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Chapter 2

A FORMAL TOTAL SYNTHESIS OF THE MARINE DITERPENOID, DIISOCYANOADOCIANE

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I. Introduction and Background

A fascinating variety of approximately 80 diterpenes possessing isonitrile and related functions have been isolated from marine sponges.¹ Three of these compounds are acyclic while the bulk of the remainder are based on one of four novel cyclic skeletons, namely kalihinane (= preamphilectane) (**1**), amphilectane (**2**), cycloamphilectane (**3**), and isocycloamphilectane (**4**)² (Figure 1), examples of which are provided in Figure 2. Wells and co-workers isolated diisocyanoadociane (**10**) as well as six other isonitriles in 1976 from a marine sponge belonging to the genus *Amphimedon* (ex. *Adocia*) collected near Townsville, Australia on the Great Barrier Reef.^{3,4} Subsequently, a further 12 related compounds were isolated from the marine sponge *Cymbastela hooperi*.⁵

Investigation of the biological activity of these compounds revealed significant antiplasmodial activity when tested *in vitro* against two clones of

FIGURE 1. Parent carbon skeletons for cyclic sponge diterpenes.

FIGURE 2. Representative isonitriles isolated from marine sponges.

the malaria parasite *Plasmodium falciparum*. The activity of the compounds towards the mammalian KB cell line was also tested in order to calculate an experimental selectivity index, which indicated whether the observed antiparasitic activity was a specific or general toxic effect. Results showed that diisocyanodociane (**10**), displays antiparasitic potency and selectivity that rivals the *in vitro* results obtained with some clinically-used antimalarial drugs.⁶ The combination of biological activity with the unusual perhydropyrene based structure makes **10** an enticing target for synthetic chemists and an elegant enantioselective synthesis (60% ee) based on sequential Diels–Alder cycloadditions has been reported by Corey and Magriotis (Scheme 1).⁷ In the final stages of their synthesis, however, the isonitrile groups were introduced without diastereochemical control. This intriguing molecule had also captured our attention⁸ and in this chapter we describe our own efforts to construct this molecule.

SCHEME 1

II. Synthesis Plan

An outline of our strategy is provided in Scheme 3 and begins with the proposed construction of the phenanthrene-derived structure **13**, which was based closely on our earlier synthesis of the phytoalexin, juncunol (**11**) (Scheme 2).⁹

SCHEME 2

After adding a suitable side chain to **13**, we envisaged that the pyrene skeleton could be completed by means of an intramolecular Michael reaction (**19** → **20**) and that the two quaternary isonitrile centers could be constructed through a double Curtius rearrangement of the bis(acyl) azide derived from dicarboxylic acid **21** (Scheme 3). This last sequence had excellent precedent in the synthesis of **22** by Piers and co-workers. (Scheme 4).¹⁰

SCHEME 3

SCHEME 4

FIGURE 3. Stereocenters under thermodynamic control.

A vital part of our plan was the controlled elaboration of the 10 stereocenters. The use of chiral benzamides in the initial alkylation, as demonstrated by Schultz and co-workers,¹¹ could reasonably be expected to elaborate the first stereogenic center (C-11) with good enantioselectivity, but we elected to postpone this option and to return later, after establishing the viability of the overall synthesis by employing racemic intermediates. To address the question of diastereochemical control, we expected that the six centers at C-1, C-3, C-4, C-11, C-13, and C-15 (Figure 3) would be under thermodynamic control through enolization of the neighboring carbonyl groups in the intermediates, while equilibration of C-4 would be feasible, provided that the planned Michael reaction was reversible.

It is well-established that metal-ammonia reductions of steroidal enones similar to **23** afford *trans*-fused products,¹² so there was every reason to expect that this process would afford the desired stereochemistry at C-8 (Scheme 5).

SCHEME 5

There is also an extensive history of stereocontrolled elaboration of quaternary carboxylic groups.¹³ As illustrated in Scheme 6, we expected simple alkylation at C-20 to proceed along the equatorial vector (steric control), whereas to achieve "axial" alkylation at C-7, we anticipated that the involvement of the C-6 carbonyl group (stereoelectronic control) would be necessary.

SCHEME 6

III. Foundations and Proof of Concept

Assembly of the hydrophenanthrene **13** proceeded according to plan as did introduction of a formyl substituent at C-1 by means of the Vilsmeier reaction, provided that one was patient with this last step (7 days!). The next stage called for selective reduction of the styryl double bond, which was carried out by Li-NH₃ reduction (*cf.* Scheme 7) to give **25**, but in modest yield (44%). The corresponding methyl ester **26** (prepared by NaClO₂ oxidation¹⁴ followed by diazomethane treatment) afforded better results, but if the deep blue reaction mixture was quenched with NH₄Cl, over-reduction occurred, affording a mixture of diol and hydroxy ester. The addition of isoprene to remove any excess metal before the NH₄Cl quench, however, resulted in a 75% yield of **27**, accompanied by a moderate amount (14%) of lactone **28**. As we have noted elsewhere, the protonation of enolate products by NH₄Cl is faster than reaction with any remaining lithium, leading to over-reduction.¹⁵

SCHEME 7

FIGURE 4. Determination of stereochemistry by NOE interaction.

The stereochemistry of **27** was determined by nuclear Overhauser effect (NOE) experiments that showed, *inter alia*, that H-9 was close to H-20, which is only possible with a *cis*-fusion of the C- and D-rings with the conformation illustrated in Figure 4; correlation spectroscopy (COSY) measurements established that the ester group was equatorial. We had hoped to obtain a product in which the C- and D-rings were *trans*-fused, corresponding to the configuration of the final target.

Nevertheless, we confidently expected that the stereochemistry could be adjusted when we came to the deletion of the C-11 substituent by means of a retro-aldol or equivalent process. Similarly, we expected that the stereochemistry at C-1 could be inverted during the planned Michael addition.

At this stage of the synthesis, we could choose to elaborate the D-ring further, or explore the construction of the A-ring. We chose the latter and to this end protected the hydroxyl function in **27** (methyl ether) before reducing the ester function with LiAlH₄ followed by oxidation, then addition of EtMgBr to afford **29**. Further protection (MOM ether), Birch reduction and acid hydrolysis afforded enone **30**, which unfortunately proved to be surprisingly resistant to conjugation. Basic catalysis was unproductive while care was required with acidic conditions to avoid loss of the MOM protecting group. Ultimately, we discovered that anhydrous HCl in THF gave the best, *albeit* rather poor, outcome. The primary yield was modest, but recycling of recovered starting material produced **31** in a total yield of 63%. Given the ease with which steroidal substrates have been converted to conjugated enones, we were disappointed with this result, but pressed on. Fortunately, reductive acylation at C-7 by lithium ammonia reduction followed by *in situ* reaction with methyl cyanofornate¹⁶ proceeded uneventfully to afford **32**, as did C-alkylation of the resulting β -keto ester (Scheme 8).

In preparation for the planned Michael reaction (Scheme 9), we introduced the Δ^4 alkene bond,¹⁷ but when we removed the MOM protecting group, cyclization of the liberated hydroxy group took place to afford **35**.

SCHEME 8

SCHEME 9

We therefore reordered the sequence as indicated, producing **37** in very modest yield, but sufficient to test the viability of the pivotal Michael process. In the event, treatment with DBU was ineffective, returning starting material, while *t*-BuOK destroyed our intermediate. However, reaction with K₂CO₃ in MeOH at room temperature for only 2 h converted **37** into **38** in 71% yield. That cyclization had occurred was apparent from the appearance in NMR spectra of a secondary methyl group at C-3 in place of the ethyl group in the side chain. The stereochemistry of **38** was not rigorously proven but the observation of *trans*-diaxial couplings between H-3 β and H-4 α (11.4 Hz), and between H-4 α and H-5 β (12.9 Hz) is consistent with the assigned structure (Figure 5).

FIGURE 5.

We were now faced with the choice of continuing the synthesis with diketone **38**, or regarding the synthesis to date as a model for an alternative approach. To correct the stereochemistry at C-11, we envisaged introduction of a carbonyl group at C-20 and removal of the substituent at C-11 by means of a retro-aldol reaction. We could then expect that diketone **42** would provide a thermodynamic sink for a series of base-catalyzed isomerizations (via enolates) as illustrated in Scheme 10. However, although the configuration at C-11 could presumably be inverted, it would require that the A-ring adopt a boat conformation as in **40**. Alternatively, a D-ring boat (as in **41**) would be enforced if inversion took place at C-1 (adjacent to the C-2 carbonyl group). Accordingly, to achieve the correct configuration at C-1 and C-11, it would be necessary to carry out a double isomerization on the 2,20-dione through a domino process.¹⁸ Unfortunately, these two carbonyl groups would then end up in identical local environments and we could expect discrimination between them would be extremely difficult. We therefore chose to return to the earlier stages of the synthesis and focus on the elaboration of the D-ring, including the establishment of a *trans*-fusion between rings C and D.

SCHEME 10

IV. Elaboration of the D-Ring

Returning to intermediate **24**, we extended the side chain and after protection (TBDMS ether) of the resulting alcohol **43**, studied its hydroboration with a view to establishing a C-20 carbonyl group (Scheme 11). This reaction gave highly variable yields of **44**, so we discontinued this approach. Instead, we oxidized **43** to ketone **45** with the Dess–Martin periodane¹⁹ and reduced this product with lithium in liquid ammonia as for ester **26** to give hydroxy ketone **46**, the stereochemistry of which was assumed to correspond to that of **27**. Removal of the styryl alkene bond in this way gave us more freedom to introduce oxygen at C-20, which we proposed to carry out by epoxidation followed by Lewis acid mediated rearrangement.

SCHEME 11

Attempts to mask the ketone function of **46** as an acetal failed, so after protection of the primary hydroxyl (MOM ether), reduction with LiAlH_4 afforded a single diastereomer that was converted into the benzoate **47**. Epoxidation proceeded smoothly, but subsequent treatment with $\text{BF}_3\text{--Et}_2\text{O}$ resulted in the formation of the cyclic ether **49**. To avoid this complication, we replaced the MOM group with acetate and then Lewis acid treatment afforded the ketone **51** as a mixture of C-15 epimers. Finally, hydroxide treatment resulted in hydrolysis of the acetate function, a retro-aldol reaction and stereochemical equilibration at C-11 and C-15 to afford **52**, the structure of which was determined by X-ray crystallography.²⁰ These results are summarized in Scheme 12.

SCHEME 12

We were now in a position to elaborate the C-20 quaternary center. As outlined in Scheme 13, this was undertaken by means of a Wittig reaction with methoxymethylene triphenylphosphorane. After hydrolysis of the resulting enol ether **53** to aldehyde **54**, we attempted C-methylation, but despite a number of precedents,²¹ this reaction failed. We therefore returned to the enol ether **53** and subjected it to a Simmons–Smith cyclopropanation.²² No matter how we tried with a variety of modifications, we could not push this reaction beyond a 40% yield. An improved yield (75%) was achieved with diazomethane– $\text{Pd}(\text{OAc})_2$,²³ but only after consuming large quantities of diazomethane. Nevertheless, acid treatment of the product **55** afforded the target aldehyde **56**.²⁴ We had expected that methylenation would have taken place on the more exposed *exo* face of **53**, resulting in the stereochemistry assigned to C-20 in **55** and therefore to **56**. Confirmation was obtained from NMR NOE correlation experiments that showed that the formyl group in **56** was *syn* to the C-12 benzylic proton.

After oxidation¹⁴ of aldehyde **56** to the corresponding acid, we submitted this product to Birch reduction. We obtained a multitude of products, however, in which the benzoate group had undergone various stages of reduction, but not, as we had planned, reductive cleavage. So we removed the benzoate group and tried the Birch reduction again. This time over-reduction occurred as a result of intramolecular protonation²⁵ and the saturated ketone **58** was obtained.

SCHEME 13

V. Elaboration of the B-ring and Exploration of the Michael Reaction

Given the modest yields in converting **52** into **56**, and the difficulties with the Birch reduction, we elected to conserve material by postponing the elaboration of the C-20 center and press on with the synthesis of the main tetracyclic structure beginning with **52**. This intermediate was reduced with L-selectride,²⁶ the resulting alcohol protected as a MOM ether, then the benzoate function replaced by a TBDMS group to afford **59** in

an overall yield of 55% for the four steps. Birch reduction (Scheme 14) proved to be stubborn, probably because of the bulky TBDMS group interfering with solvation of the radical anion intermediate.²⁷ However, a satisfactory yield of the expected dihydro product **60** could be obtained by using a massive amount of lithium metal (50 equivalents). Hydrolysis to the β,γ -unsaturated ketone was straightforward, but conjugation to give **61**, required a delicate touch to avoid partial loss of the protecting groups. This was achieved by using anhydrous HCl in THF, thereby affording a total yield of 71% over the three steps.

SCHEME 14

Reductive acylation, however, was really disappointing, affording a mixture of **62** (desired product), **63** and **64**, all in poor yields. Moreover,

although **63** behaved reasonably well when subjected to a practice C-methylation (to give **65**), C-methylation of **62** was disastrous (15% yield; 22% after recovery of starting material). We had honed this methodology on numerous similar substrates,²⁸ but were unable to identify where the problems lie, and so we regrouped, omitting the acylation step in the reduction of **61** and optimizing the yield of **64** into which we proposed to selectively introduce a Δ^4 alkene bond through Saegusa methodology,²⁹ thereby blocking C-5 enolate formation and effecting acylation at C-7 as outlined in Scheme 15. Enolization was not all that regioselective, but the "wrong" product (**61**) could be separated and recycled, while good yields were now obtained for both acylation and alkylation. The stereochemistry could again be checked by NOE difference spectra that confirmed that C-methylation had occurred on the upper face to afford **68** with the desired configuration at C-7.

SCHEME 15

We were now close to checking out the Michael reaction and, anticipating problems with intramolecular addition of the side chain hydroxyl to the Δ^4 enone if we removed the TBDMS group (*cf.* **34**→**35**), we reduced enone **68** to the alcohol³⁰ and treated this product with TBAF. Oxidation then afforded dione **69**, which was treated with a variety of bases and acids under a range of conditions in an attempt to close the A-ring (Scheme 16). In sharp contrast to our earlier experience with dione **37**, however, we were unable to induce cyclization. An inspection of

molecular models indicated that the Michael reaction was unlikely to take place with **69** since it would require the D-ring to adopt a boat conformation to bring the participating functions within bonding distance, and even then orbital overlap between the reacting centers would be poor. It appeared that an α -configured side chain could assume the necessary geometry, however. When treatment of **69** with a variety of bases returned starting material, it seemed that the side chain was more stable in the β -configuration, despite its axial nature. Nevertheless, one could expect there to be a sufficient amount of the α -epimer in equilibrium to undergo the desired cyclization. In desperation, we recalled an intramolecular Michael reaction described by Corey *et al.* during their synthesis of longifolene.³¹ They employed Et_3N -ethanediol in a sealed tube at 225 °C for 24 h. By adopting this protocol, but at more moderate conditions (150 °C), we were relieved to see cyclization with **70**, the structure being confirmed by X-ray crystallography.³² Nevertheless, the yield of only 30% was obviously unacceptable.

SCHEME 16

There were several byproducts, among which was one that had lost the ester function and so we considered a reordering of the reaction steps that would introduce the ester group after the Michael reaction. The new approach is outlined in Scheme 17. Conversion of **67** into **72** followed the same routine as for the preparation of **69** from **68**. Now, the simpler dione underwent cyclization to **73** in a yield of 68% employing the same conditions as for **69**. The methylene groups flanking the C(6) carbonyl group

in **73** are sterically equivalent except for the methyl group attached to C-3. Nevertheless, enolization with LDA followed by reaction with methyl cyanoformate³³ furnished a 9:1 mixture of the desired **75** with **74**, *albeit* in modest yield. The two keto esters were inseparable, but on treatment with K_2CO_3 in methanol, the ester substituent **74** epimerized, after which separation was possible. It was of interest that the axially substituted **77** was stable relative to **74** and the enol tautomer. Presumably, the C-3 methyl substituent destabilizes the latter two compounds because of the peri-interaction. This alternative approach came to a grinding halt, however, when once again what should have been a routine C-methylation procedure failed when applied to **75**.

SCHEME 17

Such are the subtleties of organic synthesis that we could conjecture that the sequence beginning with **52** might be better behaved with a similar starting material, namely **57**. And so, once more we altered direction with a final attempt to access a suitable tetracycle, this time returning almost to the beginning with a view to improving a number of the critical steps and streamlining some of the sequences.

VI. Improved Synthesis of an Advanced Tetracyclic Intermediate

The first part of the synthetic sequence to be improved was the preparation of ketone **45**. We had in mind for some time to investigate the possibility of preparing this intermediate directly by means of a Friedel-Crafts acylation (Scheme 18). Our first attempt using standard reagents at room temperature was a disaster. Nevertheless, it became clear that the acylation had taken place, but then cyclization had occurred to afford **78**. The problem was easily rectified by conducting the reaction at $-78\text{ }^\circ\text{C}$ for 20 min, whereby ketone **45** was obtained in 75% yield – a considerable improvement in time, effort, and yield over the original route via aldehyde **24**.

SCHEME 18

The original sequence was then followed through to enol ether **53**, but then we had to deal with the cyclopropanation reaction that had proven to be so sluggish. Fortunately, we discovered a report by Shi *et al.*³⁴ who described the preparation of a modified Simmons-Smith reagent, $CF_3CO_2ZnCH_2I$ prepared from diiodomethane, diethylzinc, and trifluoroacetic acid. This reagent worked brilliantly and allowed the preparation of acid **79** in 80% yield over the three steps from enol ether **53**. The application of the methodology that had previously been established using **59** as a model substrate, then took us through to the Michael stage without incident and with a few significant improvements, as outlined in

Scheme 19. In particular, the desired regiochemistry of enol silyl ether formation (20:1) was considerably enhanced by using TMS triflate with 2,6-lutidine, while acylation of **82** to give **83** and its alkylation to give **84** afforded enhanced yields for both steps.

SCHEME 19

We were pleasantly surprised to find that the Michael addition (Scheme 20) proceeded at a reasonable rate at a moderate temperature (70 °C) and in reasonable yield. Unfortunately, ester exchange with the ethanediol solvent resulted in a mixture of the methyl ester **86** (for which an X-ray crystal structure provided confirmation of structure)³² and the hydroxyethyl ester **87**. We also obtained dione **88** in which ester exchange had also occurred. Nevertheless, given that the ester functions

would soon be hydrolyzed, this outcome was more of an irritation than anything else.

SCHEME 20

VII. Deoxygenation, Curtius Rearrangement, and Completion of the Synthesis

The penultimate phase of the synthesis required deoxygenation of the two ketone functions. We investigated the use of a modified Wolff–Kishner reaction,³⁵ but application to a model β -keto ester was very discouraging. Sodium cyanoborohydride reduction of the toluene-sulfonyl hydrazone³⁶ of β -keto ester **89** appeared promising (Scheme 21), but when applied to **86**, we obtained a miserable 5% yield.

SCHEME 21

FIGURE 6. Structures of deoxygenated esters.

Clearly, direct reduction did not appear to have much of a future, so we turned to the Barton–McCombie protocol.³⁷ A practice run on the model keto ester **89** (Scheme 22) was very encouraging and when applied to **86** and the MOM ether of **87**, reasonable overall yields of the deoxygenated products **91** and **92** (Figure 6), respectively, were obtained.

SCHEME 22

The C-7 equatorial ester functions in both of these products was readily hydrolyzed by LiOH in aqueous methanol, but the axial ester group at C-20 was resistant to simple base-catalyzed hydrolysis. We therefore turned to the Johnson–Bartlett procedure (*n*-PrSLi/HMPA)³⁸ which afforded an excellent yield of the dicarboxylic acid **93**. A standard Curtius protocol then afforded diamine **96** as illustrated in Scheme 23. The mass spectrum of **96** was the same as that obtained for the natural material, but when we ran the ¹H-NMR spectrum of this material dissolved in CDCl₃ we found it to have significant differences with the spectrum of the material obtained from the natural product.³⁹ How could this be? Had we made a mistake over the assignment of stereochemistry along the line? This did not seem likely given that the X-ray crystal structure had confirmed the constitution of the diester **86**. We therefore suspected that the culprit was a trace of HCl in the CDCl₃ and so we compared the spectra of the TFA salts (using d₄-methanol as the solvent). This time, the spectra were almost a match, but there was a small difference with just one multiplet.

Could we cross our hearts and say that they were identical? We were aware that the comparison spectrum had been run at a different concentration, however, and when this was adjusted to be the same as that of the synthetic sample, identical spectra were obtained. Phew!

SCHEME 23

Since **96** had been previously converted back to the target diisocyanoadociane (**10**) by dehydration of the derived diformamide **97** (Scheme 24),⁴⁰ the total synthesis of **10** was complete in a formal sense.

SCHEME 24

VIII. Conclusion

With this synthesis we have demonstrated the considerable utility that benzenoid building blocks provide for the synthesis of polycyclic

molecules.⁴¹ At the beginning of the synthesis we released an array of latent functionality that allowed the expeditious assembly of a hydrophenanthrene intermediate in which one alkene function could be used to attach the elements of the fourth ring (to complete the hydrophenanthrene skeleton), while the other alkene group could be oxygenated to allow the elaboration of one of the quaternary centers. The second benzenoid unit was essentially inert while it was being carried through an extended sequence, until being ultimately transformed into a cyclohexenone moiety. However, we encountered repeated barriers to progress that leave us still puzzled, since most of the methodology was tested and found to work well on model substrates. In particular, we had difficulties with the conversion of Birch reduction products into α,β -unsaturated cyclohexenones, the low yields from reductive acylations of enones, and the failure of β -ketoesters to undergo simple alkylation reactions.

Clearly, the equilibrium between the isomeric cyclohexenones is finely balanced and even the very small structural difference between our intermediates and steroids (which behave well) is enough to tip the balance in favor of the wrong isomer. Metal-ammonia reductions of cyclohexenones with capture of the enolates by electrophiles is often technically difficult and yields tend to be modest at best.⁴² The sequence beginning with **83** in Scheme 19 is much more reliable and should have general applicability. Similarly, the cyclopropyl based method for the C-methylation of aldehydes (as in Scheme 13, but with the modified reagent $\text{CF}_3\text{CO}_2\text{ZnCH}_2\text{I}$) is a robust and effective alternative.⁴³ The failures with the classical C-methylation of several β -ketoesters remain a puzzle. Finally, we had expected problems with the pivotal Michael reaction, since the orbital line up is not as good as we would have wished. The basic idea was fine, however, and we did obtain a good yield with the simplest of the examples, namely **72** $\rightarrow$ **73**.

IX. Epilogue

Organic chemists have made enormous progress over the past four decades in developing new methods and strategies for the construction of increasingly complicated molecules. However, the efficiency, reliability, and predictability of the methodology still leaves much to be desired as confirmed by the twists and turns in the present synthesis. The assembly of polycyclic molecules is especially challenging, since extended, linear routes tend to be necessary, resulting in an inexorable decline in the

quantities of intermediates. It is therefore important that we continue to attempt difficult syntheses and in this way define the scope and limitations of our chosen procedures, as well as develop new strategies and methodology. Apart from some very notable exceptions, progress has been and will continue to be incremental, and relies on the collective efforts of a large number of synthesis groups beaver away and sharing information. This synthesis and the knowledge gained in its execution is offered as one such minor contribution to the common enterprise.

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Chapter 3

TOTAL SYNTHESSES OF ZOAPATANOL

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I. Introduction

(+)-Zoapatanol **1**, montanol **2**, tomentanol **3** and tomentol **4** are diterpenoid oxepanes isolated from the leaves of the Mexican zoapatle plant *Montanoa tomentosa*, which Mexican women have been using for centuries to prepare “tea” to induce menses, labor and to terminate early pregnancy.¹ Recent studies support the belief that zoapatanol and its metabolites might be responsible for the observed antifertility activity.² In 1979, the isolation and the structure of zoapatanol were described.³

Due to its biological profile and its challenging structure, several synthetic approaches have been described⁴ and seven total syntheses of zoapatanol have been reported^{5–11} but only two of them were enantioselective.^{10,11}

Key issues for a successful synthesis of zoapatanol **1** are the stereocontrolled construction of the oxepane ring containing the two stereogenic centers, the introduction of the (*E*)-exocyclic double bond and the installation of the nonenyl side chain. Since (+)-zoapatanol was isolated as