.6 Hz), 3.30 (1 H, d, *J* = 16.4 Hz), and 2.70 (1 H, d, *J* = 16.4 Hz) (Table 3). In addition, the IR spectrum showed a strong absorption band at 1684 cm⁻¹, suggesting a

significant change in the hydroquinone ring. Long-range proton–carbon correlations in the gHMBC data between the new olefinic protons and the carbonyl carbons indicated the presence of an α,β -unsaturated diketone system. The gHMBC extension of this system, including an isolated methylene (δ_{H} 3.30 and 2.70, δ_{C} 46.5) and a quaternary carbon (δ_{C} 50.3), established the presence of a 2,2-disubstituted dihydroquinone moiety. A linkage between the side chain and the methyl acetate group at the quaternary carbon was also evidenced by mutual gHMBC correlations between the ring and attached groups. Furthermore, 2-D NMR data identified a tetraprenyl side chain with hydroxyl groups at C-12' and C-13'. The relative stereochemical configurations at these centers were assigned as 12'R*, 13'S* based on comparison of the NMR data with those of **3** and **4**. Thus, the structure of compound **20** was that of a tetraprenyl dihydroquinone with a methyl acetate group at C-3. To our knowledge, this type of modified quinone moiety is unprecedented in algal metabolites. Although the biogenetic relation of this compound is unclear, a 1,3-shift type migration of the methyl acetate group suggests that compound **20** may be the precursor of the nahocol and isonahocol compounds.

Nahocols and isonahocols have been reported to exhibit significant antioxidant activity.¹² The compounds described here showed moderate to significant radical-scavenging activity in DPPH assays with RC₅₀ values of 11.35, 12.71, 12.43, 18.51, 17.25, 9.12, 12.55, 14.71, 23.23, 12.36, 11.72, 0.13, 0.12, 0.31, 0.33, 0.30, 0.10, 0.17, and 0.24 $\mu\text{g/mL}$ for compounds **1–19**, respectively. The 100-fold increase in radical-scavenging activity of the diphenolic isonahocols relative to the monophenolic nahocols indicated the role of the phenolic group in this activity. In the same manner, the lack of scavenging activity of **20** (RC₅₀ > 300 $\mu\text{g/mL}$) may be due to the absence of a phenolic group. None of these compounds exhibited antimicrobial activity against Gram-positive or -negative bacteria or against pathogenic fungi. Conversely, the isonahocols **12–17** and a dihydroquinone **20** showed slight activity (IC₅₀ 23–72 $\mu\text{g/mL}$) against sortase A derived from *Staphylococcus aureus*. The nahocols and sargahydroquinic acids **1–11**, **18**, and **19** showed no inhibitory activity against sortase A (IC₅₀ > 200 $\mu\text{g/mL}$).¹⁴ These compounds were, however, weakly active (IC₅₀ 50–95 $\mu\text{g/mL}$) against isocitrate lyase (ICL) derived from *Candida albicans*.¹⁵

Experimental Section

General Experimental Procedures. Optical rotation was measured on a JASCO P1020 polarimeter using a 1 cm cell. UV absorption was recorded on a Hitachi JP/U-3010 spectrophotometer. IR absorbance spectra were recorded on a JASCO FT/IR 4200 spectrophotometer. Standard NMR spectra were recorded in CDCl₃ solutions, containing Me₄Si as an internal standard, on Bruker AMX-500 and Varian Gemini-2000 spectrometers. ¹H and ¹³C NMR spectra were measured at 500 (300 MHz for Gemini-2000) and 125 MHz, respectively. High-resolution mass spectra were acquired on JEOL JMS-SX 102A and JMS-700 high-resolution mass spectrometers for electron-impact (HRE-IMS) and fast-atom bombardment (HRFABMS) experiments, respectively, and were provided by the Korean Basic Science Institute, Seoul Branch, Seoul, Korea. Molecular structures were deduced from a combination of ¹³C NMR and HREIMS or HRFABMS data. All solvents were of spectral grade or distilled from glass prior to use.

Plant Material. *Sargassum siliquastrum* (sample number SS0604) was collected by hand at the subtidal zone (0–2 m) off the southwestern shore of Jeju Island, Korea, in April 2003. A voucher specimen is currently on deposit at Hanbat National University, Taejeon, Korea, under the curatorship of B.W.C.

Extraction and Isolation. The fresh collection was immediately frozen and kept at –25 °C until chemically investigated. The specimens were lyophilized (dry wt 240 g), macerated, and repeatedly extracted with CH₂Cl₂ (4 L \times 3) and MeOH (4 L \times 3). The combined extract (199.6 g) was partitioned between *n*-BuOH (11.2 g) and H₂O (176.5 g), and the former layer was repartitioned between 15% aqueous MeOH (7.5 g) and *n*-hexane (2.9 g). The MeOH layer was separated by C₁₈ reversed-phase vacuum flash chromatography and eluted with sequential mixtures of MeOH and H₂O (elution order: 50%, 40%, 30%, 20%,

Table 3. ^1H NMR Assignments for Compounds **14**–**17**, **19**, and **20** in CDCl_3

| position | 14 | 15 | 16 | 17 | 19 | 20 |
|----------|----------------------|----------------------|----------------------|---------------------|----------------------|---------------------|
| 1 | | | | | | 6.71, d (10.6) |
| 4 | 6.56, d (2.9) | 6.54, d (3.0) | 6.56, d (3.0) | 6.53, d (3.0) | 6.38, d (3.2) | 3.30, d (16.4) |
| | | | | | | 2.70, d (16.4) |
| 6 | 6.47, d (2.9) | 6.47, d (3.0) | 6.48, d (3.0) | 6.46, d (3.0) | 6.48, d (3.2) | 6.74, d (10.6) |
| 1' | 3.34, d (7.4) | 3.32, d (7.5) | 3.33, d (7.0) | 3.30, d (7.1) | 2.70, m | 2.32, m; 2.22, m |
| 2' | 5.29, t (7.4) | 5.36, t (7.5) | 5.27, t (7.0) | 5.31, t (7.1) | 1.76, m | 4.95, t (7.7) |
| 4' | 2.07, m | 2.13, m; 2.16, m | 2.07, m | 2.15, m | 1.56, m | 1.98, m |
| 5' | 2.07, m; 2.14, m | 2.11, m; 2.15, m | 2.11, dt (6.5, 6.6) | 2.08, m | 2.13, m | 2.11, m; 1.98, m |
| 6' | 5.12, t (6.8) | 5.17, t (6.7) | 5.07, t (6.5) | | 5.14, t (8.6) | 5.05, t (6.4) |
| 7' | | | | 2.67, sextet (6.7) | | |
| 8' | 2.10, m | 2.12, m | 1.93, t (6.2) | 1.92, m; 1.59, m | 2.10, m | 2.11, m |
| 9' | 2.34, dd (14.3, 7.1) | 2.36, dd (14.3, 7.1) | 1.32, m | 1.54, m | 2.34, dd (18.0, 8.9) | 2.11, m; 2.19, m |
| 10' | 6.56, t (7.1) | 6.57, t (7.1) | 1.31, m; 1.57, m | 5.09, t (6.9) | 6.55, t (8.9) | 5.46, d (6.7) |
| 11' | | | 2.68, dd (12.8, 6.6) | | | |
| 12' | | | | 2.07, m; 1.93, m | | 3.83, d (7.2) |
| 13' | 5.29, d (9.5) | 5.32, d (9.8) | 4.87, d (9.5) | 4.86, dd (9.7, 4.4) | 5.28, dd (12.3, 6.9) | 4.28, dd (8.5, 7.2) |
| 14' | 5.00, d (9.5) | 5.00, d (9.8) | 4.97, d (9.5) | 4.95, d (9.7) | 4.98, d (12.3) | 5.19, d (8.5) |
| 16' | 1.73, s | 1.74, s | 1.79, s | 1.77, s | 1.73, s | 1.74, s |
| 17' | 1.72, s | 1.75, s | 1.71, s | 1.73, s | 1.26, s | 1.53, s |
| 18' | 1.60, s | 1.62, s | 1.55, s | 1.03, d (6.7) | 1.60, s | 1.59, s |
| 19' | 1.80, s | 1.82, s | 1.05, d (6.6) | 1.55, s | 1.81, s | 1.66, s |
| 20' | 1.83, s | 1.83, s | 1.84, s | 1.83, s | 1.83, s | 1.78, s |
| 1'' | 3.60, s | 3.60, s | 3.60, s | 3.58, s | 2.13, s | 3.07, d (17.4) |
| | | | | | | 2.30, d (17.4) |
| OMe | 3.73, s | 3.72, s | 3.73, s | 3.71, s | | 3.65, s |
| OH | ND ^a | ND | ND | 3.85, d (4.4) | 3.97, d (6.9) | |

^a ND undetected.

10% MeOH(aq), 100% MeOH) and acetone. The fraction (1.1 g) eluted with 20% MeOH(aq) was separated by C_{18} reversed-phase HPLC (YMC ODS-A column, 25% MeOH(aq)) to yield, in order of elution, compounds **4**, **12**, and **13**. These metabolites were further purified by silica HPLC (YMC-silica column, 50% EtOAc in *n*-hexane). The fraction (1.7 g) eluted with 10% MeOH(aq) was separated by C_{18} reversed-phase HPLC (25% MeOH(aq)) to yield, in order of elution, compounds **1**–**3**, **5**–**11**, and **14**–**20**. Final purification was performed with silica HPLC (YMC-silica column, 40% EtOAc in *n*-hexane for **3**, **9**, **10**, and **20**, 30% EtOAc in *n*-hexane for **16**, and 25% EtOAc in *n*-hexane for the remaining compounds). The purified metabolites **1**–**20** were isolated in the following amounts: 49.8, 7.6, 22.6, 40.4, 5.3, 2.4, 63.1, 6.9, 7.7, 2.1, 3.9, 8.4, 39.6, 4.8, 5.2, 12.6, 5.9, 2.7, 3.2, and 2.4 mg, respectively.

Nahocol A (1): colorless gum; $[\alpha]_{\text{D}}^{20} -132.4$ (*c* 0.67, MeOH); UV (MeOH) λ_{max} (log ϵ) 216 (3.89), 239 (3.94), 283 (3.65) nm; IR (ZnSe) ν_{max} 3400 (br), 2934, 1713, 1497, 1450, 1375, 1215, 1168 cm^{-1} ; HREIMS m/z 486.2957 $[\text{M}]^+$ (calcd for $\text{C}_{29}\text{H}_{42}\text{O}_6$, 486.2981).

Nahocol A₁ (2): colorless gum; $[\alpha]_{\text{D}}^{20} -127.1$ (*c* 0.13, MeOH); UV (MeOH) λ_{max} (log ϵ) 217 (4.72), 237 (4.75), 274 (4.25) nm; IR (ZnSe) ν_{max} 2958, 2928, 2872, 1729, 1579, 1462, 1379, 1286 cm^{-1} ; HREIMS m/z 486.2980 $[\text{M}]^+$ (calcd for $\text{C}_{29}\text{H}_{42}\text{O}_6$, 486.2981).

Nahocol D₂ (3): colorless gum; $[\alpha]_{\text{D}}^{20} +17.3$ (*c* 0.60, MeOH); UV (MeOH) λ_{max} (log ϵ) 215 (3.51), 291 (3.54) nm; IR (ZnSe) ν_{max} 3450, 2958, 2927, 1728, 1578, 1496, 1450, 1376, 1287, 1215 cm^{-1} ; HREIMS m/z 486.2999 $[\text{M}]^+$ (calcd for $\text{C}_{29}\text{H}_{42}\text{O}_6$, 486.2981).

Nahocol D₁ (4): colorless gum; $[\alpha]_{\text{D}}^{20} +5.8$ (*c* 0.60, MeOH); UV (MeOH) λ_{max} (log ϵ) 212 (3.62), 297 (3.62) nm; IR (ZnSe) ν_{max} 3450 (br), 2958, 2927, 1728, 1496, 1458, 1378, 1286, 1215 cm^{-1} ; HREIMS m/z 468.2871 $[\text{M} - \text{H}_2\text{O}]^+$ (calcd for $\text{C}_{29}\text{H}_{40}\text{O}_5$, 468.2876).

Compound 5: colorless gum; $[\alpha]_{\text{D}}^{20} +33.0$ (*c* 0.40, MeOH); UV (MeOH) λ_{max} (log ϵ) 246 (3.95), 292 (3.60) nm; IR (ZnSe) ν_{max} 3450 (br), 2958, 2928, 2872, 1728, 1619, 1495, 1459, 1378, 1286 cm^{-1} ; HREIMS m/z 486.2971 $[\text{M}]^+$ (calcd for $\text{C}_{29}\text{H}_{42}\text{O}_6$, 486.2981).

Compound 6: colorless gum; $[\alpha]_{\text{D}}^{20} +34.5$ (*c* 0.07, MeOH); UV (MeOH) λ_{max} (log ϵ) 254 (3.25), 294 (3.60) nm; IR (ZnSe) ν_{max} 3400 (br), 2958, 2928, 2872, 1729, 1461, 1379, 1285, cm^{-1} ; HREIMS m/z 486.2977 $[\text{M}]^+$ (calcd for $\text{C}_{29}\text{H}_{42}\text{O}_6$, 486.2981).

Compound 7: colorless gum; $[\alpha]_{\text{D}}^{20} -77.7$ (*c* 0.93, MeOH); UV (MeOH) λ_{max} (log ϵ) 217 (4.00), 242 (4.07), 293 (3.67) nm; IR (ZnSe) ν_{max} 3450 (br), 2958, 2928, 1729, 1695, 1496, 1456, 1378, 1285 cm^{-1} ; for ^1H and ^{13}C NMR data, see Tables 1 and 2; HRFABMS m/z 485.2917 $[\text{M} + \text{H}]^+$ (calcd for $\text{C}_{29}\text{H}_{41}\text{O}_6$, 485.2903).

Compound 8: colorless gum; $[\alpha]_{\text{D}}^{20} -30.1$ (*c* 0.13, MeOH); UV

(MeOH) λ_{max} (log ϵ) 216 (4.57), 238 (4.63) nm; IR (ZnSe) ν_{max} 3450 (br), 2958, 2872, 1729, 1462, 1379, 1285 cm^{-1} ; for ^1H and ^{13}C NMR data, see Tables 1 and 2; HREIMS m/z 484.2820 $[\text{M}]^+$ (calcd for $\text{C}_{29}\text{H}_{40}\text{O}_6$, 484.2825).

Compound 9: colorless gum; $[\alpha]_{\text{D}}^{20} -15.9$ (*c* 0.33, MeOH); UV (MeOH) λ_{max} (log ϵ) 217 (4.40), 236 (4.31), 274 (3.94) nm; IR (ZnSe) ν_{max} 3450 (br), 2958, 2872, 1728, 1495, 1459, 1378, 1286 cm^{-1} ; for ^1H and ^{13}C NMR data, see Tables 1 and 2; HREIMS m/z 484.2820 $[\text{M}]^+$ (calcd for $\text{C}_{29}\text{H}_{40}\text{O}_6$, 484.2825).

Compound 10: colorless gum; $[\alpha]_{\text{D}}^{20} -19.5$ (*c* 0.27, MeOH); UV (MeOH) λ_{max} (log ϵ) 216 (2.11), 242 (2.58), 291 (2.22) nm; IR (ZnSe) ν_{max} 3450 (br), 2958, 2927, 2857, 1728, 1462, 1379, 1286 cm^{-1} ; for ^1H and ^{13}C NMR data, see Tables 1 and 2; HREIMS m/z 470.3036 $[\text{M}]^+$ (calcd for $\text{C}_{29}\text{H}_{42}\text{O}_5$, 470.3032).

Compound 11: colorless gum; $[\alpha]_{\text{D}}^{20} -12.8$ (*c* 0.13, MeOH); UV (MeOH) λ_{max} (log ϵ) 215 (2.21), 223 (3.52, sh), 241.5 (2.43), 290 (2.02) nm; IR (ZnSe) ν_{max} 2958, 2927, 2871, 1728, 1691, 1600, 1463, 1379, 1284 cm^{-1} ; for ^1H and ^{13}C NMR data, see Tables 1 and 2; HREIMS m/z 466.2722 $[\text{M}]^+$ (calcd for $\text{C}_{29}\text{H}_{38}\text{O}_5$, 466.2719).

Compound 12: colorless gum; $[\alpha]_{\text{D}}^{20} -5.6$ (*c* 0.20, MeOH); UV (MeOH) λ_{max} (log ϵ) 239 (3.90) nm; IR (ZnSe) ν_{max} 3400 (br), 2958, 2928, 2872, 1729, 1579, 1462, 1379, 1286 cm^{-1} ; HREIMS m/z 468.2863 $[\text{M} - \text{H}_2\text{O}]^+$ (calcd for $\text{C}_{29}\text{H}_{40}\text{O}_5$, 468.2876).

Compound 13: colorless gum; $[\alpha]_{\text{D}}^{20} -0.5$ (*c* 1.20, MeOH); UV (MeOH) λ_{max} (log ϵ) 214 (4.99), 272 (3.99), 283 (4.01) nm; IR (ZnSe) ν_{max} 3450 (br), 2958, 2927, 1727, 1602, 1458, 1378, 1285 cm^{-1} ; HREIMS m/z 468.2873 $[\text{M} - \text{H}_2\text{O}]^+$ (calcd for $\text{C}_{29}\text{H}_{40}\text{O}_5$, 468.2876).

Compound 14: colorless gum; $[\alpha]_{\text{D}}^{20} -9.2$ (*c* 0.13, MeOH); UV (MeOH) λ_{max} (log ϵ) 245 (3.33), 274 (3.24) nm; IR (ZnSe) ν_{max} 3450 (br), 2958, 2872, 1730, 1581, 1462, 1379, 1285 cm^{-1} ; for ^1H and ^{13}C NMR data, see Tables 1 and 3; HREIMS m/z 484.2803 $[\text{M}]^+$ (calcd for $\text{C}_{29}\text{H}_{40}\text{O}_6$, 484.2825).

Compound 15: colorless gum; $[\alpha]_{\text{D}}^{20} -6.5$ (*c* 0.20, MeOH); UV (MeOH) λ_{max} (log ϵ) 216 (3.33), 240 (3.70), 274 (3.33) nm; IR (ZnSe) ν_{max} 3450 (br), 2958, 2928, 2872, 1729, 1579, 1462, 1379, 1285 cm^{-1} ; for ^1H and ^{13}C NMR data, see Tables 1 and 3; HREIMS m/z 484.2830 $[\text{M}]^+$ (calcd for $\text{C}_{29}\text{H}_{40}\text{O}_6$, 484.2825).

Compound 16: colorless gum; $[\alpha]_{\text{D}}^{20} -128.1$ (*c* 0.47, MeOH); UV (MeOH) λ_{max} (log ϵ) 212 (4.53), 292 (3.74) nm; IR (ZnSe) ν_{max} 3450 (br), 2959, 2929, 2872, 1728, 1601, 1461, 1379, 1286 cm^{-1} ; for ^1H and ^{13}C NMR data, see Tables 1 and 3; HREIMS m/z 486.2999 $[\text{M}]^+$ (calcd for $\text{C}_{29}\text{H}_{42}\text{O}_6$, 486.2981).

Compound 17: colorless gum; $[\alpha]_{\text{D}}^{20} -20.9$ (*c* 0.27, MeOH); UV (MeOH) λ_{max} (log ϵ) 217 (4.40), 236 (4.31), 274 (3.94) nm; IR (ZnSe)

ν_{\max} 3450 (br), 2958, 2928, 2872, 1729, 1579, 1462, 1379, 1286 cm^{-1} ; for ^1H and ^{13}C NMR data, see Tables 1 and 3; HREIMS m/z 486.2990 $[\text{M}]^+$ (calcd for $\text{C}_{29}\text{H}_{42}\text{O}_6$, 486.2981).

Sargahydroquinoic acid (18): colorless gum; $[\alpha]_D^{20}$ -9.3 (c 0.30, MeOH); UV (MeOH) λ_{\max} (log ϵ) 258 (1.96), 296 (1.72) nm; IR (ZnSe) ν_{\max} 3450 (br), 2959, 2926, 1727, 1655, 1462, 1379, 1286 cm^{-1} ; HREIMS m/z 426.2764 $[\text{M}]^+$ (calcd for $\text{C}_{27}\text{H}_{38}\text{O}_4$, 426.2770).

Compound 19: colorless gum; $[\alpha]_D^{20}$ -59.3 (c 0.30, MeOH); UV (MeOH) λ_{\max} (log ϵ) 250 (2.32), 298 (2.32) nm; IR (ZnSe) ν_{\max} 3450 (br), 2958, 2928, 2857, 1727, 1611, 1464, 1379, 1285 cm^{-1} ; for ^1H and ^{13}C NMR data, see Tables 1 and 3; HREIMS m/z 426.2760 $[\text{M} - \text{H}_2\text{O}]^+$ (calcd for $\text{C}_{27}\text{H}_{38}\text{O}_4$, 426.2770).

Compound 20: colorless gum; $[\alpha]_D^{20}$ -12.3 (c 0.30, MeOH); UV (MeOH) λ_{\max} (log ϵ) 215 (1.82), 241 (1.92), 294 (1.88) nm; IR (ZnSe) ν_{\max} 3500 (br), 2958, 2927, 2857, 1729, 1684, 1461, 1378, 1285 cm^{-1} ; for ^1H and ^{13}C NMR data, see Tables 1 and 3; HRFABMS m/z 469.2955 $[\text{M} - \text{H}_2\text{O} + \text{H}]^+$ (calcd for $\text{C}_{29}\text{H}_{41}\text{O}_5$, 469.2954).

Esterification with (–)-(S)- α -Methoxy- α -(trifluoromethyl)phenylacetyl (MTPA) Chloride. MTPA esterifications of compounds **1**, **2**, **5**, **7–9**, and **14–17** were carried out following the general procedure. To a solution of 1.1–1.6 mg of an alcoholic compound in 100 μL of dry pyridine was added 20 μL of (–)-(S)-MTPA chloride. The mixture was allowed to stand under N_2 at room temperature for 2 h. After the consumption of starting material was confirmed by TLC, 50 μL of H_2O , 100 μL of CH_2Cl_2 , and MeOH were added. The solvents were removed under vacuum, and the residue was separated by silica HPLC (20–30% EtOAc in *n*-hexane) to give 1.1–1.3 mg of (S)-MTPA ester. The corresponding (R)-MTPA ester was also obtained from the same esterifications with (+)-(R)-MTPA chloride. The reaction yields and ^1H NMR data of MTPA esters are summarized in the Supporting Information.

Ketal Formation of Nahocol D₂ (3). To a stirred solution of 3 mg of **3** in 3 mL of dry acetone were added 0.2 mL of 2,2-dimethoxypropane and 1.5 mg of PPTS. The mixture was refluxed under N_2 for 30 min. To quench the reaction, 0.2 mL of Et_3N was added and the resulting mixture was refluxed for 15 min. The mixture was filtered using a silica Sep-Pak column (25% EtOAc in *n*-hexane) and purified by silica HPLC (40% EtOAc in *n*-hexane), 1.8 mg: ^1H NMR (CDCl_3) δ 6.91 (1 H, d, J = 8.9 Hz, H-3), 6.66 (1 H, d, J = 2.9 Hz, H-6), 6.56 (1 H, dd, J = 8.9, 2.9 Hz, H-4), 6.02 (1 H, dd, J = 11.0, 17.6 Hz, H-2'), 5.46 (1 H, t, J = 6.9 Hz, H-10'), 5.16 (1 H, d, J = 11.0 Hz, H-1'), 5.15 (1 H, d, J = 17.6 Hz, H-1'), 5.14 (1 H, d, J = 7.8 Hz, H-14'), 5.09 (1 H, d, J = 8.9 Hz, H-6'), 4.45 (1 H, dd, J = 8.8, 7.8 Hz, H-13'), 3.95 (1 H, d, J = 8.8 Hz, H-12'), 3.66 (3 H, s, H-OMe), 3.55 (2 H, d, J = 15.9 Hz, H-1''), 2.10 (2 H, m, H-9'), 2.05 (2 H, m, H-5'), 1.97 (2 H, m, H-8'), 1.73 (3 H, s, H-16'), 1.71 (2 H, m, H-4'), 1.63 (3 H, s, H-19'), 1.62 (3 H, s, H-20'), 1.55 (3 H, s, H-18'), 1.43 (3 H, s, ketal), 1.41 (3 H, s, ketal), 1.34 (3 H, s, H-17').

Ketal Formation of Nahocol D₁ (4). **4** was prepared following the procedure for **3**. From 3.1 mg of **4** was obtained 1.2 mg of the purified ketal: ^1H NMR (CDCl_3) δ 6.93 (1 H, d, J = 8.8 Hz, H-3), 6.68 (1 H, d, J = 3.1 Hz, H-6), 6.59 (1 H, dd, J = 8.8, 3.1 Hz, H-4), 6.04 (1 H, dd, J = 10.9, 17.7 Hz, H-2'), 5.43 (1 H, t, J = 6.6 Hz, H-10'), 5.18 (1 H, d, J = 10.9 Hz, H-1'), 5.16 (1 H, d, J = 17.7 Hz, H-1'), 5.12 (1 H, t, J = 8.8 Hz, H-14'), 5.11 (1 H, 8.9 Hz, H-6'), 4.93 (1 H, dd, J = 8.8, 7.2 Hz, H-13'), 4.53 (1 H, d, J = 7.2 Hz, H-12'), 3.58 (2 H, d, J = 16.5 Hz, H-1''), 3.49 (3 H, s, H-OMe), 2.12 (2 H, m, H-9'), 2.07 (2 H, m, H-5'), 1.97 (2 H, m, H-8'), 1.74 (2 H, m, H-4'), 1.70 (3 H, s, H-16'), 1.67 (3 H, s, H-20'), 1.58 (3 H, s, H-18'), 1.58 (3 H, s, ketal), 1.51 (3 H, s, H-19'), 1.37 (3 H, s, ketal), 1.34 (3 H, s, H-17').

Ketal Formation of Isonahocol D₁ (12). From 3.1 mg of **12** was obtained 1.2 mg of the purified ketal: ^1H NMR (CDCl_3) δ 6.55 (1 H, d, J = 2.9 Hz, H-4), 6.44 (1 H, d, J = 2.9 Hz, H-6), 5.42 (1 H, t, J = 6.9 Hz, H-10'), 5.32 (1 H, t, J = 7.3 Hz, H-2'), 5.13 (1 H, d, J = 6.7 Hz, H-6'), 5.10 (1 H, d, J = 9.0 Hz, H-14'), 4.94 (1 H, dd, J = 9.0, 7.1

Hz, H-13'), 4.53 (1 H, d, J = 7.1 Hz, H-12'), 3.71 (3 H, s, H-OMe), 3.58 (2 H, s, H-1''), 3.31 (2 H, d, J = 7.3 Hz, H-1'), 2.12 (2 H, m, H-4'), 2.10 (2 H, m, H-8'), 2.10 (2 H, m, H-9'), 2.00 (2 H, m, H-5'), 1.73 (3 H, s, H-17'), 1.68 (3 H, s, H-20'), 1.65 (3 H, s, H-16'), 1.57 (3 H, s, H-18'), 1.51 (3 H, s, ketal), 1.50 (3 H, s, H-19'), 1.38 (3 H, s, ketal).

Ketal Formation of Isonahocol D₂ (13). From 3.0 mg of **13** was obtained 1.4 mg of the purified ketal: ^1H NMR (CDCl_3) δ 6.54 (1 H, d, J = 2.8 Hz, H-4), 6.45 (1 H, d, J = 2.8 Hz, H-6), 5.42 (1 H, t, J = 7.0 Hz, H-10'), 5.27 (1 H, t, J = 7.1 Hz, H-2'), 5.09 (1 H, d, J = 9.0 Hz, H-14'), 5.08 (1 H, t, J = 5.5 Hz, H-6'), 4.92 (1 H, dd, J = 9.0, 7.1 Hz, H-13'), 4.50 (1 H, d, J = 7.1 Hz, H-12'), 3.71 (3 H, s, H-OMe), 3.58 (2 H, s, H-1''), 3.32 (2 H, d, J = 7.1 Hz, H-1'), 2.12 (2 H, m, H-4'), 2.10 (2 H, m, H-5'), 2.08 (2 H, m, H-9'), 1.97 (2 H, m, H-8'), 1.70 (3 H, s, H-17'), 1.68 (3 H, s, H-16'), 1.65 (3 H, s, H-20'), 1.60 (3 H, s, H-18'), 1.51 (3 H, s, ketal), 1.50 (3 H, s, H-19'), 1.37 (3 H, s, ketal).

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Supporting Information Available: The reaction yields and ^1H NMR data of MTPA esters for compounds **1**, **2**, **5**, **7–9**, and **14–17**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References and Notes

- (1) Luckner, M. *Secondary Metabolism in Microorganisms, Plants, and Animals*; Springer-Verlag: Berlin, 1984; p 464.
- (2) Blunt, J. W.; Copp, B. R.; Hu, W.-P.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat Prod. Rep.* **2007**, *24*, 31–86, and earlier reports in the series: Alls, R.; Pioveti, L. *Biochem. Syst. Ecol.* **1995**, *23*, 723–745.
- (3) Amico, V.; Cunsolo, F.; Neri, P.; Piatelli, M.; Ruberto, G. *Phytochemistry* **1988**, *27*, 1327–1331.
- (4) Numata, A.; Kanbara, S.; Takahashi, C.; Fujiki, R.; Yoneda, M.; Usami, Y.; Fujita, E. *Phytochemistry* **1992**, *31*, 1209–1213.
- (5) Tsang, C. K.; Ina, A.; Goto, T.; Kamei, Y. *Neuroscience* **2005**, *132*, 633–643.
- (6) Mori, J.; Iwashima, M.; Takeuchi, M.; Saito, H. *Chem. Pharm. Bull.* **2006**, *54*, 391–396.
- (7) Seo, Y.; Park, K. E.; Kim, Y. A.; Lee, H.-J.; Yoo, J.-S.; Ahn, J.-W.; Lee, B.-J. *Chem. Pharm. Bull.* **2006**, *54*, 1730–1733.
- (8) Choi, B. W.; Ryu, G.; Park, S. H.; Kim, E. S.; Shin, J.; Roh, S. S.; Shin, H. C.; Lee, B. H. *Phytother. Res.* **2007**, *21*, 423–426.
- (9) Hur, S.; Lee, H.; Kim, Y.; Lee, B.; H.; Shin, J.; Kim, T.-Y. *Eur. J. Pharmacol.* **2008**, *582*, 1–11.
- (10) Jang, K. H.; Lee, B. W.; Choi, B. W.; Lee, H.-S.; Shin, J. *J. Nat. Prod.* **2005**, *68*, 716–723.
- (11) Chang, H. W.; Jang, K. H.; Lee, D.; Kang, H. R.; Kim, T.-Y.; Lee, B. H.; Choi, B. W.; Kim, S.; Shin, J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3589–3592.
- (12) Tsuchiya, N.; Sato, A.; Haruyama, H.; Watanabe, T.; Iijima, Y. *Phytochemistry* **1998**, *48*, 1003–1011.
- (13) Segawa, M.; Shirahama, H. *Chem. Lett.* **1987**, 1365–1366.
- (14) Jang, K. H.; Chung, S.-C.; Shin, J.; Lee, S.-H.; Kim, T.-I.; Lee, H.-S.; Oh, K.-B. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5366–5369.
- (15) Lee, H.-S.; Lee, T.-H.; Yang, S. H.; Shin, H. J.; Shin, J.; Oh, K.-B. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2483–2486.

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