From the ocean...
...to the clinic
Syntheses to be covered:
- Ecteinascidin 743 (Corey)
- Eleutherobin (Nicolaou)
- Salinosporamide A (Corey)
- Bryostatin 16 (Trost)
- Cabazitaxel (Novartis)
- Ecteinascidin 743 (Corey)
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Preparative HPLC has been, by far, the most useful tool for separation of complex mixtures.

Isolation of Marine Natural Products

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Diagram: Flowchart for isolation process.
Isolation is hard: case studies
Isolation: First isolated from crude ethanolic extracts from Ecteinascidia turbinata in 1969. Extracts had potent cytotoxicity (picomolar to nanomolar range), but were not fully characterized until 1990.

Biosynthesis: Structurally related to saframycins. Postulated to come from two dimerized tryrosine residues, a cysteine residue, and subsequent Mannich and Pictet-Spengler condensations.


Mechanism of action: Binds in the minor groove of DNA and alkylates guanine, disrupts the cell cycle, causes alterations in transcription, eventually leading to cell death.

Clinical trials: Involved in over 30 trials in U.S. Studies in Europe have shown promise for treating soft tissue sarcoma, a rare form of cancer that has had no new treatments in 20 years. Also, shows promise in treating drug-resistant forms of cancer possibly by interfering with p-glycoprotein production.

Studies in Europe have shown promise for treating soft tissue sarcoma, a rare form of cancer that has had no new treatments in 20 years. Also, shows promise in treating drug-resistant forms of cancer possibly by interfering with p-glycoprotein production.
Strategic bond disconnections for Ecteinascidin 743.

Pictet-Spengler

Quinone methide capture

Mannich bisannulation
Isolation:
First isolated from Eleutherobia sp. collected in Australia in 1995 by William Fenical's lab at Scripps Institution of Oceanography. Also recently isolated from a Caribbean coral Erythropodium caribaeorum.

Total Synthesis:
Nicolaou group also published syntheses of sarcodycetins (similar to eleutherobin) and analogs via solid phase.

Mechanism of action:
Mechanism of action similar to Taxol. Binds to and polymerizes tubulin.

Clinical Trials:
Currently in preclinical status.
Strategic bond disconnections for eleutheroxin.


Mechanism of action: Potent inhibitor of the proteasome by covalently binding to the active site threonine residues of the 20S proteasome.

Clinical trials: In vitro studies have shown salinosporamide A to have potent activity against several cancer cell lines. Proceeding through several phase I trials as a single agent against multiple myeloma, solid tumors, or lymphoma.

In vitro studies have shown salinosporamide A to have potent activity against several cancer cell lines. Proceeding through several phase I trials as a single agent against multiple myeloma, solid tumors, or lymphoma.
Summary of SAR done by Corey on lactacyclin and analogs.
Isolation: Found in extracts of the bryozoan Bugula neritina collected in the Gulf of California and Gulf of Mexico. Recent work has shown that it is likely produced by the symbiotic bacteria Endobugula sertula.


Clinical Trials: Bryostatin 1 involved in over 30 trials related to cancer. Trials using bryostatin 1 and its analogs have been disappointing when used alone as an anticancer agent, but when used in combination the drug shows more promise. Granted orphan drug status by FDA when used in combination with Taxol for esophageal cancer in 2001. Also being tested in trials as an anti-Alzheimer’s agent.

Mechanism of action: Can bind to protein kinase C, an enzyme involved in the upregulation and downregulation of certain proteins.

Trials using bryostatin 1 and its analagogs have been disappointing when used alone as an anticancer agent, but when used in combination the drug shows more promise.
Retrosynthetic analysis of Bryostatin 16.
Figure 4 | Synthesis of acid and alcohol. a, Synthesis of 5, Reaction conditions: (a) Grignard reagent, (b) Dess-Martin periodinane, (c) NaOH, (d) TESOT, 2,6-lutidine, DCM, 86% (96% by HPLC); (e) CH$_2$Cl$_2$, 80 °C, 97% (99% by HPLC); (f) TBAB, HOAc, THF, 90% (HPLC); (g) OF(ac)$_2$, DCE, 80 °C, 84% (HPLC); (h) TEOSOT, 2,6-lutidine, DCM, 10 °C to 0 °C, 76-79%, b, Synthesis of 6, Reaction conditions: (a) CuI (1.5 mol%), Pd(OAc)$_2$(NH)$_2$CO$_3$, (b) O$_2$ (5 atm), trifluoroacetic acid, 80 °C, 87% (HPLC); (c) CuI (1.5 mol%), Pd(OAc)$_2$(NH)$_2$CO$_3$, (d) O$_2$ (5 atm), trifluoroacetic acid, 80 °C, 96% (HPLC).
Figure 5 | Syntheses of Pyostatin 16. Reaction conditions: (a) 5, 2.46 \% (b) 50 \% (c) 19 R = PMB (d) 19 R = H (e) 70% DCM (f) 46% and 58% TFA (g) Pd(OAc)\textsubscript{2} (12 mol\%) TDMPP (15 mol\%) toluene, 56% (h) Toluene, 92% (i) DCM, 90 C, 62% (j) TBAB, 7H\textsubscript{2}P, 50 C, 92% (k) N\textsubscript{2}, DMF, 90 C, Room Temperature, 73\% (l) 20 mol\%, DCM/CH\textsubscript{3}CN, 0 C.