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Research article

Design and synthesis of resin-attachable spatane analog for prevention of sea urchin-induced seaweed loss

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Abstract

Importance of the work: This study addresses a critical environmental issue with an innovative, potentially sustainable solution. By providing hope for restoring essential coastal ecosystems, it underscores the potential positive impact of research on the environment.

Objectives: To create a new spatane-type diterpenoid analog for attachment to polymers to prevent rocky-shore denudation.

Materials and Methods: The strategy utilized the method of Salomon et al. (1991) to build a spatane framework and then transform it into a target non-natural compound, as an innovative approach in the field. The methodology involved altering the spatane framework to include a methylene chain featuring a terminal alkyne, which should be of interest to researchers.

Results: A [2+2] photocycloaddition reaction was achieved between 3-methylcyclopent-2-en-1-one and (1*R**,2*R**,4*R**)-bicyclo[2.2.1]hept-5-en-2-yl acetate to construct the core structure of the spatane diterpenoid. This reaction was efficient and laid the foundation for subsequent modifications. Through a series of reactions, including Jones oxidation, Baeyer-Villiger oxidation, and reduction using DIBAL, the key intermediate compound (23) was synthesized successfully, containing the desired spatane framework and a functional group suitable for further transformation.

Main finding: The spatane core structure was synthesized successfully and efficiently via a [2+2] photocycloaddition reaction, demonstrating the feasibility of creating a novel spatane-type diterpenoid analog to deter sea urchin grazing, instilling confidence in potential further related research.

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Introduction

Coastal areas are experiencing a phenomenon transliterated from Japanese as 'isoyake' (rocky-shore denudation), which negatively affects fishery resources and marine biodiversity. This issue involves the loss of seaweed and the degradation of rocky coastal environments that previously supported abundant seaweed growth, consequently having a major impact on marine ecosystems (Miura et al, 2018). Although several factors contribute to this problem, including high ocean temperatures and pollution, the leading cause is overgrazing by sea urchins (Belleza et al, 2023). While edible sea urchins could be harvested, those responsible for rocky-shore denudation are often of poor quality and unsuitable for consumption (Fisheries Agency, Japan. 2024), leaving this issue unresolved. This situation has resulted in decreased fishery resources and biodiversity, posing a substantial threat to sustainable fishing practices, particularly in coastal regions (Okuda, 2008).

Notably, certain compounds have been shown to suppress sea urchin-feeding behavior. One such substance is the spatane-type diterpene (1), produced by the brown alga *Dilophus okamurae* (E.Y. Dawson, 1950) (Fig. 1). The structure of this compound has been isolated and identified (Gerwick and Fenical, 1983; Kurata et al., 1988; Suzuki et al., 2002; Li et al., 2011). Furthermore, studies have indicated that sea urchins tend to avoid areas where *Dilophus okamurae* is abundant (Kurata et al., 1990).

The distinctive tricyclic structure of spatane-type diterpenoids, composed of fused 5-4-5 membered rings, would be essential for their ability to inhibit feeding. With this in mind, the current study developed a synthetic spatane analog (2) by altering the diene-containing side chain to incorporate a terminal alkyne, enabling its modification through click chemistry (Kolb et al., 2001; Tiwari et al., 2016) (Fig. 2). Various resins are accessible for clickable organic compounds (Punna et al. 2005). Attaching the spatane analog (2) to a polymer could prevent its diffusion in water (Fig. 3). The current objective was to create a synthetic substance capable of adhering to polymer-based materials, such as fishing nets, while resisting dissolution in water. This compound was designed to potentially address the issue of rocky shoreline degradation caused by sea urchins. This paper outlines the synthesis process of the custom-engineered artificial molecule.

During the 1980s, advances were made in the total synthesis of spatane-type natural products, with Salomon (1991) establishing a synthetic pathway. Several other examples of syntheses related to the spatane skeleton have also been reported. During the 2000s, Mascitti and Corey (2006) reported the synthesis of a natural product using a photochemical [2+2] cycloaddition reaction, while Miesch et al. (2013) reported the synthesis of the spatane skeleton from a bicyclo[3.2.0]heptane (Scheme 1) (Snider et al., 1985; Harmata and Rashatasakhon, 2001; Hoshikawa et al., 2012; Miesch et al., 2013). The current strategy utilized the method of Salomon et al. (1991) to build a spatane framework, which was planned to be transformed into the target non-natural compound by altering it to include a methylene chain featuring a terminal alkyne.

For the synthesis of the spatane-type diterpenoid compound (2), the current approach involved altering the ester component of compound (14) and converting it into a methylene chain with a terminal alkyne. The aim was to obtain compound (14) through the Baeyer-Villiger oxidation of compound (15), which would be generated via a [2+2] photocycloaddition reaction, followed by hydrolysis. This retrosynthetic analysis would allow the selection of commercially available 3-methylcyclopent-2-en-1-one (16) and (1*R**,2*R**,4*R**)-bicyclo[2.2.1]hept-5-en-2-yl acetate (17) as the initial reagents (Scheme 2).

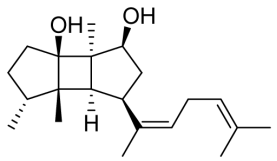

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Fig. 1 Structure of spatane-type diterpene compound (1)

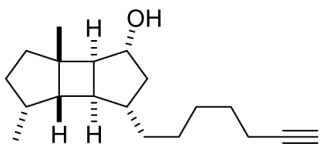


Fig. 2 Structure of non-natural spatane analog (2)

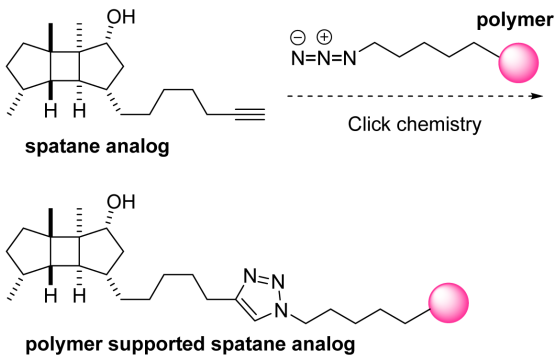
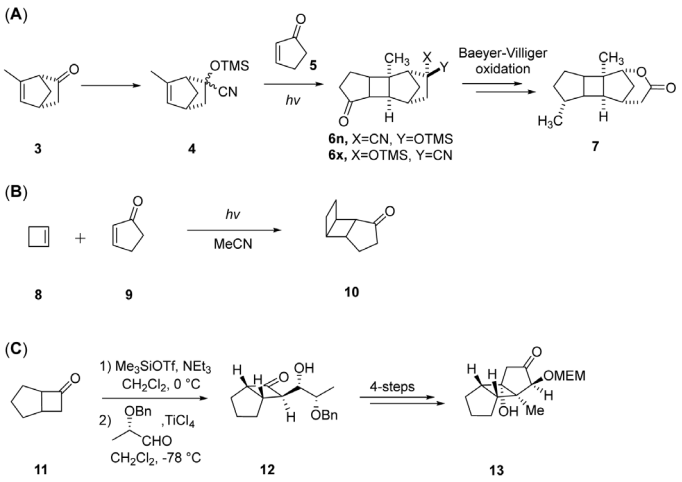


Fig. 3 Strategy for preparation of polymer-supported spatane analog using click chemistry

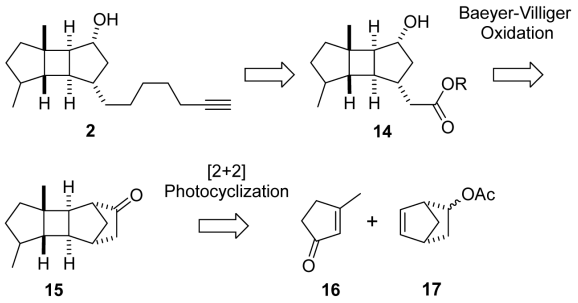


Scheme 1. Reported synthetic routes of spatane compound. (**A**) Total synthesis of spatane-type natural product (**7**) reported by Salomon et al. (1991); (**B**) Corey et al. (2006) method to construct tricyclic compound using [2+2] cycloaddition (**10**); (**C**) synthesis of spatane-type compound (**13**) reported by Miesche et al. (2013)

Materials and Methods

General methods

Unless stated otherwise, anhydrous reactions were conducted in flame-dried glassware under an atmosphere of argon using commercially available anhydrous solvents. Thin-layer chromatography (TLC) was conducted with silica gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV and molybdatophosphoric acid staining. Silica gel 60N (neutral, sphere, particle size 0.063–0.210 mm) was used for column chromatography. ^{1}H NMR spectra were recorded on a JEOL JNM-ECZ400 (400 MHz) spectrometer. Data for ^{1}H spectra were: chemical shift (δ, measured in parts per million, ppm), multiplicity, coupling constant (J), measured in herz), integration and were referenced to the residual solvent peaks of 7.26 ppm for $CDCl_3$ or 0.00 ppm for tetramethylsilane (TMS). The ^{13}C NMR spectra were reported regarding a chemical shift (at 100 MHz) and referenced to the residual solvent peak at 77.0 ppm for $CDCl_3$. High-resolution mass spectra (HRMS) were obtained using a Thermo Fisher Scientific Orbitrap Exploris 240 instrument operating in electrospray positive ionization mode.



Scheme 2. Retrosynthetic analysis of non-natural spatane analog (**2**)

Synthesis

(3aR,3bR*,4R*,5R*,7R*,7aR*,7bS*)-3a-metyl-1-oxodecahydro-1H-4,7-methanocyclopenta[3,4]cyclobuta[1,2]benzene-5-yl acetate (18)*

To a clean, dry Pyrex photoreactor under argon was added the (1*R**,2*R**,4*R**)-bicyclo [2.2.1] hept-5-en-2-yl acetate (0.15 mL, 1.0 mmol) and 3-methylcyclopent-2-en-1-one (0.10 mL, 1.0 mmol) was added in dry MeCN (15 mL). The mixture was irradiated using a light source at 356 nm for a total irradiation time of 69 hr. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The resulting material was purified using column chromatography on silica (EtOAc:Hex=1:1) to give 18 (182 mg, 71%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, s), 1.23 (6H, m), 1.68–2.68 (10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 20.1, 21.2, 23.3, 23.7, 34.1, 37.3, 38.3, 41.0, 45.1, 50.5, 52.9, 54.5, 171.1, 220.7. HRMS (electrospray ionization, ESI), *m/z* calcd for $C_{15}H_{21}O_3$ $[M+H]^+$ 249.1485, found 249.1482.

(3aR,3bR*,4R*,5R*,7R*,7aR*,7bS*)-5-hydroxy-3a-methyldecahydro-1H-4,7-methanocyclopenta[3,4]cyclobuta[1,2]benzen-1-one (19)*

Potassium carbonate (322 mg, 2.33 mmol) was added to a solution of compound 18 (289 mg,1.17 mmol) in MeOH (3 mL). The resulting reaction mixture was stirred overnight at room temperature. The reaction was quenched with NH_4Cl aq (2 mL) and the solution was extracted using EtOAc (×3). The combined organic layer was washed with water and brine and then dried over Na_2SO_4. The resulting material was purified using column chromatography on silica (EtOAc:Hex=1:1) to give the title compound 19 (217 mg, 90%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.04–2.26 (17H, m), 4.22 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 22.8, 29.2, 30.6, 32.0, 37.2, 38.0, 39.1, 40.8, 44.2, 51.2, 59.4, 217.4. HRMS (ESI), *m/z* calcd for $C_{13}H_{19}O_2$ $[M+H]^+$ 207.1380, found 207.1376.

(3aR,3bR*,4R*,7R*,7aR*,7bS*)-3a-methyloctahydro-1H-4,7-methanocyclopenta[3,4]cyclobuta[1,2]benzene-1,5(2H)-dione (20)*

To a solution of compound 19 (59 mg, 0.29 mmol) in acetone (1 mL) was added Jones reagent (1.1 mL, 0.29 mmol, 2.5M) at 0°C and the mixture was stirred at room temperature in an argon atmosphere overnight. The reaction was quenched with 2-propanol (2 mL) and the solution was extracted using EtOAc (×3). The combined organic layer was washed with water and brine and then dried over Na_2SO_4. The resulting material was filtered and the filtrate was concentrated *in vacuo* to give compound 20 (61 mg), with a 100% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.24–2.78 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 22.8, 29.9, 32.0, 37.2, 38.0, 39.1, 40.8, 44.2, 51.2, 59.4, 217.4, 219.2. HRMS (ESI), *m/z* calcd for $C_{13}H_{16}O_2Na$ $[M+Na]^+$ 227.1043, found 227.1040.

(1R,5R*,5aR*,5bS*,8aR*,8bS*)-8a-methyloctahydro-1H-1,5-methanocyclopenta[3,4]cyclobuta[1,2-c]oxepine-3,6-dione (21)*

To a solution of compound 20 (17 mg, 0.080 mmol) in dry CH_2Cl_2 (2 mL) was added *m*CPBA (14 mg, 0.080 mmol) at 0°C and the mixture was stirred for 4 hr at room temperature. The reaction was diluted with CH_2Cl_2 (2 mL) and the aqueous layer was extracted using CH_2Cl_2. The combined organic extracts were washed using saturated sodium bicarbonate (1 mL) and brine, then dried over Na2SO4 and concentrated *in vacuo* to give compound 21 (17 mg), with a 91% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.20–2.60 (12H), 4.35 (d, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 33.0, 34.0, 34.8, 36.3, 42.2, 43.9, 44.8, 46.8, 49.1, 50.3, 171.4, 213.7. HRMS (ESI), *m/z* calcd for $C_{13}H_{17}O_3$ $[M+H]^+$ 221.1172, found 221.1170.

(3aR,3bS*,6aR*,6bS*)-4-hydroxy-6-(2-oxopropyl) octahydrocyclobuta[1,2:3,4]di[5]annulen-1(2H)-one (22)*

To a solution of compound 21 (15 mg, 0.070 mmol) in MeOH (1 mL) was added NaOMe (4.0 mg, 0.070 mmol) and the mixture was stirred at room temperature in an argon atmosphere for 5 hr. The reaction was quenched using HCl aq (1 mL) and the solution was extracted with EtOAc (×3). The combined organic layer was washed using water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to yield a compound 22 (18 mg), with a 100% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.95–2.68 (17H), 3.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 29.2, 31.9, 34.0, 36.0, 39.5, 43.2, 43.9, 46.9, 49.1, 50.3, 51.6, 174.7, 215.2. HRMS (ESI), *m/z* calcd for $C_{14}H_{20}O_4Na$ $[M+Na]^+$ 275.1254, found 275.1250.

2-((3aS,3bR*,6aS*,6bR*)-3-hydroxy-3b-methyl-6-oxodecahydrocyclobuta[1,2:3,4]di[5]annulen-1-yl) acetaldehyde (23)*

To a solution 22 (37 mg, 0.15 mmol) in CH_2Cl_2 (1 mL) was added DIBAL (1.0 M) (0.19 mL, 0.19 mmol) and the resulting solution was stirred at 0ºC in an argon atmosphere for 30 min. The reaction was quenched using MeOH (1 mL), and 1 M H_2SO_4 aq (1 mL) was added to the mixture. After the mixture had been stirred for 2 hr, the solution was dried over Na_2SO_4. The solution was filtered through Celite. The resulting material was purified using preparative thin-layer chromatography (EtOAc:Hex=1:1) to give compound 23 (32 mg), with a 98% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.94–2.71 (15H), 4.25 (m, 1H), 9.72 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 23.5, 31.4, 33.2, 34.5, 35.3, 35.9, 37.1, 40.0, 44.1, 45.2, 50.2, 54.5, 202.8, 215.2.

5-Iodopent-1-yne (25)

Triphenylphosphine (1.2 g, 4.5 mmol), imidazole (0.3 g, 4.5 mmol), and iodine (1.1 g, 4.5 mmol) were added to a solution of pent-3-yn-1-ol (0.3 mL, 3.0 mmol) in anhydrous acetonitrile (5 mL). The mixture was stirred at 60°C for 4 hr. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified using column chromatography on silica (EtOAc:Hex=3:7) to give 25 (0.53 g, 92%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.99–2.02 (m, 3H), 2.32 (t, 2H), 3.31 (t, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.0, 19.3, 31.7, 69.4, 82.2.

Pent-4-yn-1-yltriphenylphosphonium iodide (26)

Triphenylphosphine (553 mg, 2.11 mmol) was added to a solution of 25 (410 mg, 2.11 mmol) in toluene (5 mL) and the mixture was stirred at 100°C overnight. The solvent was removed and column chromatography on silica (DCM/methanol, 20:1) yielded 26 (308 mg, 28%) as a white solid. Rf = 0.25 (DCM/methanol, 20:1). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.90 (m, 2H), 2.01 (t, J=2.4 Hz, 1H), 2.70 (t, 2H), 3.96 (m, 2H), 7.72 (m, 6H), 7.84 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 21.7, 22.1, 70.7, 82.3, 117.2, 130.6, 133.7, 135.3. HRMS (ESI), *m/z* calcd for $C_{23}H_{23}IP$ $[M+H]^+$ 457.0577, found 457.0568.

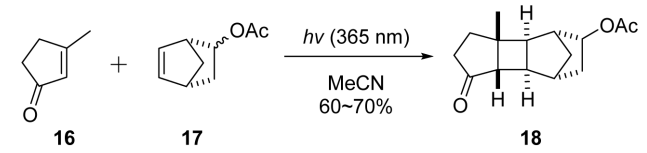
Results and Discussion

Initially, 3-methylcyclopent-2-en-1-one (16) and (1*R**,2*R**,4*R**)-bicyclo[2.2.1]hept-5-en-2-yl acetate (17) were

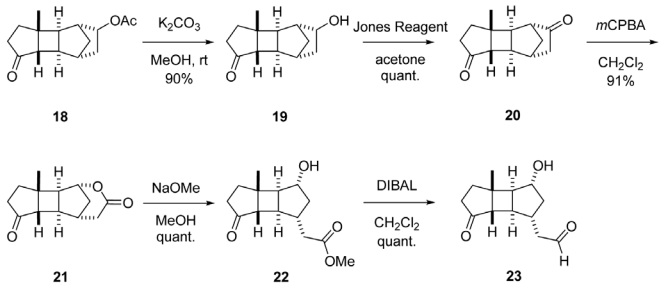
illuminated, initiating a [2+2] cycloaddition. This reaction generated a spatane skeleton, resulting in compound 18. The process was most effective when conducted in acetonitrile (MeCN) using light at a wavelength of 356 nm (Scheme 3). This wavelength proved more effective than the traditional wavelength (254 nm), which has excessive energy that can damage the product and result in a reduced yield. Next, compound (20) was synthesized via Jones oxidation of compound 19, derived from alkaline hydrolysis of compound 18. Subsequently, a Baeyer-Villiger oxidation was performed using *m*CPBA, followed by hydrolysis to yield compound 22. The final step involved the DIBAL-mediated reduction of the ester group in compound 22, producing compound 23 (Scheme 4).

It has been intended to use the Wittig reaction as the synthetic strategy to transform compound (23) into a methylene chain featuring a terminal alkyne. (Hotling et al., 2014). Commercially available pent-4-yn-1-ol (24) underwent an Appel reaction to form 5-iodopent-1-yne (25). Then, this intermediate was transformed into Wittig salt (26) (Scheme 5). The Wittig reaction between compounds 26 and 23 was unsuccessful, likely due to the instability of compound 23. The research group involved with the current study is conducting further studies on this reaction. In upcoming research, the synthesized non-natural spatane-type molecules will serve as precursors for creating methylene chains with terminal alkynes, which are essential for resin attachment. This transformation will be accomplished using Wittig reagents (26). Click chemistry will link the resulting non-natural compound (23) to polymeric materials. In addition, the established synthetic pathway will produce a range of related compounds, including stereoisomers and variants with different side-chain lengths. Bioassay techniques will be utilized to optimize the structure of the spatane-type molecule that exhibits the most potent feeding deterrent activity.

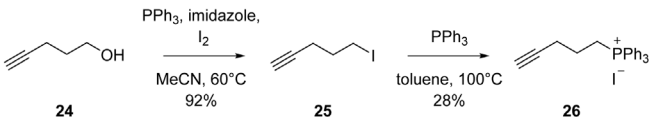
Once synthesized, compound 23 can be further modified to enable bonding with polymeric materials containing azide groups (Sibbersen et al., 2014). This innovative technique offers a way to mitigate sea urchin grazing damage on seaweed without dispersing in water. This approach remains unexplored, with manual sea urchin removal still being the primary method (Fisheries Agency, Japan. 2024). However, some regions have experienced large-scale sea urchin die-off (Roth et al., 2024), underscoring the urgent need for a new approach to grazing damage control that does not lead to species extinction. This study has presented a strategy for reducing the impact of sea urchin grazing. Furthermore, refining this method could result in more effective and precise prevention of grazing damage.



Scheme 3. [2+2] Photocyclization reaction



Scheme 4. Synthesis of compound (**23**) from compound (**18**)



Scheme 5. Synthesis of Wittig salt (**26**)

A comparable strategy has been applied in Africa, where insecticide-treated nets help to prevent malaria transmission (Paton et al., 2019). Similarly, the current approach utilizes bioactive molecules attached to polymers, potentially addressing the environmental issue of ocean desertification and benefiting the fishing industry by safeguarding fishery resources without causing unnecessary sea urchin extinction.

In conclusion, a spatane skeleton with a high yield was effectively synthesized. The spatane framework was built using a [2+2] photocycloaddition reaction. Using the method of Salomon et al. (1991), 6-methylbicyclo[2.2.1]hept-5-ene-2-one (3) was produced through a series of reactions involving vinyl acetate and methyl-1,5-cyclopentadiene. The process included a Diels-Alder reaction, followed by hydrolysis and Jones oxidation. Then, the resulting ketone (3) was transformed into a cyanohydrin silyl ether (4) by reacting it with trimethylsilyl cyanide. The spatane skeleton was successfully synthesized through a subsequent photoreaction with cyclopent-2-en-1 (5). Notably, the current method reduced the number of synthetic steps by utilizing commercially available (1*R**,2*R**,4*R**)-bicyclo[2.2.1]hept-5-en-2-yl acetate (17) as the initial compound. Additionally, the yield was enhanced by fine-tuning the reaction conditions, which included using 365 nm

wavelength light and using degassed acetonitrile as the reaction medium. The subsequent step involved transforming the newly created spatane-type compound into a methylene chain featuring a terminal alkyne (essential for resin attachment) using a Wittig reagent reaction. Linking natural products to polymers is anticipated to become a feasible solution to combat seaweed bed deterioration in the near future.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Acknowledgements

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References

Belleza, D.F.C., Urae, T., Tanimae, S., Toyama, K., Isoda, A., Nishihara, G.N. 2023. The behavior of sympatric sea urchin species across an ecosystem state gradient. PeerJ. 11: e15511. doi.org/10.7717/peerj.15511

Dawson, E.Y. 1950. Notes on some Pacific Mexican Dictyotaceae. Bull. Torrey Bot. Club 77: 83–93.

Gerwick, W.H., Fenical, W. 1983. Spatane Diterpenoids from the tropical marine algae *Spatoglossum schmittii* and *Spatoglossum howleii* (Dictyotaceae). J. Org. Chem. 48: 3325−3329. doi.org/10.1021/jo00167a033

Harmata, M., Rashatasakhon, P. 2001. A 4+3 Cycloaddition approach to the synthesis of spatol. A formal total synthesis of racemic spatol. Org. Lett. 3: 2533−2535. doi.org/10.1021/ol016200c

Hoshikawa, T., Tanji, K., Matsuo, J., Ishibashi, H. 2012. Intramolecular [2+2] cycloaddition of homoallylketenes to bicyclo[2.1.1]hexan-5-ones. Chem. Pharm. Bull. 60: 548-553. doi.org/10.1248/cpb.60.548

Hotling, S., Haberlag, B., Tamm, M., Collatz, J., Mack, P., Steidle, J. L. M., Vences, M., Schulz, S. 2014 Identification and synthesis of macrolide pheromones of the grain beetle *Oryzaephilus surinamensis* and the frog *Spinomantis aglavei*. Chem. Eur. J. 20: 3183−3191. doi.org/10.1002/chem.201304414

Kolb, H.C., Finn, M.G., Sharpless, K.B. 2001. Click chemistry: Diverse chemical function from a few good reactions. Angew. Chem. Int. Ed. Engl. 40: 2004−2021. doi.org/10.1002/1521-3773(20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5

Kurata, K., Suzuki, M., Shiraishi, K., Taniguchi, K. 1988. Spatane-type diterpenes with biological activity from the brown alga *Dilophus okamurai*. Phytochem. 27: 1321−1324. doi.org/10.1016/0031-9422(88)80185-7

Kurata, K., Taniguchi, K., Shiraishi, K., Suzuki, M. 1990. Feeding-deterrent diterpenes from the brown alga *Dilophus okamurai*. Phytochem. 29: 3453−3455. doi.org/10.1016/0031-9422(90)85256-F

Li, L., Sheng, L., Wang, C., Zhou, Y., Huang, H., Li, X., Li, J., Mollo, E., Gavagnin, M., Guo, Y. 2011. Diterpenes from the Hainan soft coral *Lobophytum cristatum* Tixier-Durivault. J. Nat. Prod. 74: 2089−2094. doi.org/10.1021/np2003325

Mascitti, V., Corey, E.J. 2006. Enantioselective synthesis of pentacycloanammoxic acid. J. Am. Chem. Soc. 128: 3118−3119. doi.org/10.1021/ja058370g

Miesch, L., Welsch, T., Miesch, M. 2013. Stereoselective cross aldol condensation of bicyclo[3.2.0]alkanones. Org. Biomol.Chem. 11: 4025-4029. doi.org10.1039/c3ob40431e

Fisheries Agency, Japan. 2024. FY2023 White paper on Fisheries Summary. https://www.jfa.maff.go.jp/e/annualreport/attach/pdf/index-17.pdf

Miura, H., Ito, Y., Suenaga, Y. 2018. Construction of climate change-adapted seaweed beds on the Japanese coast. J. Coast. Res. 85: 391−395. doi.org/10.2112/SI85-079.1

Okuda, K. 2008. Coastal Environment and Seaweed-bed Ecology in Japan. Kuroshio Science 2: 15–20.

Paton, D.G., Childs, L.M., Itoe, M.A., Holmdahl, I.E., Buckee, C.O., Catteruccia, F. 2019. Exposing *Anopheles* mosquitoes to antimalarials blocks *Plasmodium* parasite transmission. Nature. 567: 239–243. doi.org/10.1038/s41586-019-0973-1

Punna, S., Kaltgrad, E., Finn, M.G. 2005. "Clickable" agarose for affinity chromatography. Bioconj. Chem. 16: 1536−1541. doi.org/10.1021/bc0501496

Roth, L., Eviatar, G., Schmidt, L.M., Bonomo, M., Feldstein-Farkash, T., Schubert, P., Ziegler, M., Al-Sawalmih, A., Abdallah, I.S., Quod, J.P., Bronstein, O. 2024. Mass mortality of diadematoid sea urchins in the Red Sea and Western Indian Ocean. Curr. Biol. 34: 2693−2701.e4. doi.org/10.1016/j.cub.2024.04.057

Salomon, R.G. 1991. Synthesis of a cancer growth-inhibiting diterpene: Spatol (Chap 10). In: Lindberg, T. (Ed.). Strategies and Tactics in Organic Synthesis, Vol 3: Academic Press. London, UK, pp. 381-416. doi.org/10.1016/B978-0-08-092430-4.50016-0

Salomon, R.G., Sachinvala, N.D., Roy, S., Basu, B., Raychaudhuri, S.R., Miller, D.B., Sharma, R.B. 1991. Total synthesis of spatane diterpenes: The tricyclic nucleus. J. Am. Chem. Soc. 113: 3085−3095. doi.org/10.1021/ja00008a043

Snider, B.B., Hui, R.A.H.F., Kulkarni, Y.S., 1985. Intramolecular [2+2] cycloadditions of ketenes. J. Am. Chem. Soc. 107: 2194−2196. doi.org/10.1021/ja00293a074

Sibbersen, C., Lykke, L., Gregersen, N., Jørgensena, K.A., Johannsen, M. 2014. A cleavable azide resin for direct click chemistry mediated enrichment of alkyne-labeled proteins. Chem. Commun. 50: 12098−12100. doi.org/10.1039/C4CC05246C

Suzuki, M., Yamada, H., Kurata, K. 2002. Dictyterpenoids A and B, Two novel diterpenoids with feeding-deterrent activity from the brown alga *Dilophus okamurae*. J. Nat. Prod. 65: 121−125. doi.org/10.1021/np010234b

Tiwari, V.K., Mishra, B.B., Mishra, K.B., Mishra, N., Singh, A.S., Chen, X. 2016. Cu-Catalyzed click reaction in carbohydrate chemistry. Chem. Rev. 116: 3086−3240. doi.org/10.1021/acs.chemrev.5b00408