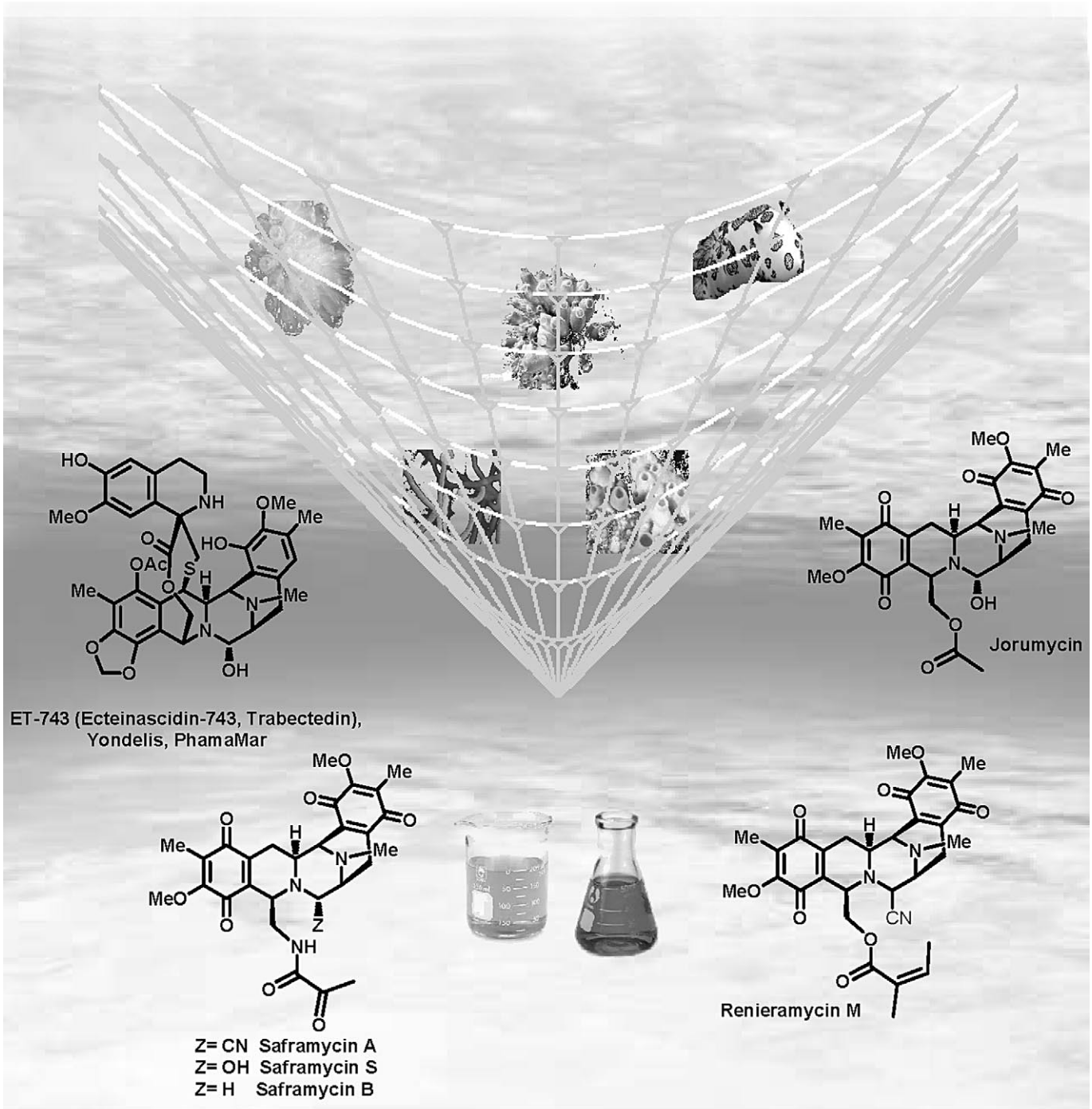
CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201000532

Recent Synthetic Approaches to 6,15-Iminoisoquino[3,2-*b*]3-benzazocine Compounds

Carmen Avendaño* and Elena de la Cuesta[a]

Dedicated to Professor José Barluenga on the occasion of his 70th birthday



Abstract: Saframycins, safracins, renieramycins, cribrostatins, and esteinascidins are 6,15-iminoisoquino[3,2-*b*]3-benzazocine compounds that constitute the largest subgroup among the antitumor antibiotics belonging to the tetrahydroisoquinoline family. Their structural complexity has led to widespread synthetic attention to obtain them in both racemic and enantiopure forms. Publication in 1996 of the first total synthesis of ecteinascidin 743 by Corey's group was an important milestone, but the development of preparative protocols for these structures has continued, offering new possibilities to exploit the biological activity of the above-mentioned natural products and their analogues. This minireview is intended to update this progress following a methodological rather than a chronological organization. Besides of a brief description of the different strategies evolved from retrosynthetic analyses, which have been organized according to the order of bonding events that will link the precursors, semisynthetic approaches and a brief account of the total syntheses of ecteinascidin 743, have been analyzed.

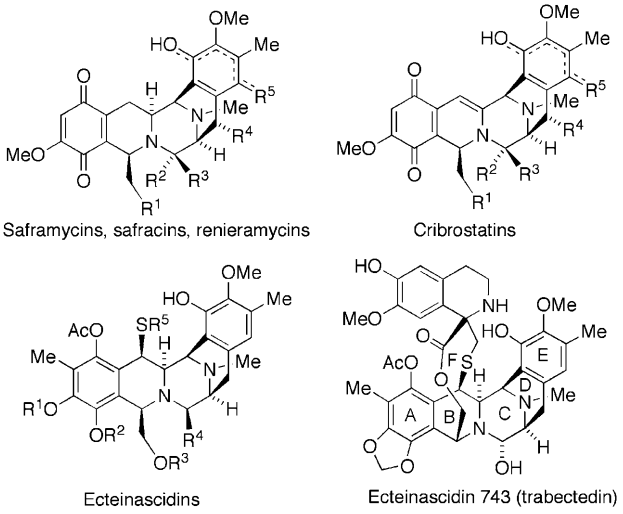
Keywords: antitumor agents · ecteinascidin 743 · synthetic methods · tetrahydroisoquinoline alkaloids

Introduction

The tetrahydroisoquinoline antitumor antibiotics have been intensively studied over the past 35 years, starting with the isolation of naphthyridomycin in 1974. In a comprehensive review on the chemistry and biology of these natural products,[1] they were classified into three different subgroups depending on their structural properties.

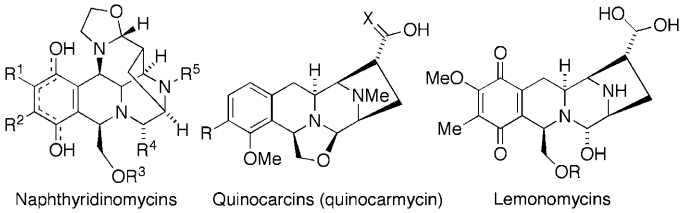
The largest one contains the saframycins, safracins, renieramycins, cribrostatins, and esteinascidins, their common structural core of five condensed six-membered rings contains a piperazine subunit and two tetrahydroisoquinoline moieties (one of them partially dehydrogenated in cribrostatins) as a quinone, hydroquinone or phenol oxidation state.

The naphthyridinomycin family is characterized by a core of six condensed rings, four of them six-membered (a piperidine, a piperazine, and a tetrahydroisoquinoline, either as a quinone or hydroquinone oxidation state), and two of them five-membered (a pyrrolidine and a oxazolidine), whereas the quinocarcin family encloses tetrazomine and lemonomycins that exhibit a piperazine and a tetrahydroisoquinoline



moieties (as a quinone, hydroquinone, or phenol oxidation state) condensed with one (pyrrolidine) or two (a pyrrolidine and a oxazolidine) five-membered rings.

The above-mentioned review covered almost all aspects of these products according to open literature reports up to



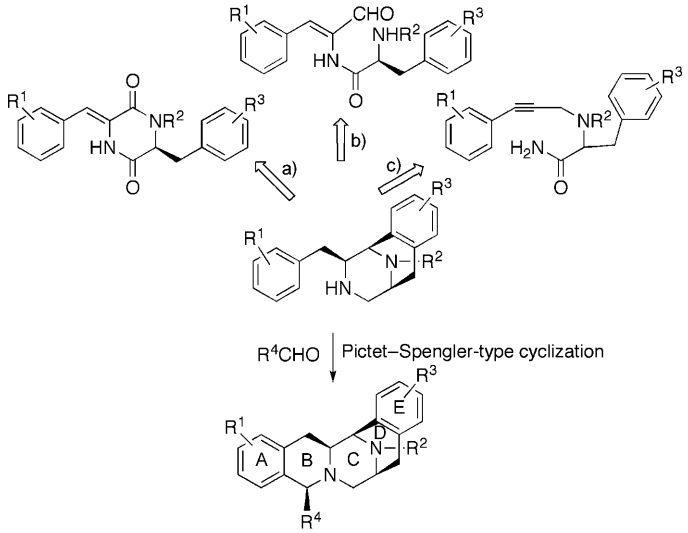
the year 2000: isolation and structure determination, biosynthesis, total syntheses (and previous synthetic studies), analogue syntheses, and biological activity. More recent reports about all of these aspects, especially on the total synthesis of naphthyridinomycin and lemonomycin families, have been reviewed by Mulzer et al. in 2008.[2] Advances in the chemistry and pharmacology of ecteinascidins,[3] and the development as the anticancer drug Yondelis of ecteinascidin 743 (ET-743),[4] have been also reported. This minireview is intended to update the synthetic approaches to the first subgroup of compounds.

Synthetic Approaches with Formation of B Ring from 2-Arylmethyl- and 3-Arylmethyl-1,5-imino-3-benzazocins

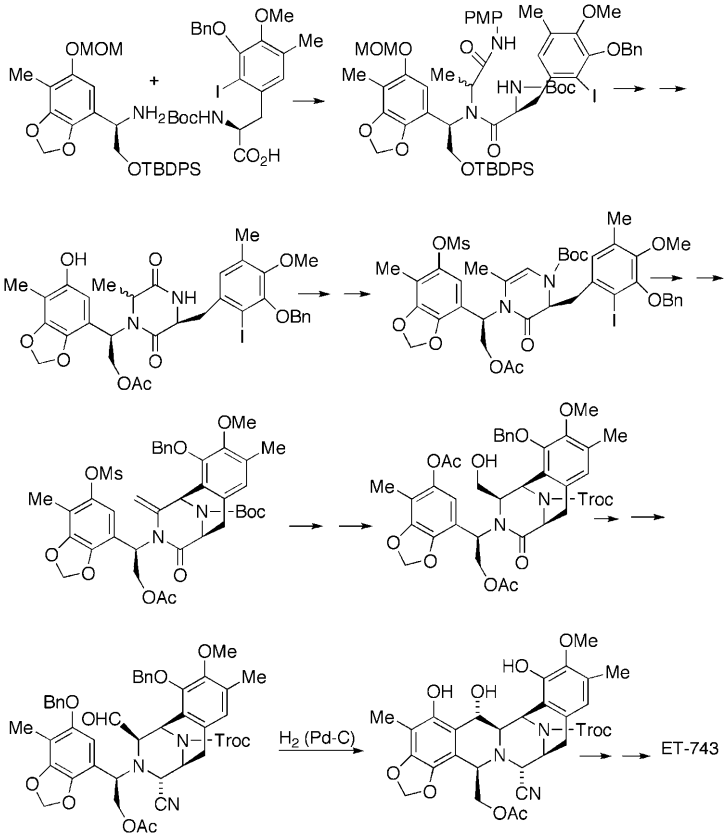
From the seminal works of the groups of Fukuyama and Kubo to achieve (±)-saframycin B,[5] many synthetic approaches have fundamental similarities in strategy by using Pictet–Spengler-type cyclizations to form the B ring[6] in an advanced step from 2-arylmethyl-1,5-imino-3-benzazocins.

[a] Prof. Dr. C. Avendaño, Prof. Dr. E. de la Cuesta
Departamento de Química Orgánica y Farmacéutica
Facultad de Farmacia, Universidad Complutense
Pza. Ramón y Cajal s/n 28040-Madrid (Spain)
Fax: (+34) 913941822
E-mail: avendano@farm.ucm.es

The tricyclic system, which contains the CDE moiety, is usually generated through *N*-acyliminium-mediated cyclizations from piperazine precursors obtained by double aldol condensation of 2,5-piperazinediones and aromatic aldehydes[5b]



Scheme 1. Formation of ring B from 2-arylmethyl-1,5-imino-3-benzazocins.



Scheme 2. Fukuyama's total synthesis of ET-743. Boc = *tert*-butyloxycarbonyl, Bn = benzyl, MOM = methoxymethyl, TBDPS = *tert*-butyldiphenylsilyl, PMP = *p*-methoxyphenyl, Troc = 2,2,2-trichloroethoxycarbonyl.

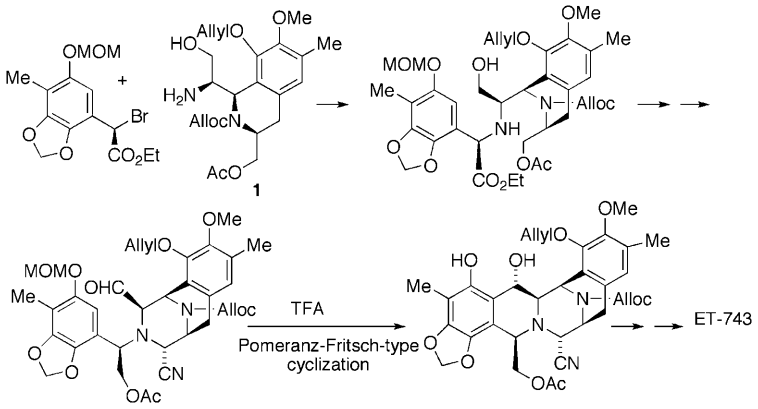
(Scheme 1a) or by stepwise procedures[5a] (Scheme 1b). These procedures were reviewed in reference [1]. Herein, we will mention a recently reported stepwise procedure in which the tricyclic system has been generated through the Lewis acid catalyzed hydroamidation of alkynylamides[7] shown in the retrosynthetic analysis given in Scheme 1c.

Less frequent is the use of Pomeranz–Fritsch-type cyclizations to form the B ring from 3-arylmethyl-1,5-imino-3-benzazocin derivatives. This approach, which has the main advantage of accessing a pentacyclic compound with a C(14)-hydroxy function that is suitable for the immediate construction of the F ring, has been followed by the groups of Fukuyama[8] (Scheme 2) and by Zhu[9] (Scheme 3) in their total syntheses of ecteinascin 743. Both syntheses mainly differ in the strategy used to obtain the tricyclic aldehyde envisaged as an appropriate platform for the preparation of the pentacyclic benzyl alcohol designed as the key intermediate.

In Fukuyama's synthesis, two highly functionalized derivatives of (*R*)-phenylglycinol and (*S*)-iodophenylalanine were incorporated into a piperazine-2,5-dione by means of a Ugi's four-component condensation reaction with acetaldehyde and *p*-methoxyphenyl isocyanide (Scheme 2). After conversion of the piperazinedione into an enamide through partial reduction and subsequent acid treatment, this intermediate was cyclized by an intramolecular Heck reaction that generated the D ring. The epoxidation and methanol addition of the exocyclic double bond in this tricyclic compound was followed by a diastereoselective acyliminium ion mediated reduction to give a 2-hydroxymethyl-1,5-imino-3-benzazocin derivative that, after several reactions to afford

Prof. Carmen Avendaño López received her doctoral degree in Pharmacy at the Complutense University of Madrid (UCM) in 1970. She became Full Professor of Organic Chemistry at the Department of Organic and Pharmaceutical Chemistry of this university in 1986. She has acted as the Head of this Department during several periods and is responsible of one of its research groups. Her original research activities have focused on the development of synthetic methodologies to obtain biologically active molecules, mainly analogues of antitumor natural compounds.

Prof. Elena de la Cuesta Elósegui received her doctoral degree in Pharmacy at the Complutense University of Madrid (UCM) in 1981. She spent one year in a postdoctoral stay in l'école Polytechnique with the Professor F. Mathey in 1989. Her research interests lie across the heterocyclic chemistry to obtain biologically active molecules, analogues of antitumor natural compounds.



Scheme 3. Zhu's total synthesis of ET-743. Alloc = allyloxycarbonyl, TFA = trifluoroacetic acid.

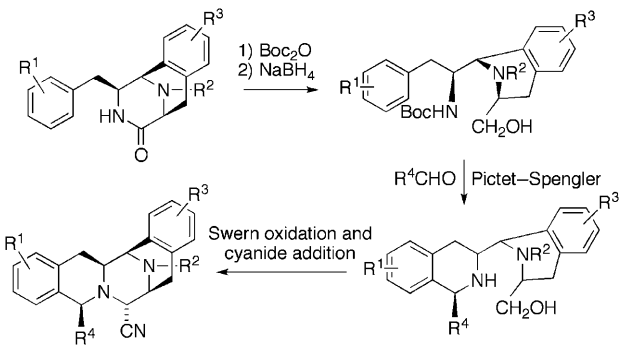
the aminonitrile function, was submitted to Dess–Martin oxidation and cyclization.

In the more convergent strategy of Zhu (Scheme 3), an α-bromo-α-aryl-substituted ethyl acetate was coupled with the isoquinoline fragment **1**, which contains the DE rings and was formed through a first condensation of the (*S*)-Garner aldehyde (see Scheme 11 below) and L-3-hydroxy-4-methoxy-5-methyl phenylalaninol.

Synthetic Approaches with Formation of C Ring from (1,3′)-Bis-tetrahydroisoquinolines

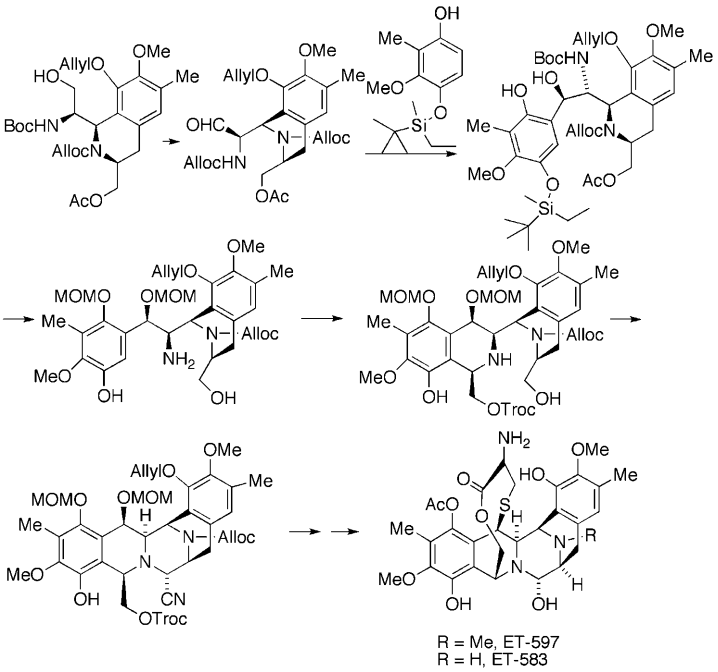
In these approaches, the C ring is generated in the final steps by oxidative condensation followed by cyanide addition of (1,3′)-bis-tetrahydroisoquinoline derivatives. This method was used by Fukuyama et al. in the first total synthesis of (±)-saframycin A.[10] The precursors were originated by reductive opening of the piperazine ring in 2-arylmethyl-1,5-imino-3-benzazocin compounds (Scheme 4).

The *N*-Boc derivative of **1** (see Scheme 3) was used by Zhu et al. in the asymmetric total synthesis of ecteinascidins 597 and 583.[11] The pentacyclic core was obtained after a phenolic aldol condensation followed by Pictet–Spengler and intramolecular Strecker reactions (Scheme 5).



Scheme 4. Formation of ring C from bis-tetrahydroisoquinoline derivatives.

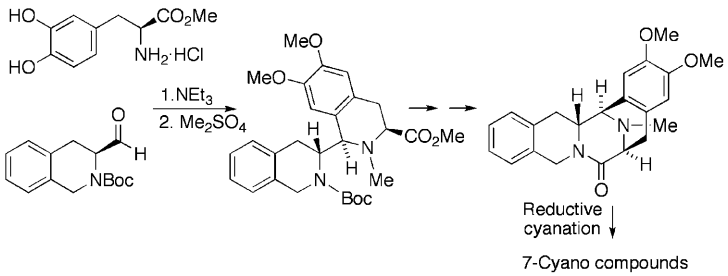
Suitable (1,3′)-bis-tetrahydroisoquinolines have been directly obtained by the Pictet–Spengler reaction of 3-(3,4-dihydroxyphenyl)alanine (L-DOPA) methyl ester derivatives and *N*-Boc-tetrahydroisoquinoline-3-carbaldehyde. This reaction showed complete *cis*-stereoselectivity, but the integrity of the 3′-stereocenter is sensitive to epimerization.[12] Hydrolysis of the ester moiety followed by *N*-Boc cleavage al-



Scheme 5. Synthesis of ecteinascidins 597 and 583 through (1,3′)-bis-tetrahydroisoquinoline intermediates.

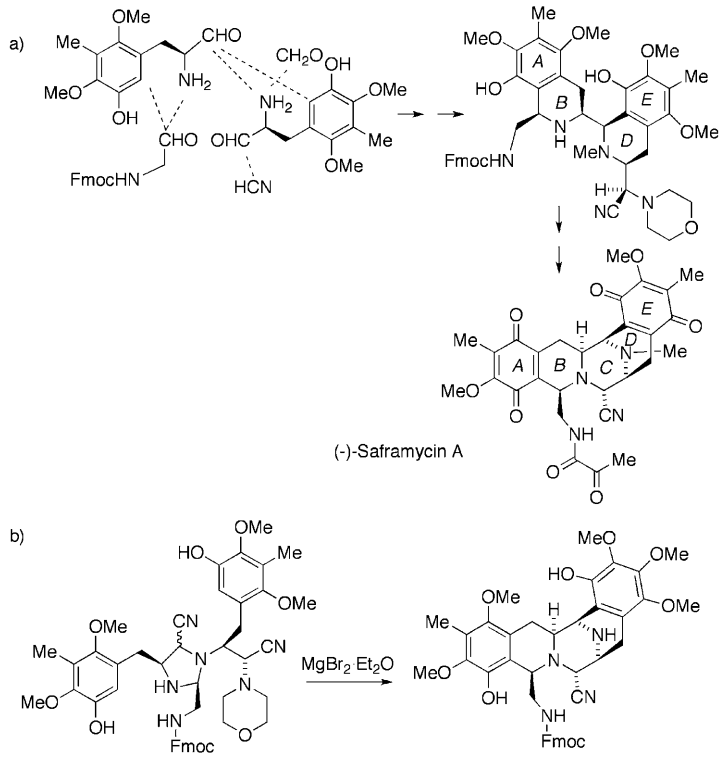
lowed, through intramolecular peptide coupling, cyclization to petacyclic lactams that were submitted to subsequent reductive cyanation[13] (Scheme 6).

In the first asymmetric synthesis of (−)-saframycin A,[14] the envisioned strategy to obtain the key (1,3′)-bis-tetrahydroisoquinoline intermediate was to assemble two optically active α-amino aldehydes (one of them masked as an α-morpholino nitrile) with three other simple components: hydrogen cyanide, formaldehyde, and α-amino acetaldehyde. The C ring was generated by the sequential formation of an iminium ion by cleavage of the morpholino nitrile blocking group, addition of the secondary amine present in the B ring, expulsion of morpholine, and trapping of the resultant iminium ion by cyanide. The target product was finally obtained by *N*-acylation of the deprotected NH_2 group and ox-



Scheme 6. Synthesis from (1,3′)-bis-tetrahydroisoquinolines obtained by a Pictet–Spengler reaction.

idative demethylation (Scheme 7a). A variant of this strategy allowed the synthesis of the saframycin skeleton from a "trimer" containing three α-amino acetaldehyde components[15] (Scheme 7b).

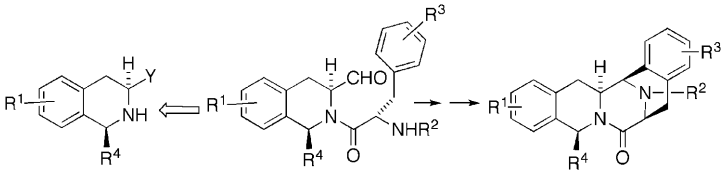


Scheme 7. Myers's approaches of (−)-saframycin A. Fmoc = 9-fluorenylmethoxycarbonyl.

A successful adaptation of this method to a 10-step solid-supported synthesis, suitable for the preparation of large numbers of diverse saframycin analogues with deep-seated structural modifications, has opened the way toward the construction of large-scale libraries.[16]

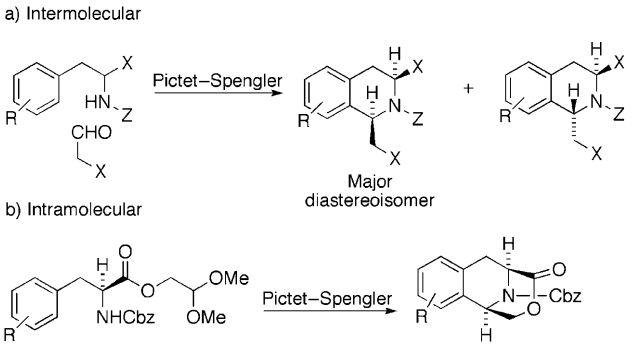
Synthetic Approaches with Formation of CD Rings from *cis*-1,3-Disubstituted Tetrahydroisoquinolines

This is a very frequent strategy in which the starting compound, which contains the AB rings, is a *cis*-1,3-disubstituted tetrahydroisoquinoline that is derived to permit the formation of CD rings through *N*-acylimininium-mediated cyclizations in the later steps of the process (Scheme 8).



Scheme 8. Formation of CD rings from 1,3-*cis*-disubstituted tetrahydroisoquinolines.

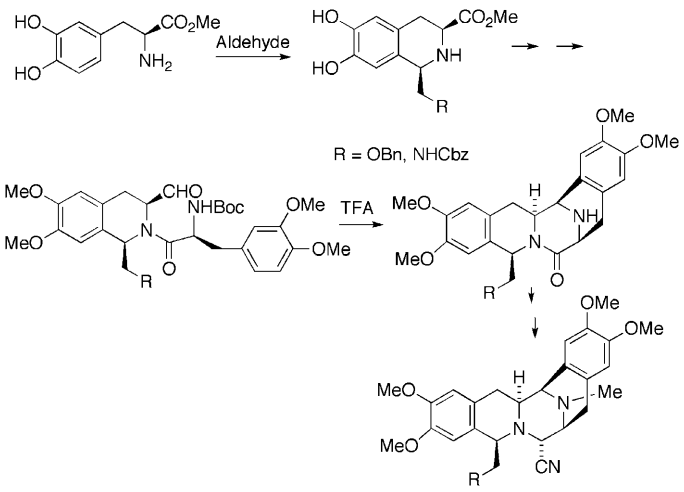
The starting compounds here are usually obtained from phenethylamines (enantiomerically pure in asymmetrical syntheses) through inter- or intramolecular Pictet–Spengler-type cyclizations (Scheme 9). Since the intermolecular version of this classic procedure may give the 1,3-*cis*-diastereoisomers as the major, but not exclusive products, the diastereoselective problem is solved in intramolecular cyclizations, such as that shown in Scheme 9b; this method was used by Corey in the first enantioselective total synthesis of ET-743 (see Scheme 26 below).[17] In this case, the starting material was obtained through condensation of allyl 2,2-dimethoxyethyl malonate and the adequate benzaldehyde derivative, selective allyl ester cleavage, Curtius rearrangement of an acylazide intermediate, addition of benzyl alcohol to the corresponding isocyanate, and catalytic hydrogenation of the double bond with [Rh(cod){(*R*,*R*)-dipamp}][BF_4] (cod = 1,5-cyclooctadiene, (*R*,*R*)-dipamp = (*R*,*R*)-ethylenebis[(*o*-anisyl)phenylphosphine]).



Scheme 9. Pictet–Spengler-type cyclizations of phenethylamines. Cbz = carbobenzyloxy.

Liu and co-workers have followed this methodology to obtain simplified analogues of saframycins through a condensation of formaldehyde and L-DOPA methyl ester.[18]

Other pentacyclic compounds were obtained from *cis*-1,3-disubstituted tetrahydroisoquinoline derivatives with benzyloxymethyl or carbobenzoxyaminomethyl side chains[19] (Scheme 10). More recently, renieramycin G was synthesized by this group in 21 steps through a linear sequence employing L-tyrosine methyl ester as the chiral starting material.[20]



Scheme 10. Synthesis of pentacyclic compounds from L-DOPA methyl ester.

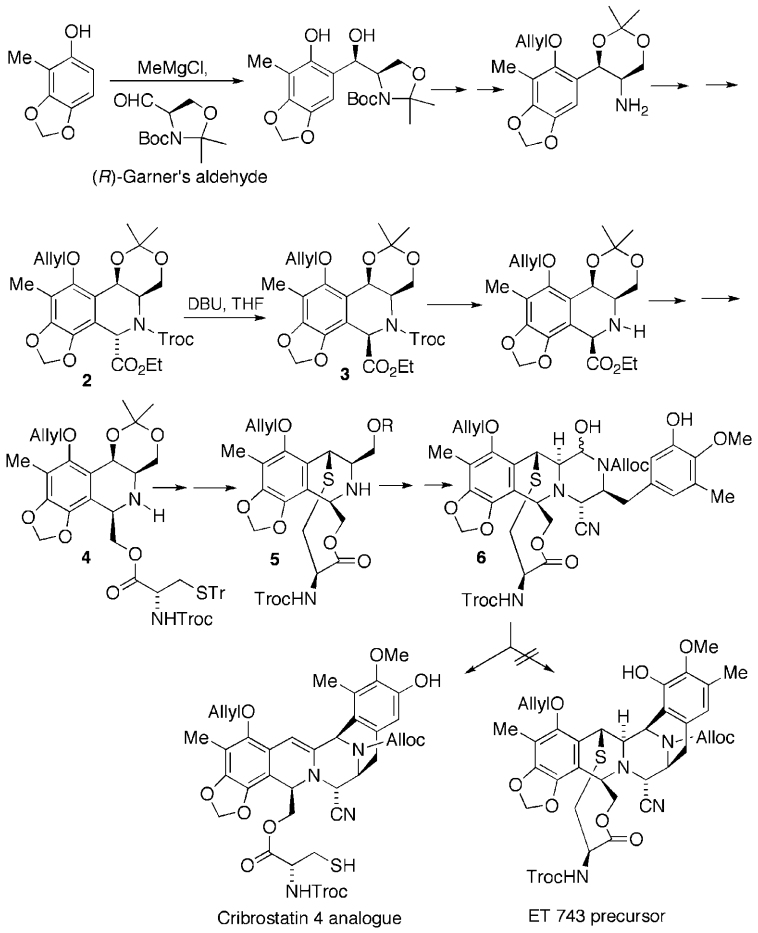
A common alternative to obtain 1,3-*cis*-tetrahydroisoquinolines is the equilibration of 1,3-*trans* isomers. In the synthetic studies by Zhu et al. toward ET-743,[21] compound **2** was obtained by intermolecular Pictet–Spengler cyclization of an enantiomerically pure phenethylamine and ethyl glyoxalate, which was epimerized with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give the 1,3-*cis* isomer **3** (Scheme 11).

In a domino process, the TFA-mediated detritylation of the sulfide function in compound **4**, followed by fragmentation of the dioxane ring, macrocyclization with formation of a C–S bond, and *O*-tritylation, gave **5**. However, the acid-promoted cyclization of the derivative **6** gave an analogue of cribrostatin 4,[22] instead of the expected hexacyclic ET-743 precursor, because this treatment resulted in the cleavage of the C–S bond with opening of the F ring.

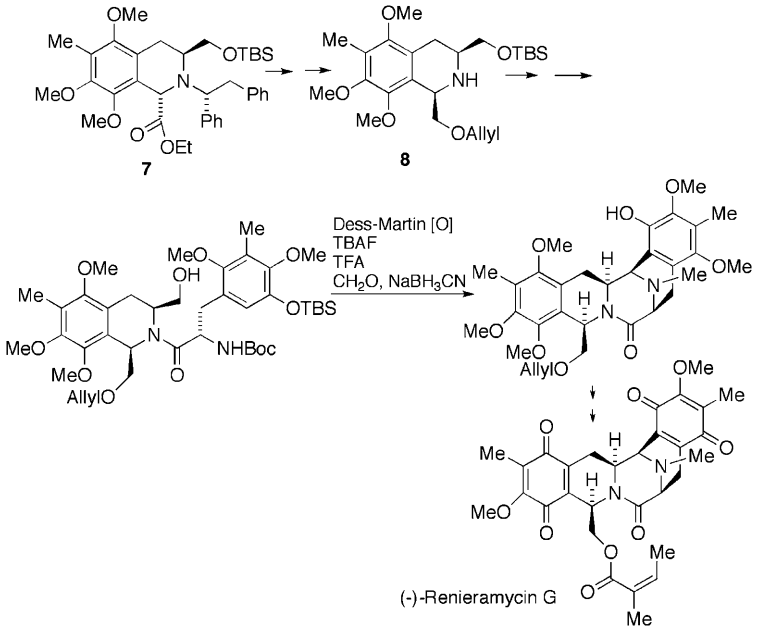
Equilibration with DBU of the *trans*-carboethoxy group in **7** gave the 1,3-*cis*-tetrahydroisoquinoline **8**, used in the asymmetric total syntheses developed by Williams and coworkers[23] for (−)-jorumycin, (−)-renieramycin G, 3-*epi*-jorumycin, and 3-*epi*-renieramycin G. See for instance the synthesis of (−)-renieramycin G given in Scheme 12.

It is interesting to note that subtle changes in the reaction sequence may determine inverse diastereoselectivity in the *N*-acyliminium-mediated cyclization that generates CD rings with epimerization of the 14a stereocenter (Scheme 13).

Another alternative to obtain *cis*-1,3-disubstituted tetrahydroisoquinolines, which was developed by Magnus et al.,[24] is the ionic reduction of the double bond C(3)=C(4) in 1-substituted-*N*-acyl-1,2-dihydroisoquinolines. These compounds were obtained by the reaction of *ortho*-iodobenzylimines with propargylic alcohol derivatives, followed by nucleophilic addition, and *N*-acylation. The C(1)-stereogenic center induced the desired 1,3-*cis* relationship through hydride addition from the less-hindered face. Probably, the C(1) substituent adopts an axial conformation in the iminium ion intermediates to avoid steric interactions with the *N*-acyl group and the *peri*-hydrogen atom (Scheme 14).

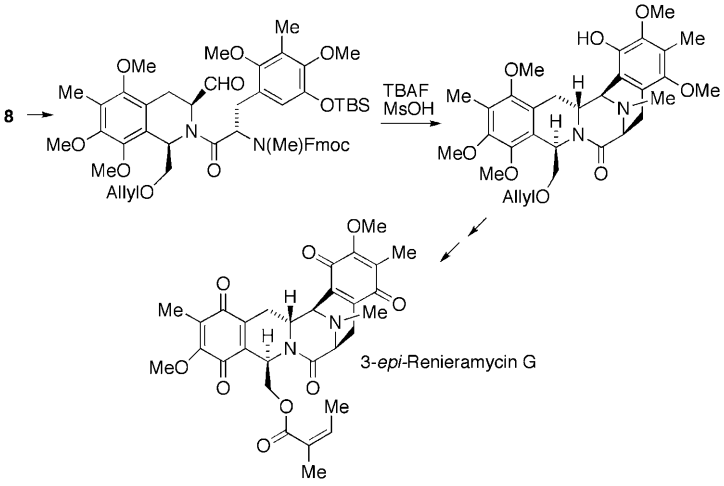


Scheme 11. Synthetic studies by Zhu et al. toward ET-743 from tetrahydroisoquinolines.

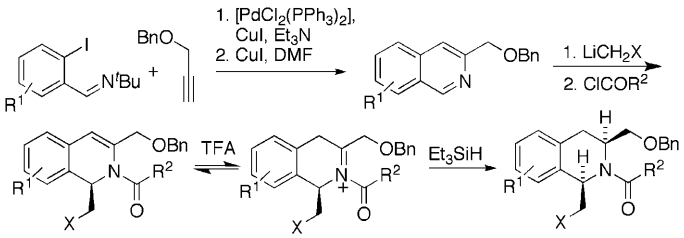


Scheme 12. Synthesis of (−)-renieramycin G.

The use of *cis*-1,3-disubstituted tetrahydroisoquinolines as starting materials is also frequent in protocols aiming to synthesize compounds related to cribrostatin 4, which are characterized by the presence of a double bond in the AB-isoquinoline portion. The olefinic moiety of the pentacyclic core of these compounds is flexibly poised for either saturation to produce saframycins[20] or functionalization at C-14 for the closure of ring F in sulfur-containing precursors. For instance, the asymmetric synthesis of compound **10** developed by Williams and co-workers,[26] began with the synthesis of a phenethylamine fused with an azetidinone ring (Scheme 16).

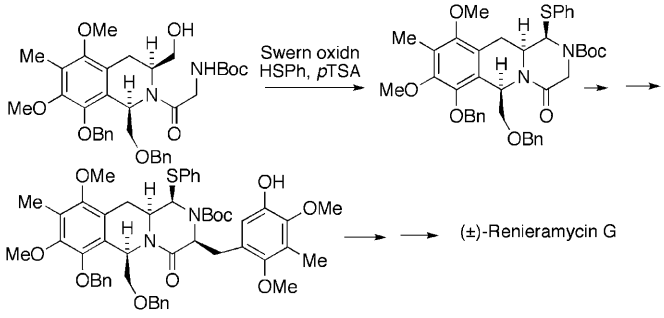


Scheme 13. Synthesis of 3-*epi*-renieramycin G. TBAF = tetrabutylammonium fluoride, MsOH = methane sulfonic acid.



Scheme 14. Ionic reduction of 1-substituted-*N*-acyl-1,2-dihydroisoquinolines.

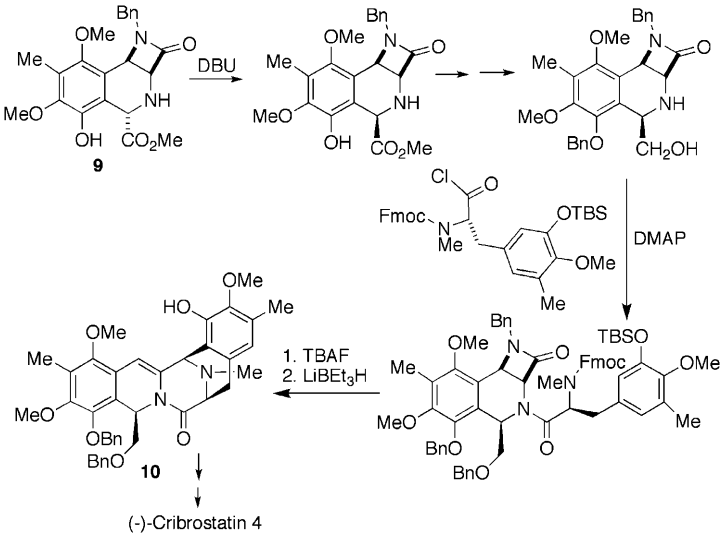
This approach was lately employed in the synthesis of (±)-renieramycin G (Scheme 15).[25]



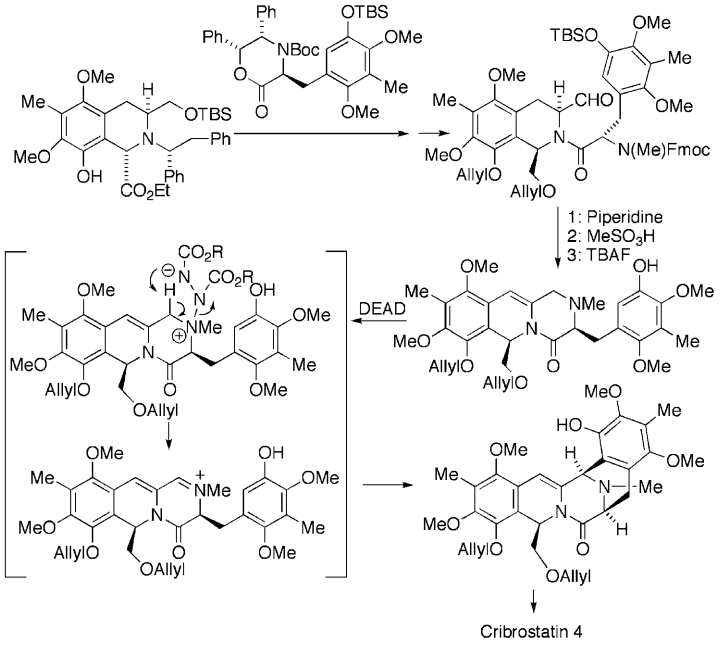
Scheme 15. Synthesis of (±)-renieramycin G. *p*TSA = *p*-tolunesulfonic acid.

This starting compound was obtained through a Staudinger reaction between the corresponding *N*-benzylimine and a chiral ketene generated from an enantiomerically pure arylmethylglycine chloride derivative, followed by elimination of the chiral auxiliary and deprotection of a phenol group. Its Pictet–Spengler cyclization with methyl glyoxalate gave the tetrahydroisoquinoline **9**, which was transformed, as indicated, into (−)-cribrostatin 4 (Scheme 16).[27]

The regio- and diastereochemistry of the final *N*-acyliminium-mediated cyclization that generates CD rings has been studied in the same group,[28] showing that oxidation of the allylamine substructure present in 11,11a-unsaturated pyrazino[1,2-*b*]isoquinolin-4-ones may be performed with *N*-bromosuccinimide (NBS) or with other oxidants to achieve the required iminium cations to be captured by the arene ring E.[29] The same group discovered an unprecedented diethylazodicarboxylate (DEAD)-mediated dehydrogenation that was used to generate an immediate precursor of cribrostatin 4 (Scheme 17).[30]



Scheme 16. Synthesis of cribrostatin 4 related compounds. DMAP = 4-dimethylaminopyridine.



Scheme 17. Cribrostatin 4 related compounds obtained through DEAD-mediated oxidation.

Synthetic Approaches with Formation of CD Rings from 1,4-Disubstituted Tetrahydroisoquinolines

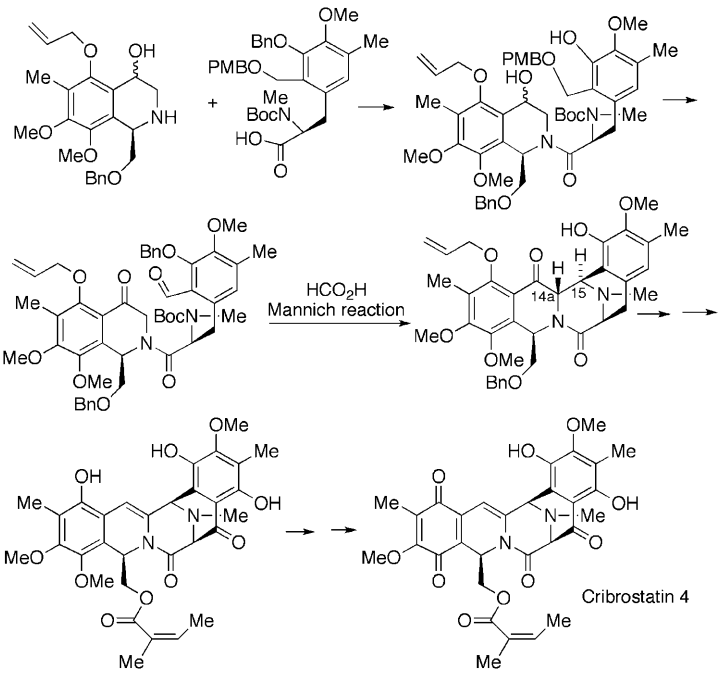
This approach was followed by Danishefsky et al. in the first enantioselective synthesis of cribrostatin 4.[31] It involved a convergent coupling of two extremely functionalized enantiopure compounds followed by a Mannich cyclization to establish the pentacyclic core. Oxidation at the C-5 position, which stabilizes the E ring against oxidation, and *O*-acylation of the deprotected hydroxymethyl side chain, was followed by selective oxidation of the A ring to quinone (Scheme 18). The stereochemical outcome of the Mannich cyclization (i.e., whether the relationship between H-14a and H-15 emerges as *syn* or *anti*) was recently studied in detail, concluding that the cyclization of the iminium species onto the isoquinoline C(3)–C(4) enol occurs from the face opposite to that of the resident C(1)-benzyloxymethyl group.[32]

Synthetic Approaches with Formation of D Ring from Pyrazino[1,2-*b*]isoquinoline Compounds

In this approach, the precursors, which contain ABC rings, are 6-substituted 2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-diones with a 6,11a-*cis*-stereochemistry or 6-substituted 2,3-dihydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-diones. They give the pentacyclic core through their (3*S**,6*S**,11a*S**) or (3*S**,6*S**)-3-arylmethyl derivatives after a reductive cyclization process.

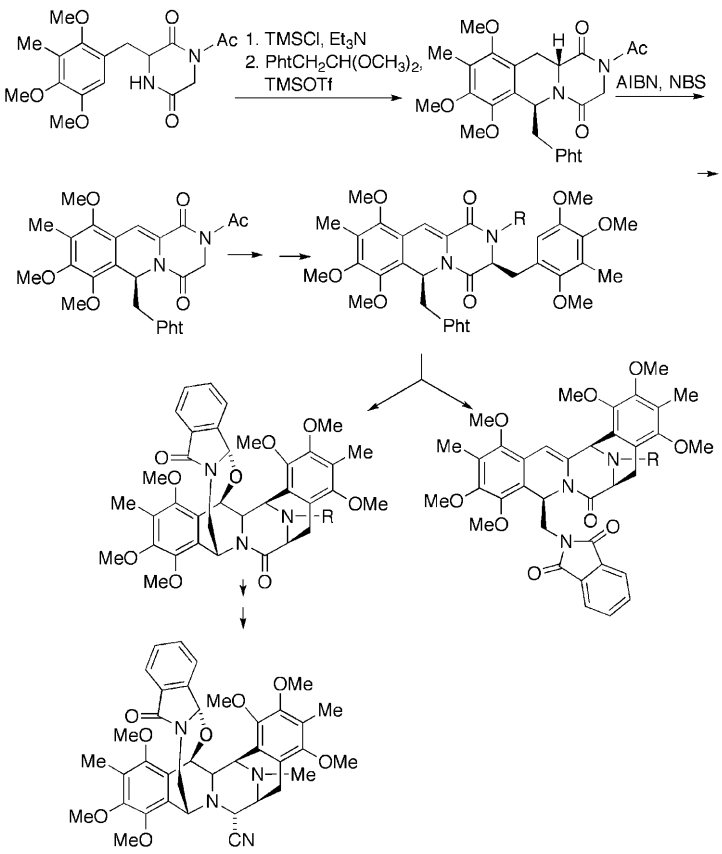
The ABC-tricyclic compounds are usually achieved from 3-arylmethylpiperazine-2,5-diones through *N*-alkylation of the N(4)–C(5)-lactam function with aldehydes, followed by an acid-promoted intramolecular Friedel–Crafts 6-*exo-trig* cyclization of the *N*-α-hydroxyalkyl derivatives thus obtained.[33] The previous activation of the lactam function as an *O*-trimethylsilyl derivative and the use of acetals as electrophiles greatly improve the yields.[34,35]

These cyclizations usually proceed from the *E* isomers of *N*-acyliminium intermediates with less steric interactions between the aldehyde or acetal chain and the C(5)-carbonyl group than the *Z* isomers. Consequently, the major products are usually the 6,11a-*trans* isomers. This methodology was



Scheme 18. The synthesis of cribrostatin 4 by Danishefsky and co-workers. PMB = *p*-methoxybenzyl.

used to obtain a precursor of phthalascidin[36] analogues (Scheme 19).[34c,37] In this work, the 6,11a-*trans* isomers were epimerized at C-11a through a radical bromination followed by catalytic hydrogenation of the 11,11a-dehydro intermedi-

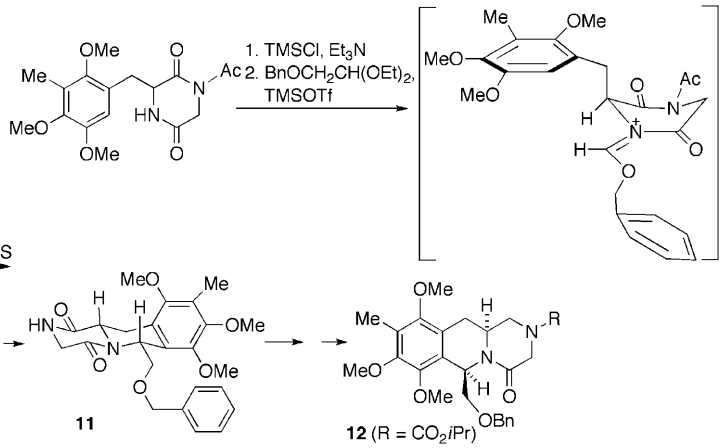


Scheme 19. Synthesis of phthalascidin analogues. Pth = phthalimido, AIBN = 2,2′-azobisisobutyronitrile, Tf = triflate.

ate produced by spontaneous dehydrohalogenation, but the sequence was performed on the unsaturated intermediates to give 3-arylmethyl derivatives through an aldol-type condensation and a subsequent catalytic hydrogenation. These compounds gave octa- or pentacyclic derivatives through partial reduction of two or one amide functions, respectively, and generation of *N*-acyliminium cations with or without a conjugate intramolecular addition.[38]

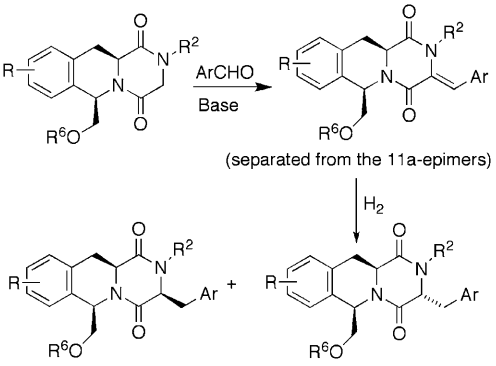
The greater conformational freedom of some side chains, makes the *Z* isomers of *N*-acyliminium species that mediate the 6-*exo*-*trig* cyclization more stable, which resulted from the attack of the aromatic ring from the *Re* face. Compounds such as **11**, with a *syn*-relationship between the H-6 and H-11a protons, were the only products. This compound was converted into the interesting cytotoxic agent **12** through reduction of the C(1)-lactam function (Scheme 20).[39]

Aldol-type condensations of 6,11a-*trans* isomers of 2,3,11,11a-tetrahidro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-diones with benzaldehydes were efficient. However, for



Scheme 20. *N*-Alkylation/cyclization of 3-arylmethylpiperazine-2,5-diones and 2-benzyloxyacetaldehyde dimethyl acetal.

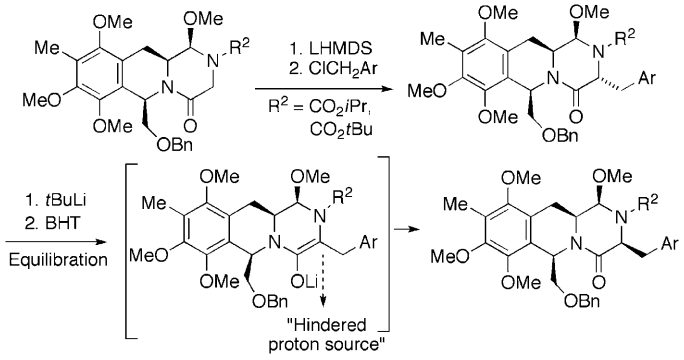
6,11a-*cis* isomers, such as **11**, it was necessary to carefully select the base and the C(6) side chain because of the lability of the 11a proton in basic media.[40] Although the H(11a) proton is more acid than the H(3) proton, the use of potassium *tert*-butoxide as a bulky base allowed the generation of the C(3)-enolate and its subsequent reaction with aromatic aldehydes, but the catalytic hydrogenation of the exocyclic double bond was not diastereoselective because the conformational freedom of the C(6)-benzyloxymethyl chain makes the two faces of the double bond equally accessible to hydrogen transfer. Reductions with zinc/acetic acid[41] or with diimide[42] gave also an equimolecular mixture of diastereomers at C-3 (Scheme 21).



Scheme 21. Aldol condensation/reduction of 2,3,11,11a-tetrahidro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-diones.

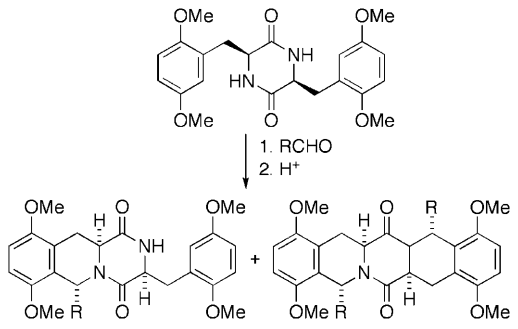
Although other side chains at C-6 permitted control of hydrogen addition from the α face,[43] the C(3)-alkylation of 1-methoxy compounds was considered to be a better option because deprotonation at the C(11a)-position and the hydrogenation of the exocyclic double bond were eluded. These starting materials were obtained through activation of the C(1) carbonyl group, partial reduction, and methanol addition. Alkylation of the enolates with benzyl halides occurred from the α face of the piperazine ring, but the de-

sired C(3)-epimers (the *all-cis* kinetically controlled products) were obtained by equilibration through deprotonation and subsequent stereoselective reprotonation with a solution of di-*tert*-butylhydroxytoluene (BHT) as a hindered proton source (Scheme 22).[44]



Scheme 22. C(3)-Alkylation of 6-substituted 6,11a-*cis*-1-methoxypyrazino[1,2-*b*]isoquinolin-4-ones. LHMDS = lithium hexamethyldisilazide.

Other groups have studied the use of 3,6-bis-arylmethylpiperizine-2,5-diones, obtained by double aldol condensation/hydrogenation of 2,5-piperazinediones and aromatic aldehydes,[5b] as starting materials. This approach eludes the arylmethylation of the tricyclic ABC system, but requires a chemoselectively controlled mono-Pictet–Spengler cyclization to avoid formation of the linearly fused pentacyclic system (Scheme 23).[45]



Scheme 23. Pictet–Spengler cyclizations of 3,6-bis-arylmethylpiperizine-2,5-diones.

Due to steric interactions between the C(3) and C(6) side chains, which have to adopt nearly axial positions in *all-cis* compounds, formation of the D ring from 6-substituted 3-arylmethyl-3,6,11a-*cis*-pyrazino[1,2-*b*]isoquinolin-4-ones or 3-arylmethyl-3,6,11a-*cis*-1-methoxypyrazino[1,2-*b*]isoquinolin-4-ones following intramolecular Pictet–Spengler conditions[46] competes with elimination of the 11a proton to give enamides (Scheme 24a). Cyclizations of 3-(2,5-dimethoxy)-benzyl derivatives were especially difficult because of the steric effect of the *o*-methoxy groups, but they were convenient for the C(3) epimers (Scheme 24b).[43]

Superacid-catalyzed reactions of *all-cis* tricyclic precursors, by using trifluoromethanesulfonic acid, gave the cyclization products in good yields, probably through *C*,*N*-biscationic intermediates that are more reactive than iminium cations (Scheme 25).[47]

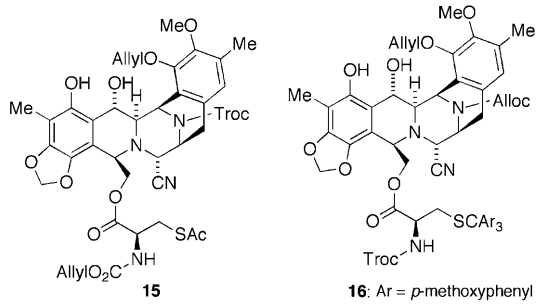
A Brief Summary of ET-743 Total Syntheses and Semisynthetic Approaches

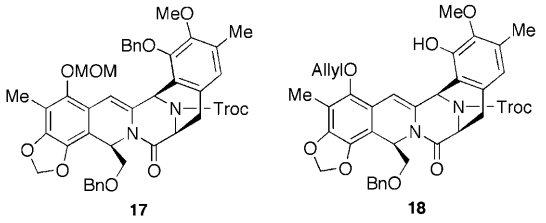
Ecteinascidins are marine natural products and attractive candidates for development as anticancer agents because of their potent antiproliferative activity against a variety of tumor cells. The low amounts present in its natural source, the tunicate *Ecteinascidia turbinata*, made it necessary to find efficient synthetic procedures to develop the lead compound Yondelis (trabectedin, ET-743).[4] This is the first marine anticancer agent approved in the European Union and lately in other countries for patients with soft sarcoma; its application for ovarian cancer treatment is also under discussion.

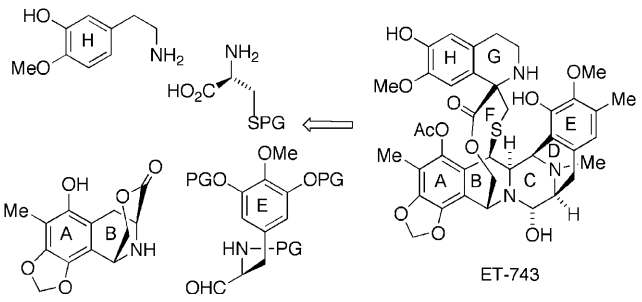
The first total synthesis of ecteinascidin 743 developed by Corey's group[17] was based on biomimetic disconnections leading to four "amino acid" subunits (Scheme 26). Starting from sesamol, chirality was introduced by asymmetric hydrogenation of a precursor of the tricyclic lactone bearing AB rings by using the Knowles catalyst (Scheme 9b), while the E ring was incorporated in a protected amino aldehyde. Twelve steps were required from sesamol to get the coupling of these two main building blocks, and other twenty steps to get the natural product.

The pentacyclic intermediate **13** was obtained through a Mannich bisannulation and the improved synthesis of this intermediate[48] was utilized by Martínez and Corey in their total synthesis of ET-743[49] and its simpler analogue phtalascidin.[36a] Among the powerful transformations applied in the full process, the generation and capture of a quinone methide[50] by the cysteine sulfur atom to construct the 10-membered lactone was so relevant that it was followed in the semisynthesis of ET-743 developed in Pharmamar.[51] With more or less variations, it was also used in the formal or total syntheses of ET-743 reported so far. Corey and coworkers generated the quinone methide by "dehydration" of the α-hydroxycarbonyl portion of intermediate **14**, which was produced in the oxidation with benzeneseleninic anhydride of the phenol function in a derivative of **13** (Scheme 27).

The groups of Fukuyama,[8] Zhu,[9] Danishefsky,[32] and Williams[27] generated the quinone methide by "dehydration" of 14-hydroxyphenols. These precursors originated from the approaches by the groups of Fukuyama and Zhu in the formation of the B ring (see Schemes 2 and 3), giving rise to compounds **15** and **16**. In contrast, the 14-hydroxy function was generated in the approaches used by the groups of Danishefsky and Williams by epoxidation/reduction of 14,14a-unsaturated intermediates **17** and **18**, respectively.

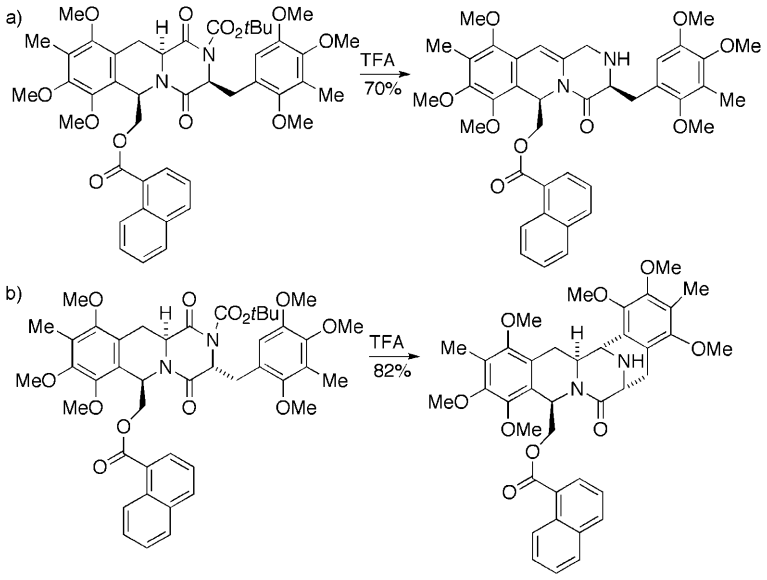




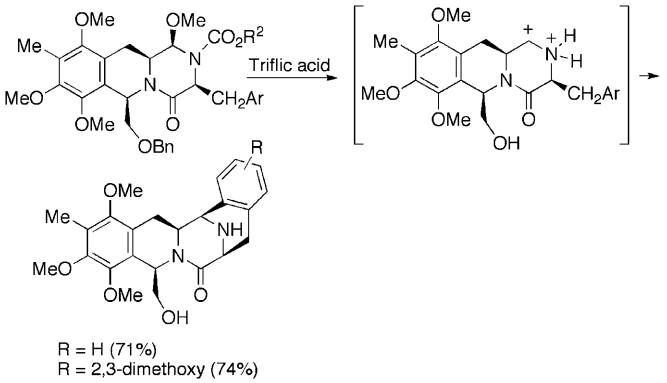


Scheme 26. Retrosynthetic analysis of the approach used by Corey et al. for the total synthesis of ET-743. PG = protecting group.

In spite of their success, these total syntheses are not suitable for manufacturing ET-743 on an industrial scale. Fortunately, a semisynthetic process starting from cyanosafracin B, an antibiotic obtained by fermentation from the bacteria *Pseudomonas fluorescens*, solved the supply problem of producing the drug economically on a multigram scale (Scheme 28).[51] This fermentation process has been also applied for the semisynthesis of other ecteinascidins.[52] One interesting compound among these new structures is Zalypsis,[53] which is currently in clinical development for the treatment of solid tumors and hematological malignancies.[54]



Scheme 24. Formation of the D ring.



Scheme 25. Superacid-catalyzed cyclizations.

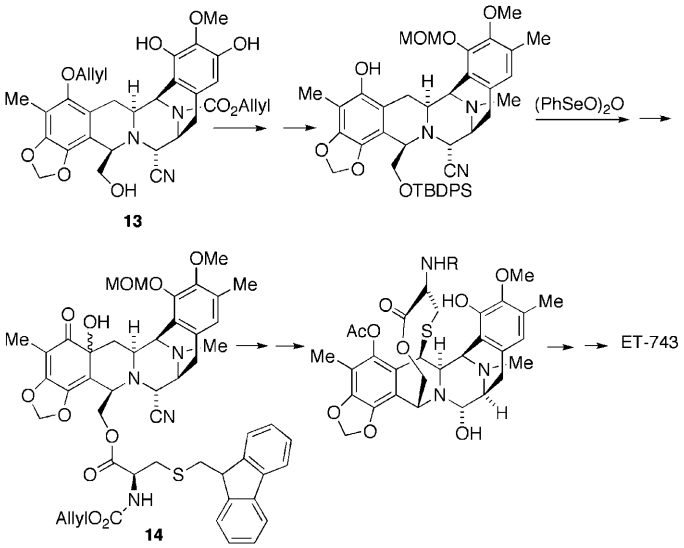
Conclusion and Outlook

Besides the above-reported synthetic strategies, over the last 10 years, new antitumor antibiotics belonging to the tetrahydroisoquinoline family have been isolated and studied as cytotoxic compounds.[55] Many transformations of the substituents in the pentacyclic core to establish structure–activity relationships have also been reported,[19,56] along with reports of hybrid structures that contain portions of two subfamilies have been obtained or isolated from the nature.[57]

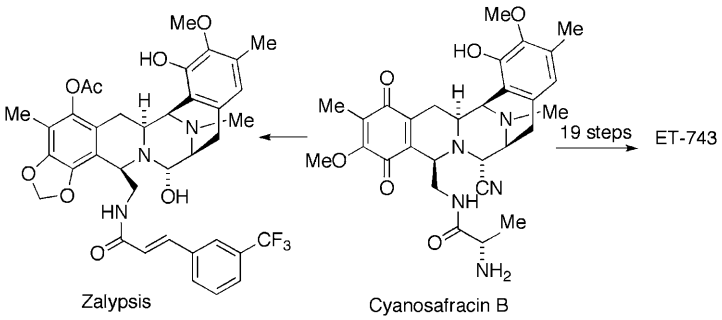
The findings reported herein highlight that, although the ideal synthesis of these complex heterocyclic systems is still far away, many synthetic achievements have paved the way toward this aim.

Acknowledgements

This work was supported by Comunidad Autónoma de Madrid (Group 920234 grant).



Scheme 27. Last steps in Corey's total synthesis of ET-743.



Scheme 28. Semisynthesis of ET-743 and other promising anticancer agent.

[1] J. D. Scott, R. M. Williams, *Chem. Rev.* **2002**, *102*, 1669–1730.
[2] P. Siengalewicz, U. Rinner, J. Mulzer, *Chem. Soc. Rev.* **2008**, *37*, 2676–2690.
[3] I. Manzanares, C. Cuevas, R. García-Nieto, E. Marco, F. Gago, *Curr. Med. Chem. -Anti-Cancer Agents* **2001**, *1*, 257–276.
[4] C. Cuevas, A. Francesch, *Nat. Prod. Rep.* **2009**, *26*, 322–337.
[5] a) T. Fukuyama, R. A. Sachleben, *J. Am. Chem. Soc.* **1982**, *104*, 4957–4958; b) A. Kubo, N. Saito, H. Yamato, K. Masubuchi, M. Nakamura, *J. Org. Chem.* **1988**, *53*, 4295–4310.
[6] The two rings of the tetrahydroisoquinoline moiety condensed by its β-face with the piperazine core may be named as AB or as DE rings. Here we follow the first system.
[7] S. Obika, Y. Yasui, R. Yanada, Y. Takemoto, *J. Org. Chem.* **2008**, *73*, 5206–5209.
[8] A. Endo, A. Yanagisawa, M. Abe, S. Tohma, T. Kan, T. Fukuyama, *J. Am. Chem. Soc.* **2002**, *124*, 6552–6554.
[9] J. Chen, X. Chen, M. Bois-Choussy, J. Zhu, *J. Am. Chem. Soc.* **2006**, *128*, 87–89.
[10] T. Fukuyama, L. Yang, K. L. Ajeck, R. A. Sachleben, *J. Am. Chem. Soc.* **1990**, *112*, 3712–3713.
[11] J. Chen, X. Chen, M. Willot, J. Zhu, *Angew. Chem.* **2006**, *118*, 8196–8200; *Angew. Chem. Int. Ed.* **2006**, *45*, 8028–8032.
[12] S. Aubry, S. Pellet-Rostaing, B. Fenet, M. Lamaire, *Tetrahedron Lett.* **2006**, *47*, 1319–1323.
[13] S. Aubry, S. Pellet-Rostaing, J. F. Chabert, S. Ducki, M. Lamaire, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2598–2602.
[14] A. G. Myers, D. W. Kung, *J. Am. Chem. Soc.* **1999**, *121*, 10828–10829.
[15] A. G. Myers, D. W. Kung, *Org. Lett.* **2000**, *2*, 3019–3022.
[16] A. G. Myers, B. A. Lanman, *J. Am. Chem. Soc.* **2002**, *124*, 12969–12971.
[17] E. J. Corey, D. Y. Gin, R. S. Kania, *J. Am. Chem. Soc.* **1996**, *118*, 9202–9203.
[18] Y.-F. Tang, Z.-Z. Liu, S.-Z. Chen, *Tetrahedron Lett.* **2003**, *44*, 7091–7094.
[19] Z.-Z. Liu, Y. Wang, Y.-F. Tang, S.-Z. Chen, X.-G. Chen, H.-Y. Li, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1282–1285.
[20] X. W. Liao, W. Liu, W. F. Dong, B. H. Guan, X.-G. Chen, Z.-Z. Liu, *Tetrahedron* **2009**, *65*, 5709–5715.
[21] X. Chen, J. Chen, M. De Paolis, J. Zhu, *J. Org. Chem.* **2005**, *70*, 4397–4408.
[22] G. R. Pettit, J. C. Knight, J. C. Collins, D. L. Herald, R. K. Pettit, M. R. Boyd, V. G. Young, *J. Nat. Prod.* **2000**, *63*, 793–798.
[23] J. W. Lane, Y. Chen, R. M. Williams, *J. Am. Chem. Soc.* **2005**, *127*, 12684–12690.
[24] P. Magnus, K. S. Matthews, V. Lynch, *Org. Lett.* **2003**, *5*, 2181–2184.
[25] P. Magnus, K. S. Matthews, *J. Am. Chem. Soc.* **2005**, *127*, 12476–12477.
[26] a) B. Herberich, M. Kinugawa, A. Vazquez, R. M. Williams, *Tetrahedron Lett.* **2001**, *42*, 543–546; b) W. J. Jin, S. Metobo, R. M. Williams, *Org. Lett.* **2003**, *5*, 2095–2098.
[27] G. Vincent, R. N. Williams, *Angew. Chem.* **2007**, *119*, 1539–1542; *Angew. Chem. Int. Ed.* **2007**, *46*, 1517–1520.
[28] G. Vincent, J. W. Lane, R. N. Williams, *Tetrahedron Lett.* **2007**, *48*, 3719–3722.
[29] a) M. E. Flanagan, R. M. Williams, *J. Org. Chem.* **1995**, *60*, 6791–6797; b) J. D. Scott, R. M. Williams, *Angew. Chem.* **2001**, *113*, 1511–1513; *Angew. Chem. Int. Ed.* **2001**, *40*, 1463–1465; c) J. D. Scott, R. M. Williams, *J. Am. Chem. Soc.* **2002**, *124*, 2951–2956.
[30] G. Vincent, Y. Chen, J. W. Lane, R. M. Williams, *Heterocycles* **2007**, *72*, 385–398.
[31] C. Chan, R. Heid, Sh. Zheng, J. Guo, B. Zhou, T. Furuchi, S. J. Danishefsky, *J. Am. Chem. Soc.* **2005**, *127*, 4596–4598.
[32] S. Zheng, C. Chan, T. Furuuchi, B. J. D. Wright, B. Zhou, J. Guo, S. J. Danishefsky, *Angew. Chem.* **2006**, *118*, 1786–1791; *Angew. Chem. Int. Ed.* **2006**, *45*, 1754–1759.
[33] C. W. Ong, H. C. Lee, *Aust. J. Chem.* **1990**, *43*, 773–775.
[34] a) J. F. González, E. de La Cuesta, C. Avendaño, *Tetrahedron Lett.* **2003**, *44*, 4395–4398; b) J. F. González, E. de La Cuesta, C. Avendaño, *Tetrahedron* **2004**, *60*, 6319–6326; c) J. F. González, L. Salazar, E. de La Cuesta, C. Avendaño, *Tetrahedron* **2005**, *61*, 7447–7455.
[35] M. Yokoya, O. Karachi, N. Saito, *Heterocycles* **2008**, *76*, 1497–1509.
[36] a) E. J. Martínez, T. Owa, S. L. Schreiber, E. J. Corey, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 3496–3501; b) E. J. Martínez, E. J. Corey, T. Owa, *Chem. Biol.* **2001**, *8*,1151–1160.
[37] J. F. González, E. de La Cuesta, C. Avendaño, *Bioorg. Med. Chem.* **2007**, *15*, 112–118.
[38] For a recent review on 2,5-piperazinedione-derived acyliminium cations, see: C. Avendaño, E. de La Cuesta, *Curr. Org. Synth.* **2009**, *6*, 143–168.
[39] a) I. Ortín, J. F. González, E. de La Cuesta, C. Manguan-García, R. Perona, C. Avendaño, *Bioorg. Med. Chem.* **2008**, *16*, 9065–9078; b) I. Ortín, J. F. González, E. de La Cuesta, C. Manguan-García, R. Perona, C. Avendaño, *Bioorg. Med. Chem.* **2009**, *17*, 8040–8047.
[40] C. Avendaño, N. Cabezas, E. de La Cuesta, J. F. González, *ARKIVOC* **2005**, *ix*, 30–38.
[41] E. J. Corey, D. S. Watt, *J. Am. Chem. Soc.* **1973**, *95*, 2303–2311.
[42] a) For a general review of reductions with diimide, see: D. J. Pasto, R. T. Taylor, *Organic Reactions* (Ed.: L. A. Paquette), Wiley, New York, **1991**, pp. 91–155; b) for reduction of compounds with multiple unsaturations on solid supports, see: K. R. Buszek, N. Brown, *J. Org. Chem.* **2007**, *72*, 3125–3128.
[43] I. Ortín, J. F. González, E. de La Cuesta, C. Avendaño, *Tetrahedron* **2009**, *65*, 2201–2211.

[44] S. D. Bull, S. G. Davies, S. W. Epstein, V. A. Ouzman, *Tetrahedron: Asymmetry* **1998**, *9*, 2795–2798.
[45] Y.-A. Chang, T.-H. Sun, M. Y. Chiang, P.-J. Lu, Y.-T. Huang, L.-C Liang, Ch.-W Ong, *Tetrahedron* **2007**, *63*, 8781–8787.
[46] J. J. N. Veerman, S. B. Robin, B. T. B. Hue, D. Girones, F. P. J. Rutges, J. H. van Maarseveen, H. Hiemstra, *J. Org. Chem.* **2003**, *68*, 4486–4494.
[47] I. Ortín, J. F. González, E. de La Cuesta, C. Avendaño, *Tetrahedron* **2009**, *65*, 9944–9951.
[48] E. J. Martínez, E. J. Corey, *Org. Lett.* **2000**, *2*, 993–996.
[49] E. J. Martínez, E. J. Corey, *Org. Lett.* **1999**, *1*, 75–77.
[50] R. W. VandeWater, T. R. R. Pettus, *Tetrahedron* **2002**, *58*, 5367–5405.
[51] C. Cuevas, M. Pérez, M. J. Martín, J. L. Chicharro, C. Fernández-Rivas, M. Flores, A. Francesch, P. Gallego, M. Zarzuelo, F. de La Calle, J. García, C. Polanco, I. Rodriguez, I. Manzanares, *Org. Lett.* **2000**, *2*, 2545–2548.
[52] R. Menchaca, V. Martínez, A. Rodríguez, N. Rodríguez, M. Flores, P. Gallego, I. Manzanares, C. Cuevas, *J. Org. Chem.* **2003**, *68*, 8859–8866.
[53] C. Cuevas, I. Manzanares, M. Pérez, M. J. Martín, A. Rodríguez, S. Munt (Pharma Mar, S.A.), ES 2231486T3, **2003**.
[54] J. F. M. Leal, V. García-Hernández, V. Moneo, A. Domingo, J. A. Bueren-Calabuig, A. Negri, F. Gago, M. J. Guillén-Navarro, P. Avilés, C. Cuevas, L. F. García-Fernández, C. M. Galmarini, *Biochem. Pharmacol.* **2009**, *78*, 162–170.
[55] N. Oku, S. Matsunaga, R. W. M. van Soest, N. Fusetani, *J. Nat. Prod.* **2003**, *66*, 1136–1139.
[56] a) A. G. Myers, A. T. Plowright, *J. Am. Chem. Soc.* **2001**, *123*, 5114; b) N. Saito, C. Tanaka, Y.-I. Koizumi, K. Suwanborirux, S. Amnuoypol, S. Pummangura, A. Kubo, *Tetrahedron* **2004**, *60*, 3873–3881; c) J.-R. Spencer, M. Sendzik, J. Oeh, P. Sabbatini, S. A. Dalrymple, C. Magill, H. M. Kim, P. Zhang, N. Squires, K. G. Moss, J. Sukbuntherng, A. G. Myers, M. J. Green, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4884–4888; d) P. Puthongking, C. Patarapanich, S. Amnuoypol, K. Suwanborirux, A. Kubo, N. Saito, *Chem. Pharm. Bull.* **2006**, *54*, 1010–1016; e) P. A. Ceballos, M. Pérez, C. Cuevas, A. Francesch, I. Manzanares, A. M. Echavarren, *Eur. J. Org. Chem.* **2006**, 1926–1933; f) B. J. D. Wright, C. Chan, S. J. Danishefsky, *J. Nat. Prod.* **2008**, *71*, 409–414.
[57] N. Daikuhara, Y. Tada, S. Yamaki, K. Charupant, S. Amnuoypol, K. Suwanborirux, N. Saito, *Tetrahedron Lett.* **2009**, *50*, 4276–4278.

Published online: June 8, 2010

