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Stereoselective Synthesis (Part D)

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FOREWORD

The synthesis of complex natural products has attracted the efforts of the foremost organic chemists, both because many natural products have exhibited significant biological activity and because they have taxed the ingenuity of many brilliant minds towards developing synthetic routes to them. During the last decade, organic synthesis has evolved in an accelerated manner, particularly in the field of stereoselective methods for the synthesis of natural products of increasing complexity.

The present volume is the sixth of this series, and the fourth devoted to stereoselective synthesis. The articles included in this volume cover the synthetic approaches to marine terpenoids, allenic and acetylenic carotenoids, gibberellins, antheridiogens, fungal metabolites, macrocyclic antibiotics, sugar analogues, peptidoglycan analogues, chemical defense agents in ants, medium sized ring heterocycles, *Strychnos* alkaloids, semiochemicals and bioregulators. It is hoped that the authoritative reviews written by distinguished scientists will prove to be informative and interesting to the readers and draw the same positive response as the previous volumes of this series.

I wish to express my sincere thanks to Mr. Zahir Shah, Mr. Ejaz Ahmad Soofi and Miss Khurshid Zaman for their assistance in the preparation of the index. I am also grateful to Mr. Asif Mehmood Raja and Mr. Habib Alam for the index typing and Mr. Mahmood Alam for secretarial assistance.

October 1989

Atta-ur-Rahman, *Editor*

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CONTENTS

Stereoselective Synthesis

Total Synthesis of Polycarbocyclic Marine Terpenoids*

J. D. Martin

1 INTRODUCTION

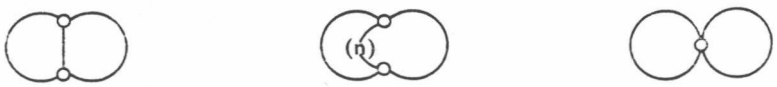
For some years now, natural products of marine origin have been the subject of frequent and continuing reviews based on both structural and synthetic aspects (refs. 1-5). Total and partial syntheses of marine natural compounds have been treated in a number of monographs, e.g. P. Scheuer's Marine Natural Products: Chemical and Biological Perspectives, Volumes 1-5, which dealt with selected classes such as carotenoids, sterols, terpenoids, indoles, etc. There also exist numerous general monographs on the synthesis of carbohydrates, prostaglandins, antibiotics and alkaloids, in which marine compounds are included. All these reviews share a common feature, they classify the material by structural types or following a phylogenetic organization. Only recently comprehensive and systematic approaches treating the synthesis of natural compounds from a methodological point of view have appeared (refs. 6-7).

The great number and the variety of compounds of marine origin that have been synthesized in the last ten years permit us to generalize on the strategic principles, methods and synthetic procedures employed. The marine molecules which have most interested synthetic chemists can be grouped as follows: medium and large size heterocycles and isolated carbocyclic systems in which the *cyclization reaction* is often the key step in the synthesis; and polycarbocyclic systems, where the *phase during which the carbocyclic framework is assembled* represents in general the most prominent aspects of the synthetic sequence. The first group of compounds is currently the subject of intensive research and excellent reviews are appearing (e.g. ref. 8). The varied methodology followed and the diversity of synthesized polycarbocyclic marine molecules fully justify the compilation studied here. The great majority of synthesized polycarbocyclic compounds are of a terpenoid nature. Hence,

*Dedicated to Professor Felix Serratosa of Barcelona University.

even in the awareness that the syntheses of marine compounds such as, for example, the carbocyclic polyketides ptilocaulin (ref. 9) or halenaquinol (ref. 10) could perfectly well be included, I have dealt exclusively with terpenoids to avoid incurring in an equivocal generalization in the title of this work.

With polycarbocyclic systems, three annulations of bicyclic subsystem types can be conceived (refs. 6-7): (a) *fused* (ortho-condensed) rings **A** in which the peripheral bonds are linked by a cross piece bond; (b) *bridged* rings **B** in which the cross piece is made up of n atoms where n≥1; and (c) *spirocyclic* subsystem **C** with a single pivot atom connecting both rings. The retrograde pathways to these target molecules could be devised by disconnections at or outside the annulation sites through one- or two-bond disconnections. In the synthetic sense, the bicarbocyclic subsystems could be derived by joining the second ring to the already existing cyclic system, or bisecting a ring by way of a crosspiece bond to enlarge the number of cycles by one.



A **B** **C**

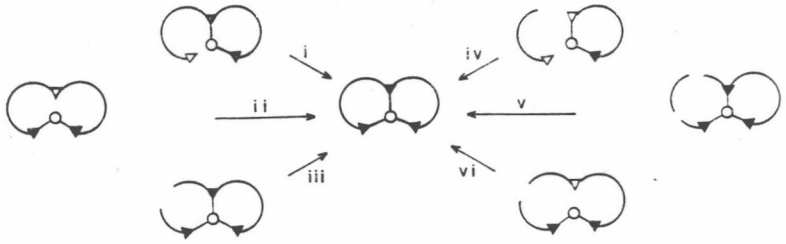
In the different sections of this report, syntheses are classified according to the mode of formation of strategic bonds. Whenever possible, the strategic principles are grouped under a common heading, which will allow the reader to compare the different methods applied for assembling the same or closely related carbocyclic frameworks in the crucial steps. Annulation methods, during which a ring is attached to a pre-existing system, are generally recognized as such when the two new carbon-carbon bonds are formed in timely related processes (ref. 6). When a large number of steps separate both carbon-carbon bond formations, the concept of annulation is no longer adequate and emphasis will then be placed upon the cyclization process. The ring closure simply consists of an intramolecular connection of one or both ends of a chain. Another important strategy for the construction of polycarbocyclic systems rests on modification of already existing cycles, e.g. by contraction or expansion. A number of cyclic compounds are available, and these may represent a convenient starting point to perform a synthesis.

2 FUSED SYSTEMS

Many polycyclic terpenoids contain fused (*ortho-condensed*) systems; it is therefore not surprising that the synthesis of these structural blocks has received considerable attention from organic chemists.

2.1 BICARBOCYCLIC FUSED SYSTEMS

The strategies used for construction of these systems (Scheme 1) may employ cyclizations at or outside the annulation sites, following a one-bond cyclization processes: *path i*, *ii*, or *iii*, or two-bond annulation methodology: *path iv*, *v* or *vi*.

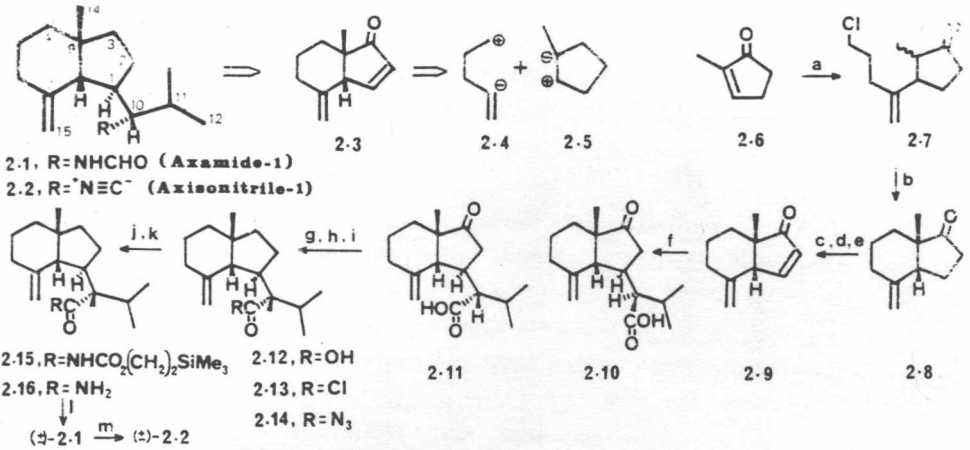


Scheme 1.

A number of marine terpenoids contain fused cyclopropane ring systems, e.g. the subsystem [3.1.0]. The synthetic approach to this type of annulation usually employs [2+1] addition of carbene or its equivalent, generated from a diazo compound, to a double bond, or the Simmons-Smith reaction and is not discussed here.

2.1.1 The bicyclo[4.3.0]nonane group

Annulation of the cyclohexane ring system. The unique approach based on this strategy has been reported by Piers (refs. 11-12) in the racemic syntheses of axamide-1 (**2.1**) and axisonitrile-1 (**2.2**), two related sesquiterpenes isolated among others from the Mediterranean sponge *Axinella cannabina* (refs. 13-16). These total syntheses are based on the analysis in which the axane skeleton is envisioned as derivable from the *cis*-fused bicyclic ketone **2.3**, *via* Michael addition of the *iso*-butyl appendage from the sterically more accessible convex face (Scheme 2). The hidrindane system was accomplished by a four-carbon polar annulation on a cyclopentane dipolar synthon. In a synthetic sense, the methylenecyclohexane annulation sequence was achieved by cuprous bromide-catalyzed conjugate addition of 2-(5-chloro-1-pentenyl) magnesium bromide to 2-

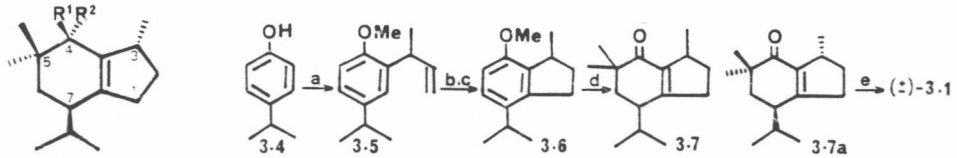


Scheme 2. (**a**) 2-(5-Chloro-1-pentenyl)magnesium bromide (1.3 equiv), CuBr.Me_2S (0.32 equiv), $BF_3.Et_2O$ (1.3 equiv), THF, -78°C, 3 h, 89%; (**b**) KH, THF, r.t., 2 h, 85%; (**c**) i-Pr_2NLi, THF, -78°C; TMSCl, -78°C → r.t., 1.5 h; (d) NBS, THF, 0°C, 15 min; (**e**) LiBr, Li_2CO_3, N,N-dimethylformamide, reflux, 3 h, 77%, three steps; (**f**) 3-methyl-1,1-bis(trimethylsiloxy)-1-ne, $TiCl_4$, CH_2Cl_2, -78°C, 2 h, 88% (mixture, ratio 3:2, **2.11:2.10**); (**g**) H_2N-NH_2, diethylene glycol, 110°C, 3 h → 190°C, 30 min, 90%; (**h**) $(COCl)_2$, PhMe, r.t.; (**i**) NaN_3, acetone-H_2O, 0°C; (j) PhMe, 80°C, 2 h→$Me_3SiCH_2CH_2OH$, PhMe, 80°C, 20 h, 89%, three steps; (**k**) n-Bu_4NF, THF, 50°C, 72%; (l) CH_3CO_2CHO, Et_2O, r.t., 10 h, 90%; (m) p-toluenesulfonyl chloride, pyridine, r.t., 3 h, 86%.

methyl-2-cyclopenten-1-one (**2.6**), followed by intramolecular cycloalkylation of the resulting product **2.7** to afford the *cis*-fused bicyclic ketone **2.8**, which was transformed by conventional methods into the enone **2.9**. Stereoselective titanium tetrachloride-catalyzed conjugate addition of 3-methyl-1,1-bis (trimethylsiloxy)-1-butene to the less hindered face of the enone group gave a 3:2 mixture of the keto acids **2.10** and **2.11**, which were separated. Removal of the keto function from **2.11** by Wolff-Kishner reduction gave the acid **2.12**. Conversion of the carboxylic acid **2.12** into the acyl azide **2.14**, *via* the chloride **2.13**, was accomplished by standard reactions. Curtius rearrangement of **2.14**, followed by reaction of the resulting isocyanate with 2-trimethylsilylethanol, afforded the carbamate **2.15**, which was converted into the primary amine **2.16**. Formylation of **2.16** gave (±)-axamide-1 (**2.1**), which was efficiently dehydrated to yield (±)-axisonitrile-1 (**2.2**).

Annulation of the cyclopentane ring system. The non-regular sesquiterpenes brasilenol (**3.1**), epibrasilenol (**3.2**), and brasilenol acetate (**3.3**) were isolated from specimens of the mollusc *Aplysia brasiliana* and from samples of the red alga *Laurencia obtusa* (ref. 17). A short racemic synthesis of brasilenol has been disclosed

(ref. 18) (Scheme 3). The synthesis involves, as initial steps, transformation of 4-isopropylphenol (**3.4**) to the anisole **3.5** by Claisen rearrangement of the crotyl ether derivative followed by methylation. Conventional hydroboration-oxidation of **3.5** provided a

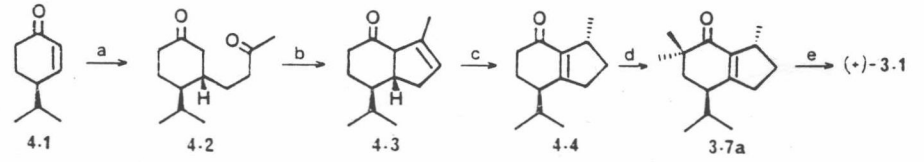


3.1, R^1=H, R^2=OH (**Brasilenol**)
3.2, R^1=OH, R^2=H (**Epibrasilenol**)
3.3, R^1=H, R^2=OAc (**Brasilenol acetate**)

Scheme 3. (**a**) K_2CO_3, $CH_3CH{=}CHCH_2Br$, acetone, reflux, 6 h, 97%; N,N-dimethylaniline, reflux, 12 h, 93%; NaH, MeI, THF, r.t., 2 h, 85%; (**b**) B_2H_6, THF, r.t., 5 h → 30% H_2O_2, 50°C, 4 h, 75%; Jones reagent, 0°C, 30 min, 73%; PPA, 60°C, 12 h, 63%; (**c**) LAH, THF, 2 h, 99%; 10% Pd-C, H_2, AcOH, 98%; (**d**) Li, $MeNH_2$, t-BuOH, -40°C, 30 min → H^+, SiO_2 separation, 43%; LDA, THF, MeI, -78°C, 1 h, 82-85%; $RhCl_3$, Δ, SiO_2 separation **3.7a**; (**e**) $LiB(C_2H_5)_3H$, THF, -78°C, 2 h, 73%.

carboxylic acid which was cyclized by acid treatment to an indanone derivative further reduced to the indane **3.6**. Lithium reduction of **3.6** followed by dimethylation of the resulting enone gave the target **3.7** from which the *trans*-isomer **3.7a** was isolated. Reduction of **3.7a** was highly stereoselective and gave essentially (±)-brasilenol (**3.1**).

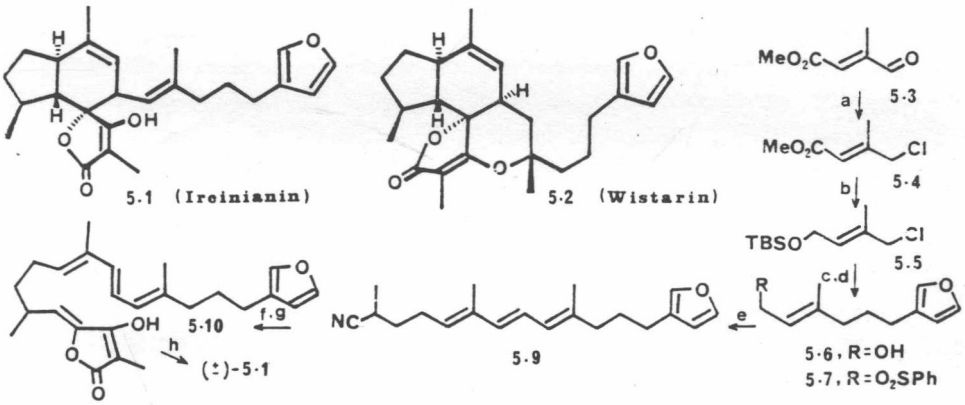
A total synthesis of natural (+)-brasilenol has been described by Greene (ref. 19) following a general method in which the three-carbon building block is made up by the organometallic reagent carrying a masked carbonyl group as electrophile. The nucleophilic center is the carbon bearing the metal. This synthon is added to the enone double bond and the procedure is terminated by aldolization of the deprotected carbonyl group with the cyclohexanone moiety (ref. 20) (Scheme 4). Starting from (R)-(-)-cryptone (**4.1**), copper-catalyzed Michael addition of 3-butenylmagnesium bromide followed by Wacker oxidation gave the dione **4.2**, which was further submitted to aldol cyclization to give **4.3**. Palladium-catalyzed



Scheme 4. (**a**) 3-Butenylmagnesium bromide, CuI, -20°C, 30 min → 0°C, 2 h, 97%; $PdCl_2$, O_2, CuCl, DMF-H_2O, THF, 3 h, 79%; (**b**) t-BuOK, t-BuOH, 15 min, 84%; (**c**) 10% Pd-C, H_2, PhH, 60°C, 63%; (**d**) $LiN(i\text{-}C_3H_7)_2$, THF, CH_3I, 84%; (**e**) $LiB(C_2H_5)_3H$, THF, -78°C, 92%.

isomerization of **4.3** proceeded readily to give exclusively the *trans*-product **4.4**. The completion of the synthesis was achieved by α-dimethylation of **4.4** to give brasilenone **3.7a** followed by stereoselective reduction to (+)-brasilenol (**3.1**). The synthesis establishes the absolute stereochemistry of the marine natural product as well as that of the two congeneric metabolites.

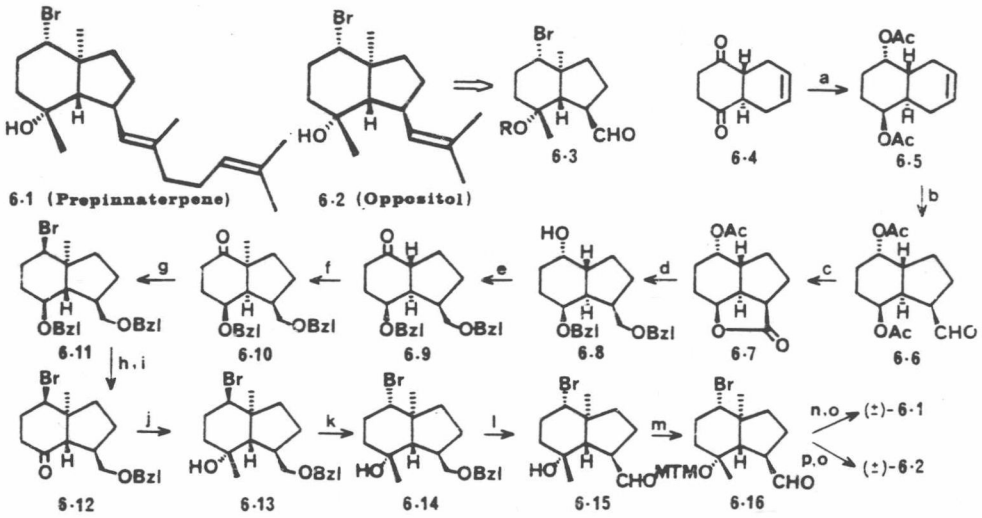
Intramolecular Diels-Alder reaction. The course of the intramolecular [4+2] addition for the formation of a hydrindane from an acyclic 1,3,8 nonatriene with a *trans*-3-double bond occurs preferentially to give *trans*-annulated products due to less steric strain in the transition state (refs. 21-22). Ircinianin (**5.1**) (ref. 23) and wistarin (**5.2**) (ref. 24) are two unusual tetronic acid sesterterpenes, isolated from the sponge *Ircinia wistarii*, that contain a *trans*-fused bicyclo[4.3.0]nonane system. Both compounds appear to result from a [4+2] cycloaddition reaction of the suitable linear precursor **5.10**. Yoshii has exploited this suggested biogenetic approach to the synthesis of (±)-ircinianin (Scheme 5) (ref. 25). The synthesis begins with aldehyde reduction and subsequent chlorination of methyl γ-oxosenecioate (**5.3**) to afford the chloride **5.4**. Ester reduction to the corresponding alcohol followed by silylation provided the allylic chloride **5.5**, which was coupled with 2-(3-furyl)ethylmagnesium bromide to produce, after desilylation, the furylalcohol **5.6**, further converted to the sulfone **5.7** by conventional methodology. Addition of the lithiated sulfone **5.7** to the readily available aldehyde **5.8**, prepared by allylic oxidation



Scheme 5. (**a**) $NaBH_4$, MeOH; NCS, Me_2S, CH_2Cl_2, 80%; (**b**) DIBAH, THF; TBSCl, imidazole, DMF, 58%; (**c**) 2-(3-furyl)ethylmagnesium bromide, Li_2CuCl_4; aq HF, CH_3CN, 41%; (**d**) NCS, Me_2S, CH_2Cl_2; $PhSO_2Na$, DMF, 71%; (**e**) n-BuLi, THF, -78°C, NC⁓⁓⁓O (**5.8**); BzCl; Na-Hg, THF-MeOH, 32%; (**f**) LDA, methyl 2-methyltetronate, HMPA, THF, -78°C; $(CF_3CO)_2O$, r.t.; DBU, r.t., 40%; (**g**) n-PrSLi, HMPA, 63%; (**h**) PhH, reflux, 60 min, 72%.

of propiononitrile and the 5-bromo-2-methyl-2-pentene α-alkylation product, gave, after benzoylation and reductive elimination of the α-benzoylsulfone moiety, the conjugated triene **5.9**. Reduction of **5.9** and hydrolysis of the resulting aldimine gave an unstable aldehyde which was allowed to react with 4-lithiated methyl 2-methyltetronate and converted to the condensation product **5.10**. The intramolecular Diels-Alder reaction conducted on **5.10** proceeded smoothly to yield (±)-ircinianin (**5.1**).

Bicyclo[4.3.0]nonanes from modifications of other polycarbocyclic systems. Prepinnaterpene (**6.1**), isolated from the red alga *Laurencia pinnata* (ref. 26), is considered to be the biosynthetic precursor of a group of brominated diterpenes which possess an unprecedented *trans*-fused bicyclo[4.3.1]nonane skeleton with which it co-occurs (refs. 27-28). The recently reported synthesis by Masamune (ref. 29) of racemic prepinnaterpene (**6.1**) and its related sesquiterpene oppositol (**6.2**), natural components of the alga *L.*



Scheme 6. (**a**) LAH , THF, r.t., 20 min; Ac_2O, Pyridine, DMAP, 60%, two steps; (**b**) O_3, CH_2Cl_2, -78°C → Zn, AcOH-H_2O; p-TsOH, PhH, reflux, 40 min; H_2, 10% Pd-C, EtOH, r.t., 0.5 h, 63%, three steps; (**c**) Jones ragent, acetone, 0°C, 10 min; LAH, THF, -20°C, 2 h, 81%, two steps; (**d**) EtOCH=CH_2, PPTS, CH_2Cl_2, r.t., 0.5 h; LAH, THF, 0°C, 1 h, BnBr, KH, DMF, r.t., 20 min; 0.5 M HCl, r.t., 1.5 h; (**e**) PCC, CH_2Cl_2, r.t., 1.5 h; (**f**) HCO_2Et, NaOEt, PhH, 0°C → r.t., 40 min; n-BuSH, p-TsOH, $MgSO_4$, PhH, r.t., 16 h; MeI, t-BuOK, DME, -78°C, 1 h; KOH, DEG, reflux (bath temp 130-140°C), 10 h, 80%, four steps; (**g**) $NaBH_4$, MeOH, 0°C→40 min; MsCl, CH_2Cl_2, 0°C, 40 min; Bu_4NBr, toluene, 95-97°C, 20 h; (**h**) H_2, 10% Pd-C, 1M HCl, EtOH, r.t., 1 h; BnBr, NaH, DMF, -70°C, 40 min, 97% two steps; (**i**) PCC, CH_2Cl_2, r.t., 6 h, 98%; p-TsOH, CH_2Cl_2, r.t., 15 h, 96%; (**j**) MeLi, ether, -20°C, 0.5 h, 100%; (**k**) Bu_4NBr, toluene, 115°C, 2 days; (**l**) H_2, 10% Pd-C, 1M HCl, EtOH, r.t., 1 h; PDC, CH_2Cl_2, r.t., 4 h, 92%, two steps; (**m**) DMSO, Ac_2O, AcOH, r.t., 10 h; (**n**) $Ph_3P{=}C(CH_3)(CH_2)_2CH{=}C(CH_3)_2$, THF, 10 min; (**o**) MeI, $NaHCO_3$, acetone-H_2O, 55°C, 12 h; (**p**) $Ph_3P{=}C(CH_3)_2$, THF, 0°C, 10 min.