Recent synthesis of marine natural products with antihypertensive activity: An overview

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Abstract

Many natural products from marine sources are endowed with promising anti hypertensive activity, thus representing invaluable leads in the plans for drug discovery. In this context, organic synthesis plays a decisive role in confirming (or revising) the chemical structures of the natural compounds allowing also access to suitable amounts of the target (and its analogs) for structure activity relationship (SAR) investigations. In this overview, we focus on the total and partial synthesis of marine metabolites and their related compounds discussing the retro synthetic analysis of the strategies adopted used in treatment of hypertension.

Keywords: Marine, Anti hypertensive Activity, Synthesis of Marine metabolites.

Introduction

The antihypertensives are a class of drugs that are used to treat hypertension (high blood pressure).[1] Evidence suggests that reduction of the blood pressure by 5–6 mmHg can decrease the risk of stroke by 40%, of coronary heart disease by 15–20%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease. There are many classes of antihypertensives, which lower blood pressure by different means; among the most important and most widely used are the thiazide diuretics, the ACE inhibitors, the calcium channel blockers, the beta blockers, and the angiotensin II receptor antagonists or ARBs.Which type of medication to use initially for hypertension has been the subject of several large studies and resulting national guidelines. The fundamental goal of treatment should be the prevention of the important endpoints of hypertension, such as heart attack, stroke and heart failure. The several classes of antihypertensives differ in side effect profiles, ability to prevent endpoints, and cost. The choice of more expensive agents, where cheaper ones would be equally effective, may have negative impacts on national healthcare budgets.[2] As of 2009, the best available evidence

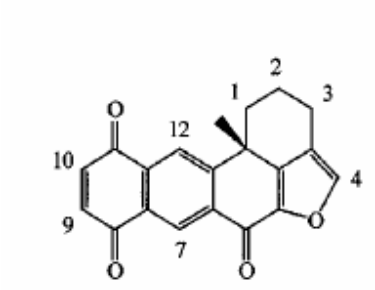
favors the thiazide diuretics as the first-line treatment of choice for high blood pressure when drugs are necessary.[3]

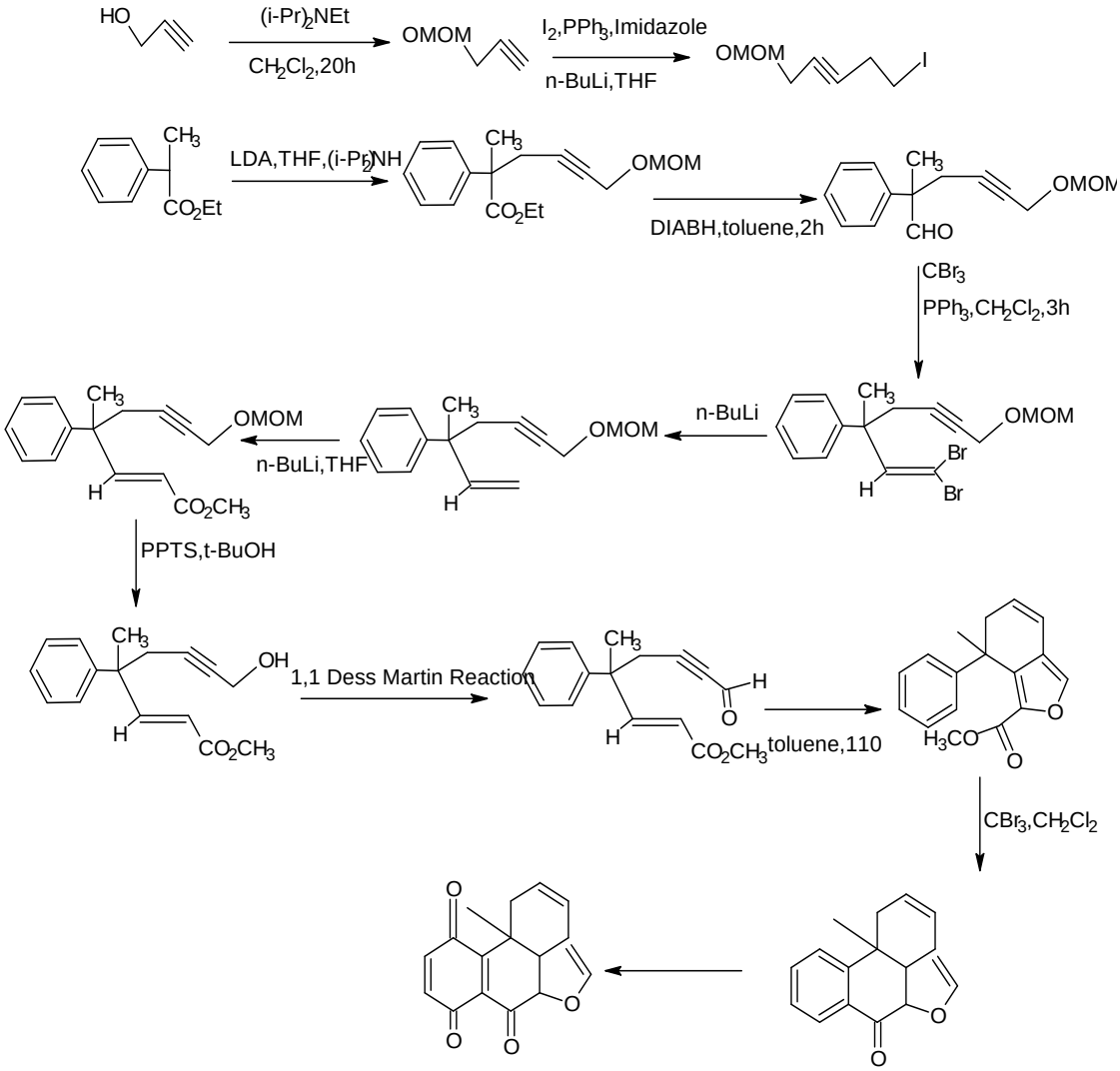
Available agents
1.1 Diuretics
1.2 Adrenergic receptor antagonists
1.3 Adrenergic receptor agonists
1.4 Calcium channel blockers
1.5 ACE inhibitors
1.6 Angiotensin II receptor antagonists
1.7 Aldosterone antagonists
1.8 Vasodilators
1.9 Centrally acting adrenergic drugs

The choice between the drugs is to a large degree determined by the characteristics of the patient being prescribed for, the drugs' side-effects, and cost. For example, asthmatics have been reported to have worsening symptoms when using beta blockers. Most drugs have other uses; sometimes the presence of other symptoms can warrant the use of one particular antihypertensive (such as beta blockers in case of tremor and nervousness, and alpha blockers in case of benign prostatic hyperplasia). The JNC 7 report outlines compelling reasons to choose one drug over the others for certain individual patients.[4]

Marine organisms, particularly sponge invertebrates and associated bacteria, are a prolific source of novel biologically active compounds with unusual, and often complex, structures. The harsh environment that marine sponges inhabit, together with their lack of physical defenses, requires that these organisms develop chemical deterrents to aid their survival. As a result, many of their associated secondary metabolites exhibit exceptional levels of biological activity, often combined with unique modes of action. However, the potential therapeutic utility of marine-derived natural products is hampered not only by the limited supply, but often also by their incomplete stereo chemical assignment. In both these respects, total synthesis can provide a powerful solution.

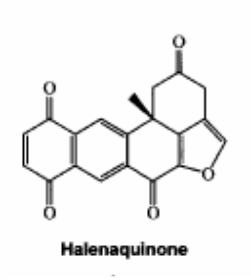
1. Synthesis of Xestoquinone [5]
A strategy for synthesis of the furan-fused tetracyclic system of Xestoquinone was explored through a model study. Using 3-butyn-1-ol as a starting material, 5-iodo-1-methoxymethoxy pentyne was prepared in 5 steps. Reaction of ethyl 2-phenylpropanoate with gave ethyl 7-methoxymethoxy-2-methyl-2-phenyl-5-heptynoate in 88% yield, and then methyl 9-oxo-4-methyl-4-phenyl-2,7-nonadiynoate ,the key intermediate, was synthesized in 6 steps from the ester **6**. Intramolecular cycloaddition reaction of afforded isobenzofuran in 5% yield, which was converted to the tetracyclic structure in the presence of Lewis acid.

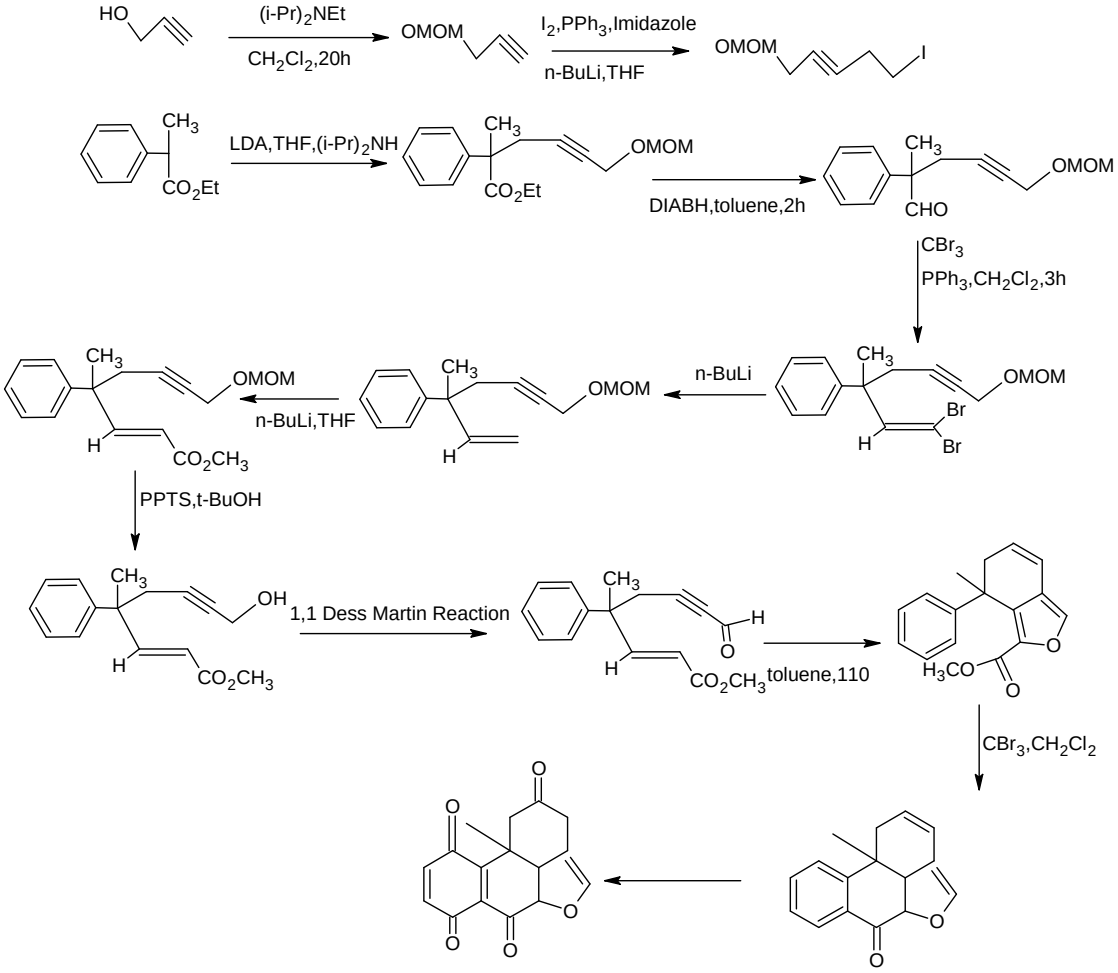




Scheme: Synthesis of Xestoquinone

2. Synthesis of Halenaquinone [5]



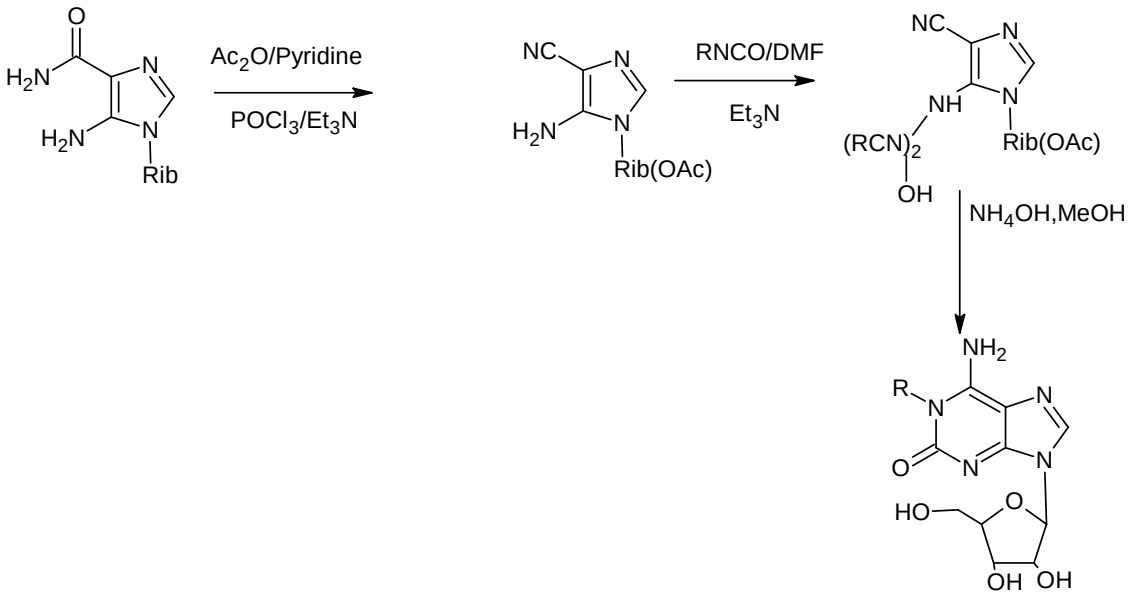


Scheme: Synthesis of Halenaquinone

3. Synthesis of N^1- Alkylisoguanosines [6]

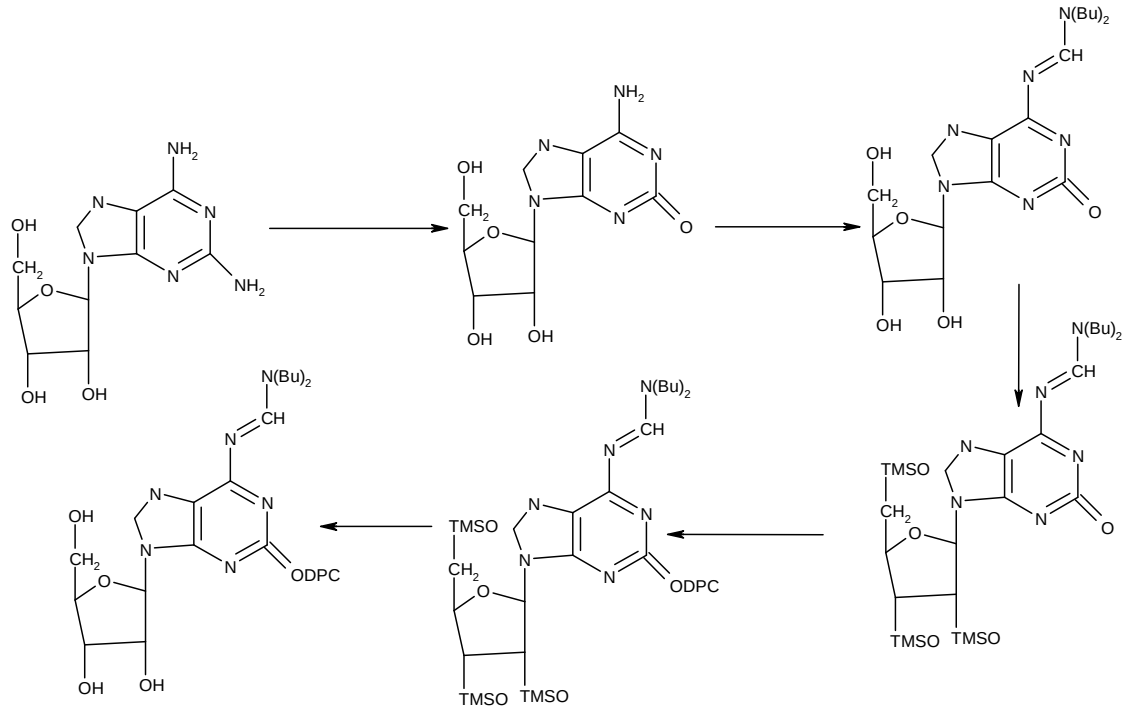
N^1- Alkylisoguanosines were synthesized. Their chemical and physical properties and biological activities were compared with those of marine natural product, doridosine. N^1-Alkylisoguanosines appears to exist in the structure of N^1-alkyl-6-amino-2-oxo-β-D-ribofuranosyl purine, in water, dioxane, acetonitrile and dimethyl sulfoxide solution. The

biological activity of N^1- ethylisoguanosines was run on guinea pig atria and the same type of activity of doridosine was found, but ca. half of that from doidosine (N^1- methylisoguanosines).



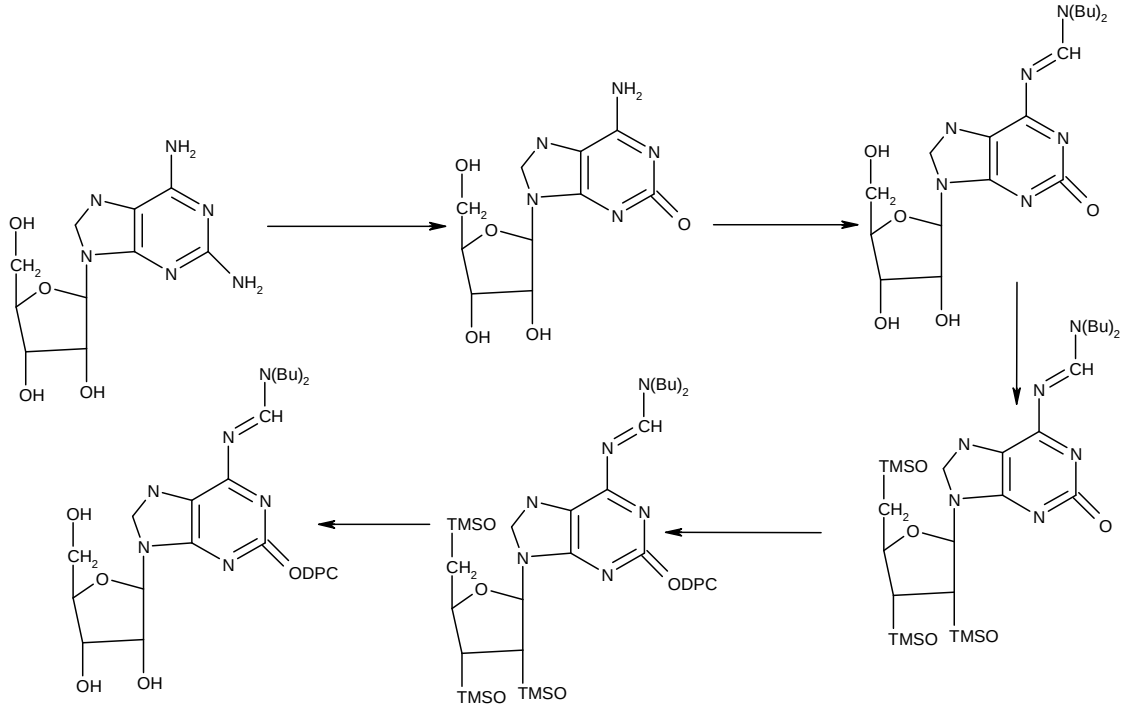
Scheme: Synthesis of N^1- Alkylisoguanosines

4. Synthesis of 2'-Deoxyisoguanosine 5'-Triphosphate [7]



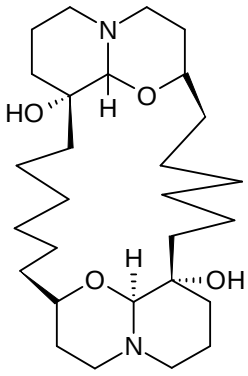
Scheme: Synthesis of 2'-Deoxyisoguanosine 5'-Triphosphate

5. Synthesis of 2'-Deoxy-5-methylisocytidine 5'-Triphosphate [7]



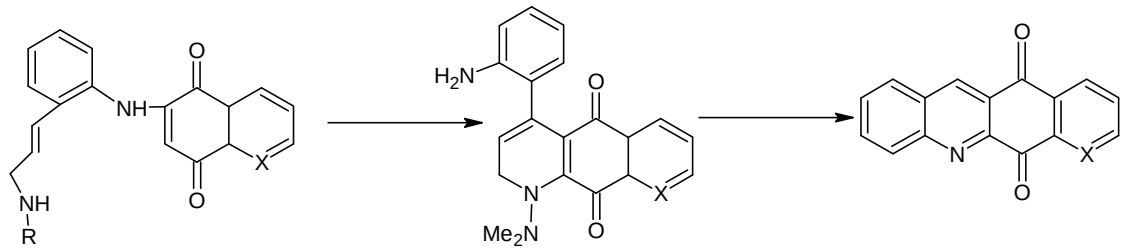
Scheme: Synthesis of 2'-Deoxy-5-methylisocytidine 5'-Triphosphate

6. Synthesis of Araguspongine C [8]



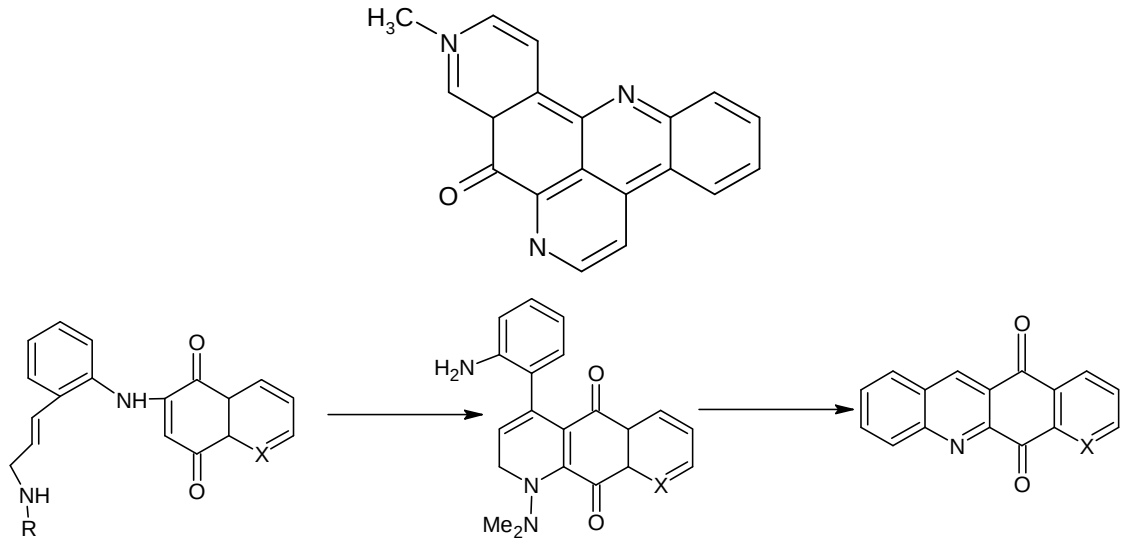
Araguspongine C

7. Synthesis of pyridoacridines [9]



Scheme: Synthesis of pyridoacridines

8. Synthesis of Deoxyamphimedine [10]



Scheme: Synthesis of Deoxyamphimedine

Conclusion

Natural products traditionally have played a pivotal role in drug discovery and in particular the uniqueness of marine metabolite core structures makes these compounds of interest in the development of pharmaceutical agents, in particular the anti hypertensive here discussed. In these studies, chemical synthesis still represents a route of choice showing its potential to confirm or revise the chemical structures of the natural products and to allow the access to related compounds for structure activity relationship investigations. The actual interest in this field is confirmed by several reports on the synthesis of marine natural products with anti hypertensive activity. This overview focuses on the main aspects of such reports strongly relying on the corresponding retro synthetic sequences.

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