Enantioselective Total Synthesis of Marine Alkaloids, Manzamine A and Related Compounds

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A review of our studies toward the enantioselective total synthesis of ircinal A, manzamine A and related compounds is presented in detail.

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1. Introduction.

Manzamine alkaloids are a family of marine sponge metabolites that exhibit cytotoxic activity against leukemia, antibiotic activity, as well as significant antimalarial activity [1-3]. The unprecedented structures of their highly functionalized heterocyclic ring systems and their remarkable biological properties have attracted considerable attention as challenging synthetic targets (Figures 1 and 2).

While the simplest congener, manzamine C **3**, and related compounds have been previously synthesized by us [4] and Langlois' group [5], the more complex manzamine A has been a more challenging target [6]. Considerable effort has been directed toward the synthesis of **1**. Quite recently, Winkler [7], Martin [8] and their respective co-workers succeeded in an elegant total synthesis of manzamine A and its related compounds.

We have also been interested in developing efficient routes to tetraazacyclic intermediate **5** based on the initial construction of tricyclic intermediate, **4** either 1) by an intermolecular Diels-Alder reaction of functionalized dihydropyridinone as a dienophile with siloxydienes, leading to the construction of a *cis* relationship in the central AB ring system of this unique structure, followed by intramolecular Michael addition to the tricyclic core **4** and successive construction of **5** (path a), or 2) by an intramolecular approach (path b). We have also examined path c, which is suitable for the construction of an AB ring system, especially for the β-carboline connection [9] (Scheme 1).

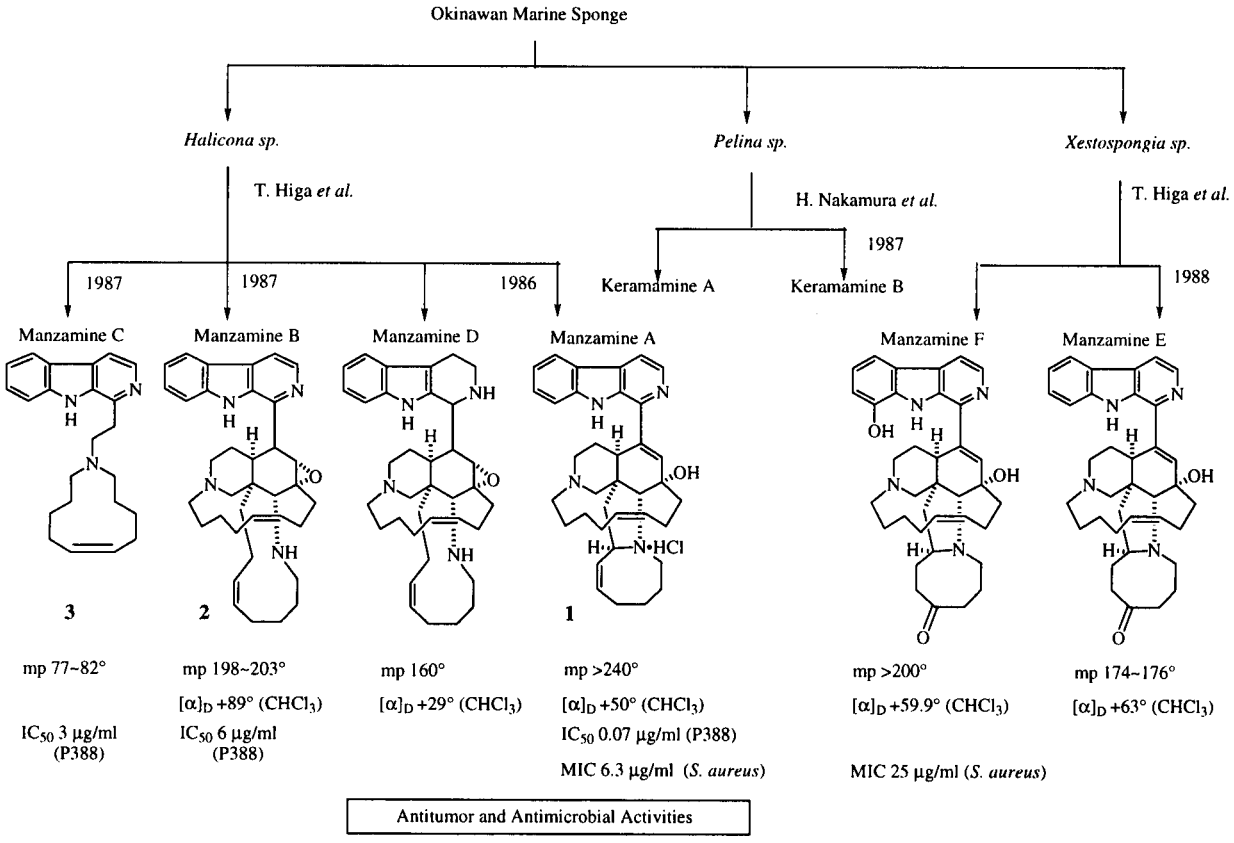


Figure 1. Isolation of Manzamines A-F.

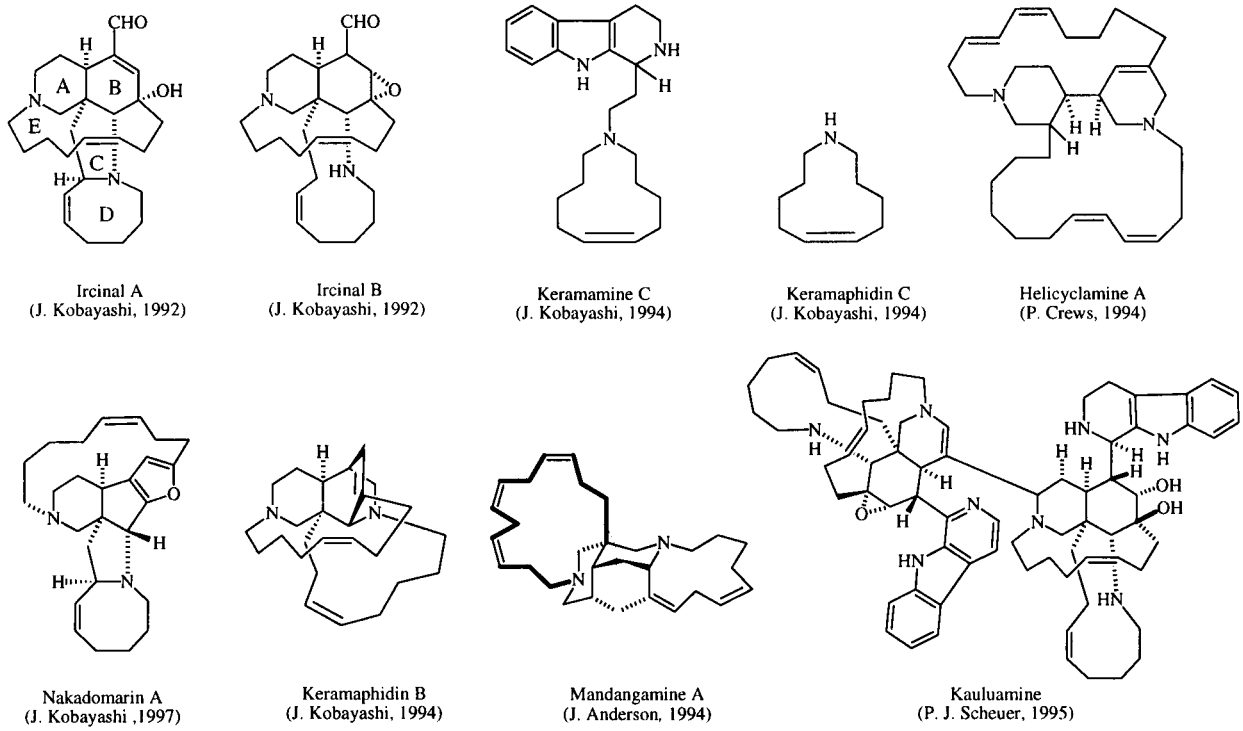
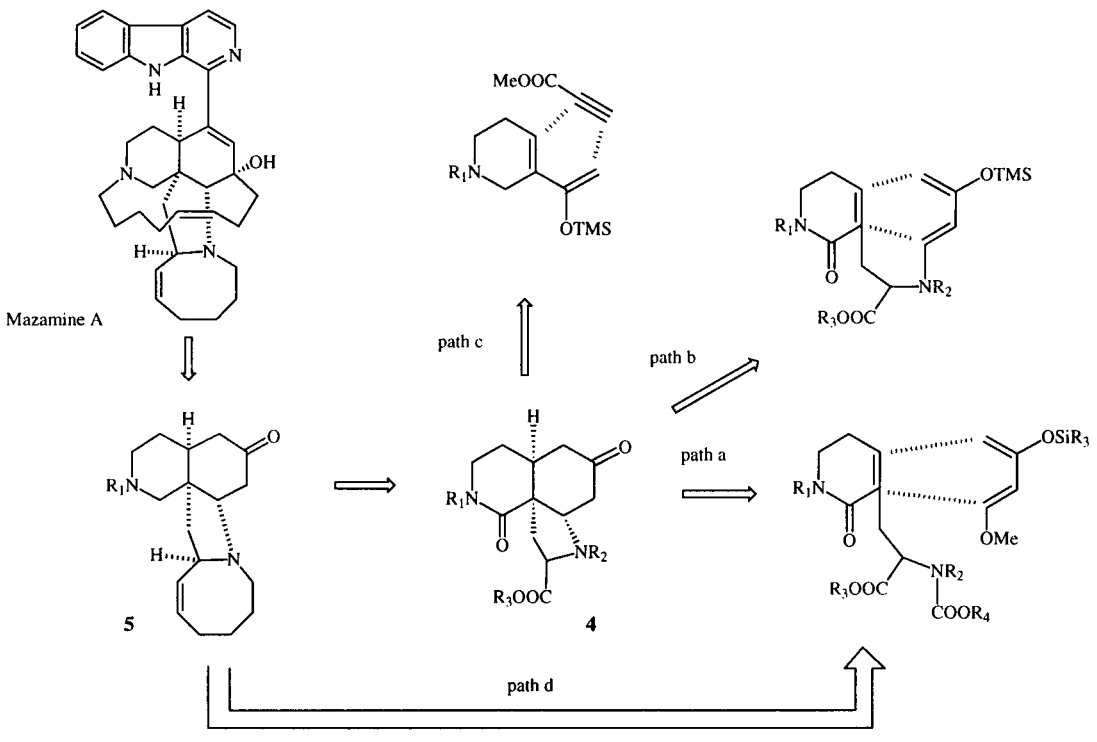


Figure 2. Isolation of Manzamine Family.

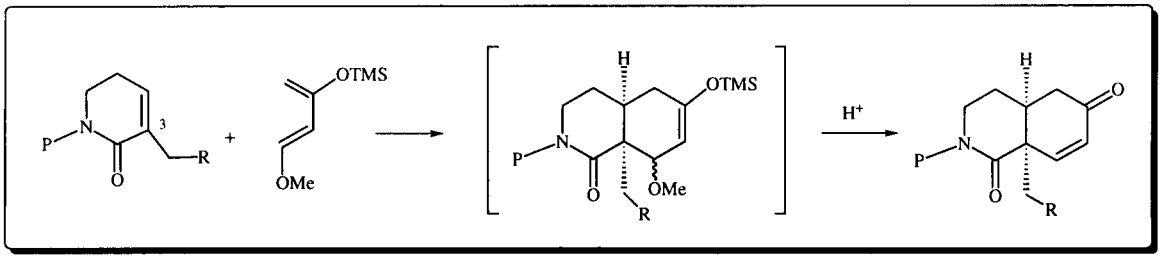
Scheme 1



2. Synthesis of the Tetracyclic Core Structure (±)-20.

We were originally uncertain whether this cycloaddition was feasible. Therefore, we first investigated the effect of the protecting group at the nitrogen and the substituent at the 3-position of the dienophile as well as the reaction conditions for an effective Diels-Alder reaction (Scheme 2).

Scheme 2



Diels-Alder Reaction of 3-Alkyldihydropyridinone

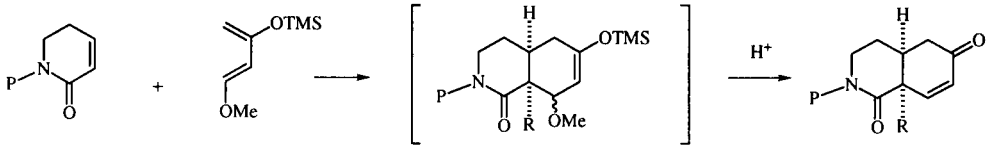
1 Effects of the Substituents

- *N*-Protecting Group
- Substituent at C-3

2 Conditions for Effective Diels-Alder Reaction

Table 1

Reaction of *N*-Substituted-3,4-dihydropyridinone in Diels-Alder Reaction



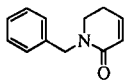
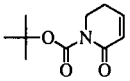
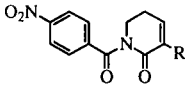
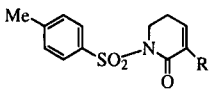
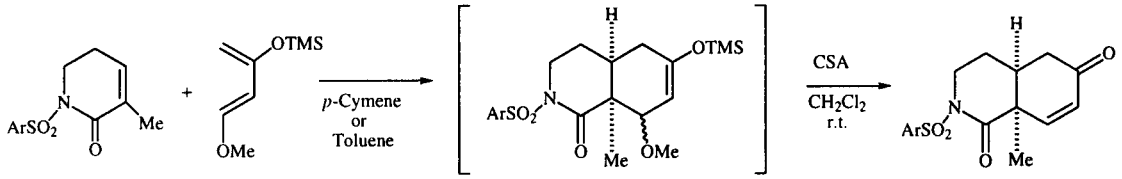
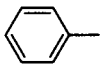
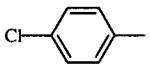
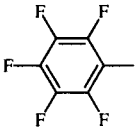
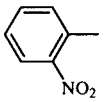
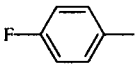
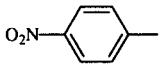
		Condition	Time	Yield (%)	Calculation (PM3) HOMO	LUMO
		Xylene , reflux	5 h	N R	-9.3140	-0.0264
		Xylene , reflux	5 h	N R	-9.9066	-0.2951
	R = H	Xylene , reflux	5 h	57 %	-10.1647	-1.6840
	R = Alkyl	Xylene , reflux	5 h	N R	—	—
	R = H	Xylene , reflux	5 h	50 %	-10.2008	-0.6289
	R = Me	*p*-Cymene , reflux	5 h	45 %	-10.0993	-0.7028

Table 2



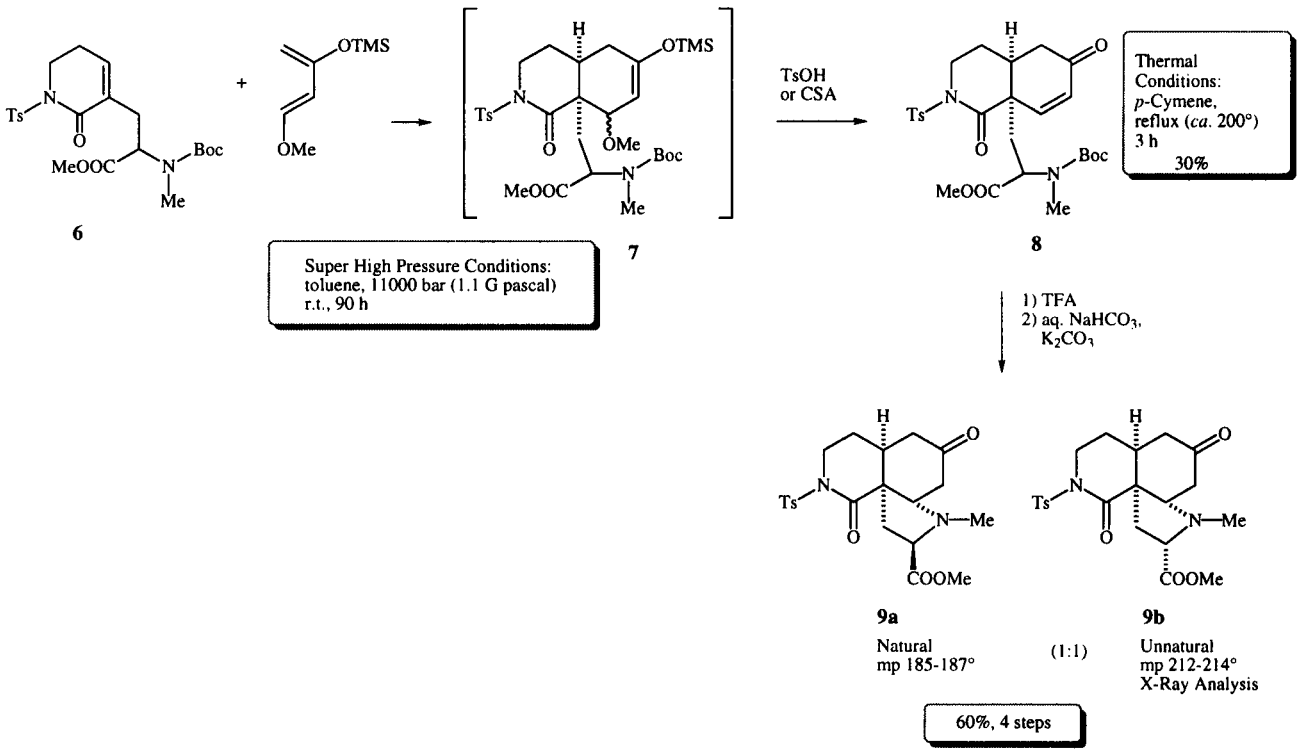
Run	Ar =	Temp (°C)	Time (h)	Yield	Based on Recovered SM
1		180	10	65 %	88 %
2		180	10	79	98
3		110	39	0	-
4		180	6	53	56
5		110	15	45	48
6		180	6	52	66
7		110	30	65	94
8		180	6	53	-
9		180	6	64	-

Our initial studies along path c revealed that *N*-alkyl-protected (*i.e.*, P_1 = alkyl) dihydropyridinones were quite sluggish towards dienes, even in an intramolecular case, and that the *N*-protecting group needed to have an electron-withdrawing character for successful intermolecular cycloadditions [10]. Further insight into these thermal transformations led us to select *N*-benzenesulfonyl dihydropyridinones or *p*-chlorobenzenesulfonyl derivatives as a dienophile, in view of the thermal stability of the *N*-arylsulfonyl group (Tables 1 and 2). As expected, in a model study using a simple dienophile with an amino acid residue, we found that *N*-tosyl-3-alkyldihydropyridinone **6** undergoes a Diels-Alder reaction with Danishefsky diene under conventional thermal conditions to give **7**, which after treatment with acid followed by base was converted to the expected enone **8** in *ca.* 30% yield. We achieved a more facile construction of tricyclic ketone **9** using a high-pressure Diels-Alder reaction of **6** with Danishefsky diene followed by deprotection and base-catalyzed Michael addition for an overall yield of 60% in 4 steps [10] (Scheme 3).

The new dienophiles **10** and **11**, each of which has a $COCF_3$ protecting group instead of a thermally unstable BOC group, were found to be suitable due to their ease of preparation [11] and their appropriate reactivity in the Diels-Alder reaction under thermal conditions [12]. Thus, treatment of **10** and **11**, respectively, with Danishefsky's diene in refluxing *p*-cymene gave the corresponding enones **12** and **13**.

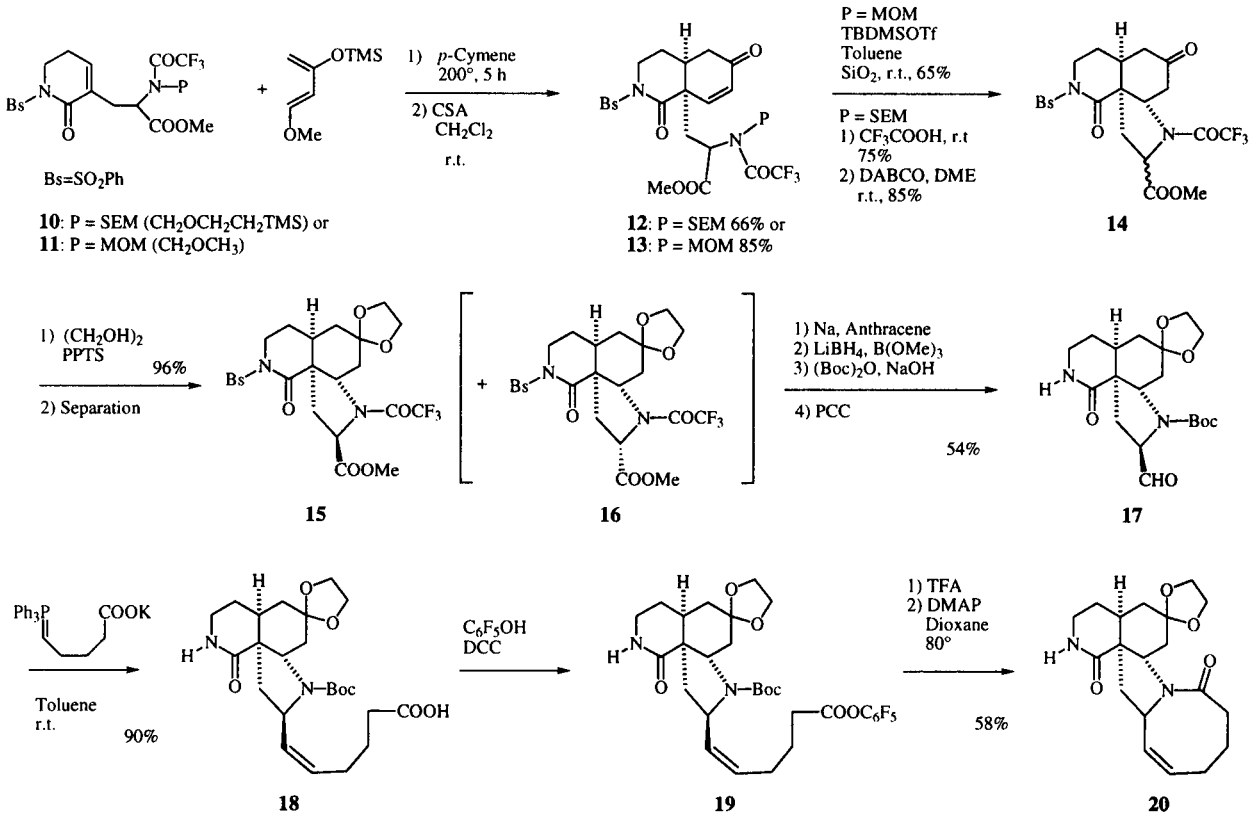
The SEM enone **12** was deprotected by trifluoroacetic acid (TFA) to give the NH-enone, which was readily converted to the tricyclic system **14** by brief treatment with 1,4-diazabicyclo[2.2.2]octane (DABCO) at room temperature. Subsequent ketalization of **14** afforded the stable ketal **15** and **16** as a *ca.* 1:1 diastereoisomeric mixture, which could be easily separated by recrystallization from dichloromethane/diethyl ether, while the diastereomers corresponding to **14** could be separated by column chromatography. For a large-scale preparation, these deprotection-cyclization-ketalization steps were conveniently conducted without purification, to give the desired isomer **15** in 30% yield from the *N*-SEM dienophile **10**. Another efficient preparation of **14** was realized by the reaction of *N*-MOM adduct **13** with triethyl triflate (TESOTf) in the presence of silicon dioxide powder and sodium sulfate (Scheme 4).

Scheme 3



6 7 8

Scheme 4



The benzenesulfonyl group that was used for nitrogen protection and to activate dihydropyridinone as an efficient dienophile for successive cycloaddition now had to be removed after the Diels-Alder reaction to prevent ring-opening due to the instability of benzenesulfonyl lactam toward nucleophiles.

Subsequent selective deprotection of the benzenesulfonyl group was best carried out using sodium/anthracene in 1,2-dimethoxyethane (DME) at -60°. Next, the reductive removal of the CF_3CO group by lithium borohydride/trimethoxyboroxine followed by protection of the newly generated NH group by a BOC group gave the aldehyde **17** (87% yield in 3 steps). Expedient conversion of **17** to the precursor **19** was followed by closure of the azocine lactam ring to give the desired tetracyclic core structure **20** in a racemic form [12].

3. Synthesis of Optically Active Dienophiles.

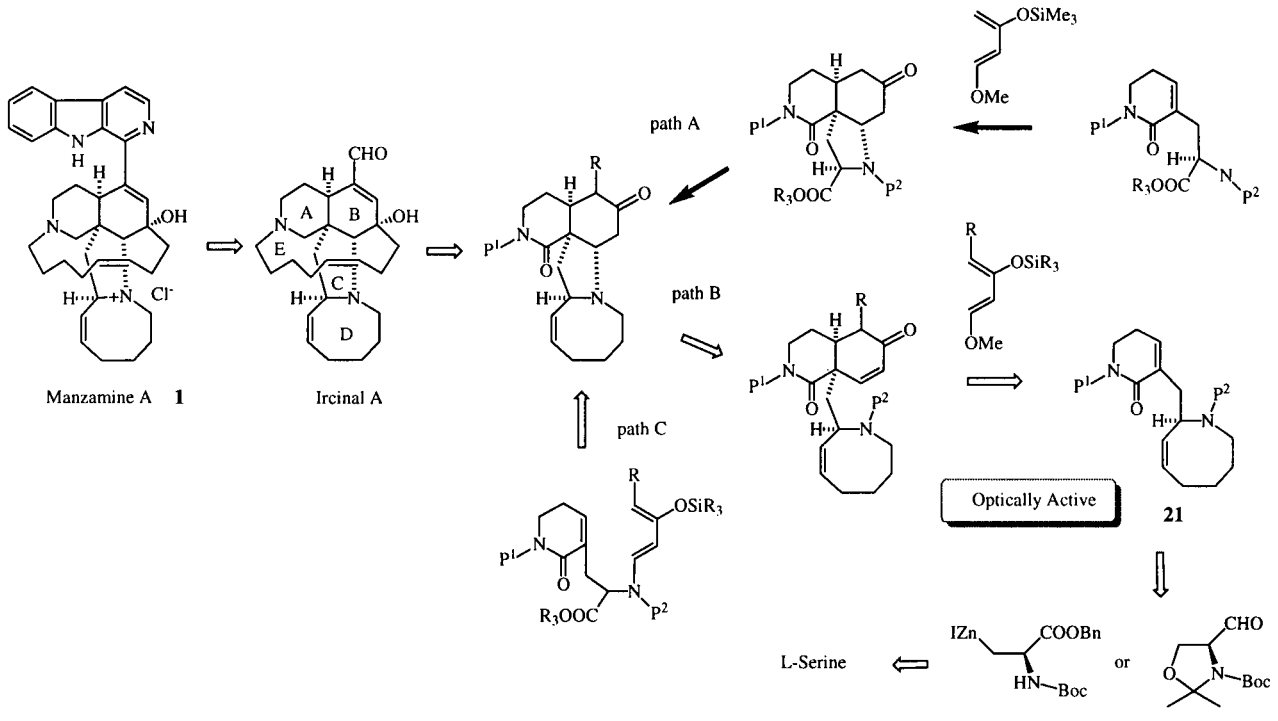
Based on these results, some dihydropyridinones emerged as potential precursors for the construction of a highly functionalized perhydroisoquinoline ring system in our synthetic approaches to the manzamine alkaloids **1**. We envisioned that the development of a general and efficient synthesis for dihydropyridinone derivatives with a chiral side chain would significantly enhance the utility of our Diels-Alder methodology. Therefore, we next focused our attention on the synthesis of the optically active tetracyclic core structure **5** *via* a more efficient method based on the Diels-Alder reaction of siloxydienes with new dienophiles such as **21**, as shown in Scheme 5. We planned to investigate two synthetic routes to **21** (Scheme 6).

We initially investigated the feasibility of a coupling reaction of vinyl iodide **22** with a chiral organozinc reagent **23** in the presence of Pd catalyst under various conditions to introduce the chiral amino acid unit into the 3-position of the pyridinone ring system (Scheme 7).

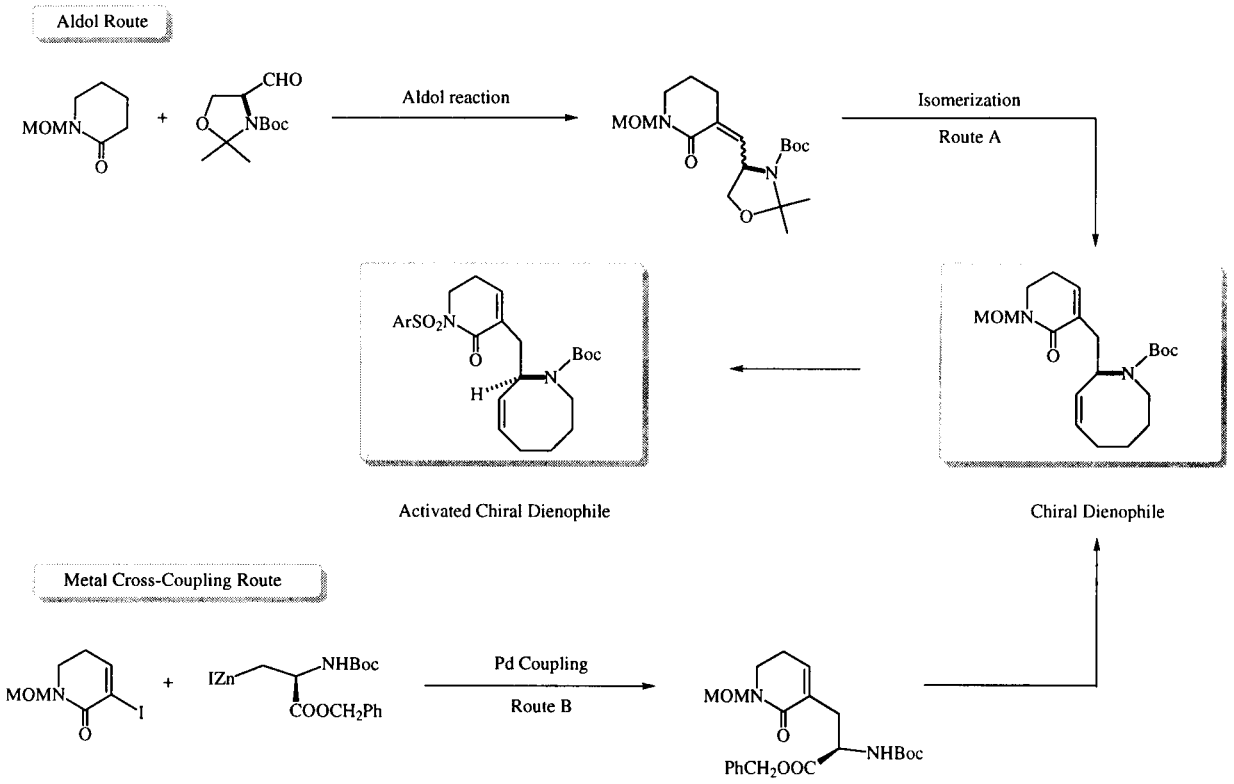
Among the catalyst systems examined, bis(benzonitrile)palladium(II) chloride (0.2 eq) combined *in situ* with tri-*o*-tolylphosphine (0.4 eq) in DMF provided a suitable catalytic species. Under these conditions, dihydropyridinone **25a** was produced in the best yield (37%). However, a similar reaction of oxazolidine derivative **24** failed to give **25b**. Therefore, we investigated another efficient route to obtain **20** which involved the aldol reaction of **26** with Garner aldehyde **27**.

The coupling reaction of **27** with *N*-MOM-piperidone **26** under basic conditions (lithium bis(trimethylsilyl)-amide in tetrahydrofuran) gave the corresponding alcohols as a mixture of two diastereomers **28** in a yield of 80-90%, which were then dehydrated to give **29** under usual conditions. After purification, only *exo*-enones (**29**, *E* and *Z* mixture) were obtained in a 1.5:1 ratio (91% combined yield), which were then subjected to the critical double-bond isomerization to an *endo* cyclic position, as in **30**. Extensive experimentation under various conditions using a previously reported protocol (triethylsilane, chlorotris-

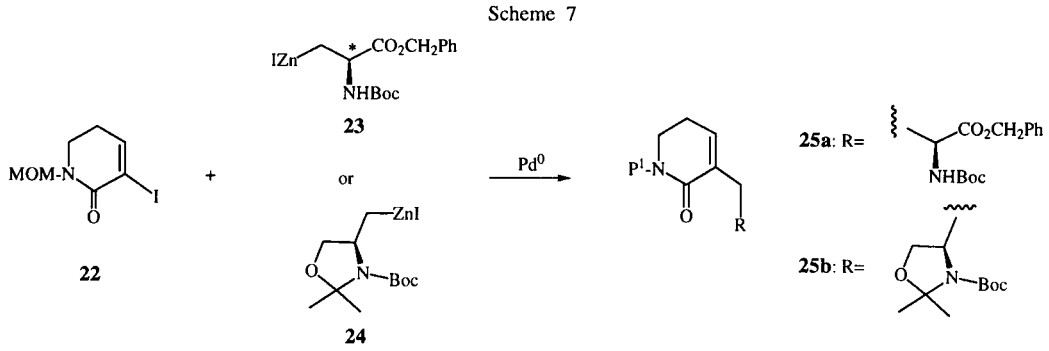
Scheme 5



Scheme 6



Scheme 7

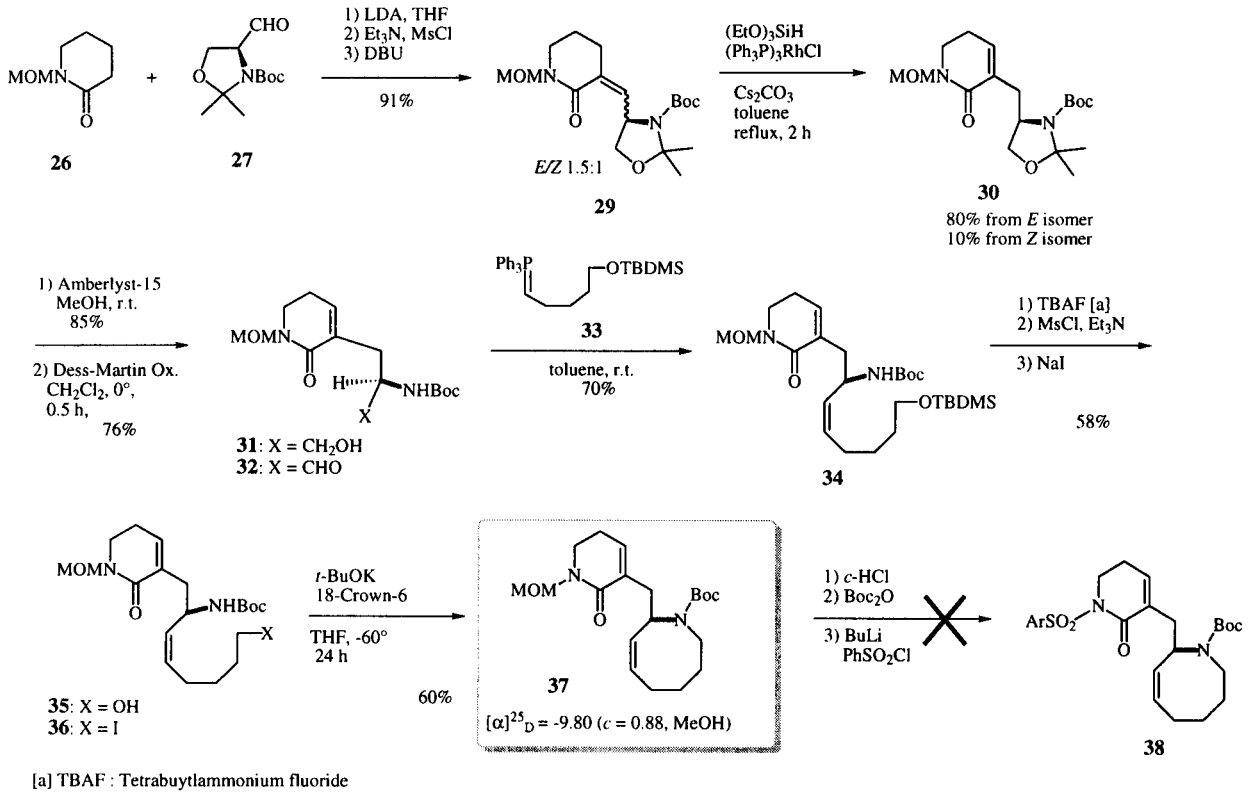


(triphenylphosphine)rhodium(I), toluene, reflux) [13] gave more satisfactory results, but further optimization was needed. A high-yield isomerization reaction was finally realized when the silane was changed to triethoxysilane and the reaction was conducted in the presence of cesium carbonate. In this way, the chiral dihydropyridinone derivative **30** was obtained in 80% yield from the major isomer (*E*)-**29**. Deacetonization of **30** gave aminoalcohol **31**, which was then oxidized to the labile aldehyde **32** by Dess-Martin periodinane in excellent yield (Scheme 8).

For elongation of the C5-carbon chain, Wittig reaction of **32** with the protected ylide **33** was carried out to give the desired product **34** in 70% yield, which was in turn deprotected to the corresponding alcohol **35**.

The stage was now set for the crucial azocine ring-forming step. There are two options for activation of the hydroxyl group towards azocine ring closure. Our previous protocol [14] suggested the use of a tosylate rather than iodide for such cyclization. However, conversion of **35** to the *O*-monotosylate was simply accompanied by *N*,*O*-ditosylation, which did not lead to the desired cyclized product, but rather gave a simple elimination product. Alcohol **35** was converted to iodide **36** *via* mesylation followed by treatment with sodium iodide. The iodide **36** underwent cyclization in the presence of 18-

Scheme 8

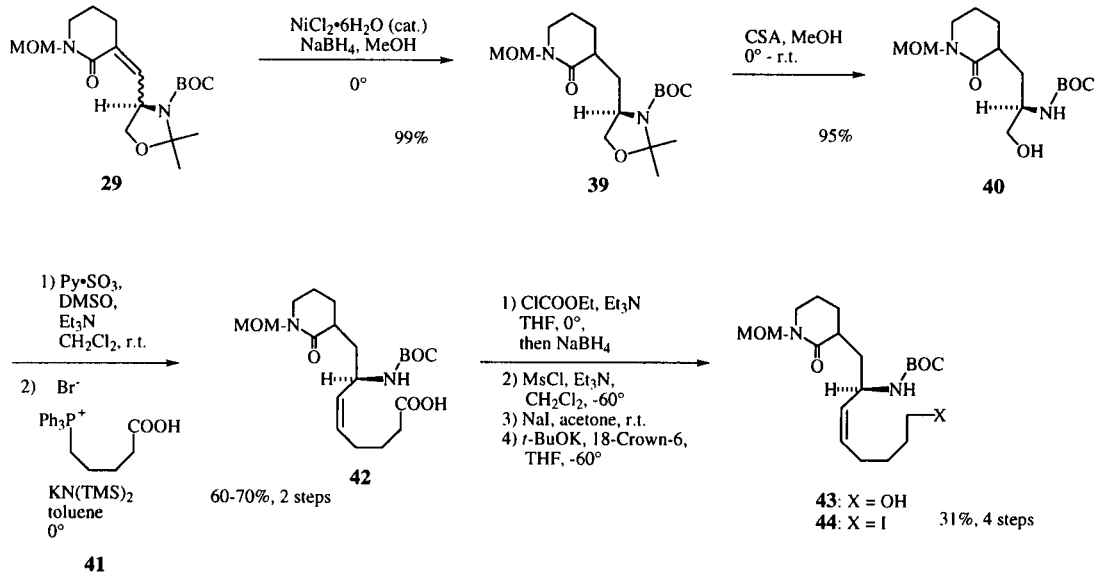


[a] TBAF : Tetrabuytlammonium fluoride

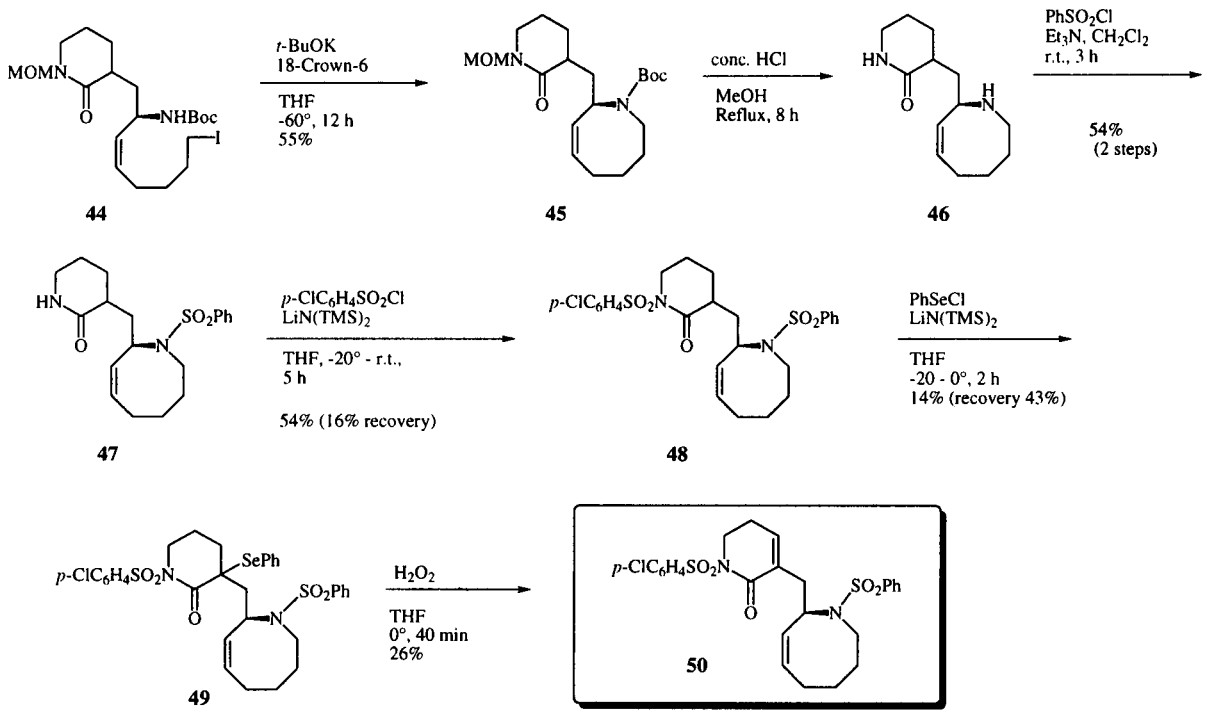
crown-6 and potassium *t*-butoxide (*t*-BuOK) to give the desired chiral azocine **37** in moderate yield (60-70%) [15]. However, unexpectedly, replacement of the MOM group by a benzenesulfonyl group to give **38** proved unsuccessful. Therefore, we decided to explore the introduction of the double bond functionality at the 3-position of pyridinone at a later stage of the synthesis. Accordingly, we first reduced the *exo* double bond with nickel(II) chloride/sodium borohydride to *N*-MOM-piperidone **39**. Treatment of **39** with camphor sulfonic acid (CSA) gave **40** (Schemes 9 and 10).

Oxidation of **40** with pyridine•sulfurtrioxide-dimethyl sulfoxide-triethylamine [16], followed by Wittig reaction with potassium 5-(triphenylphosphoranylidene)pentanoate

Scheme 9



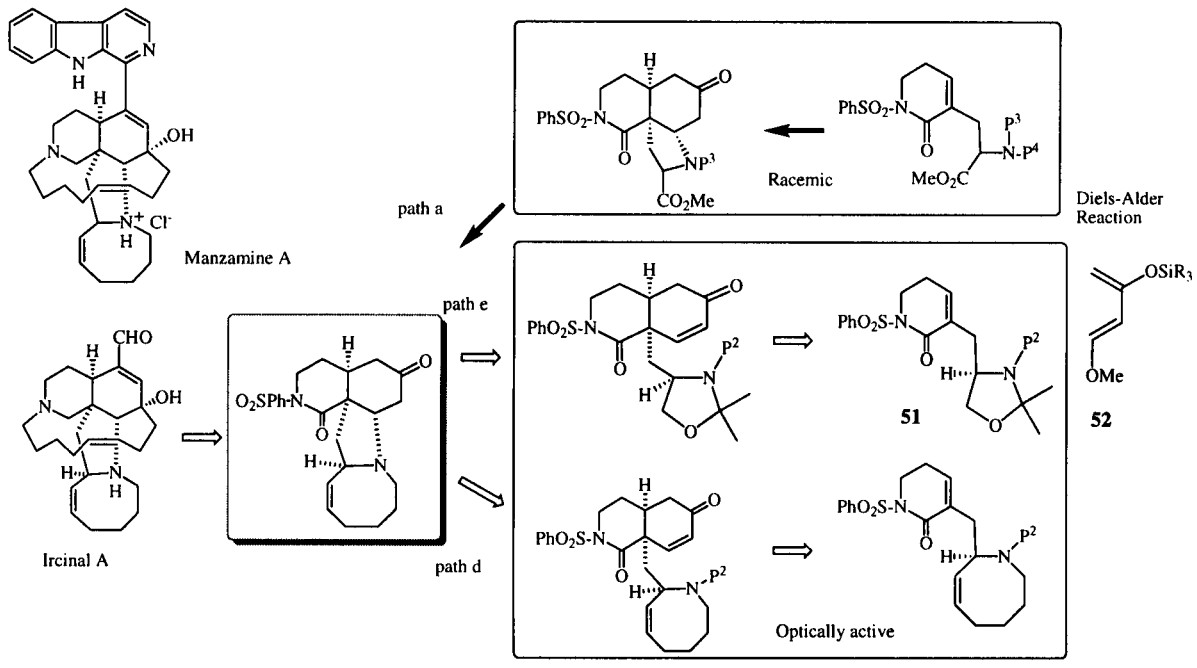
Scheme 10



(**41**), gave compound **42** in 60-70% yield. The acid was then converted to the alcohol **43** *via* reduction of the mixed anhydride formed *in situ*. Reaction conditions similar to those used for the formation of **37** were used in the conversion of **44** to **45**.

Deprotection of **45** was best carried out by treatment with concentrated hydrochloric acid (HCl) in refluxing methanol to afford the unprotected azocine derivative **46**, which gave **47** after benzenesulfonylation of the secondary nitrogen. Further treatment of **47** with arylsulfonyl

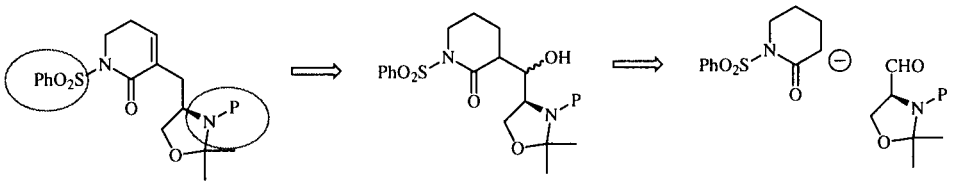
Scheme 11



chloride under strong basic conditions gave **48**, which was converted to the desired dienophile **50** *via* phenylselenation followed by oxidative elimination. However, the yields of the last steps were low. This prompted us to develop an alternative synthesis of chiral dienophiles **51** which already carried a benzenesulfonyl group, and were much easier to prepare on a multimolar scale (Scheme 11, path e). This new dienophile could be obtained by the aldol reaction of the protected serinal with *N*-benzenesulfonyl lactam (Scheme 12).

Dehydration of **55** *via* mesylation followed by treatment with DBU gave **56**. Originally, we had envisioned installing the C3-C4 double bond through *exo-endo* isomerization. In previous studies, we succeeded in isomerization of the *exo*-enone **29** to the *endo*-enone **30** using silane-rhodium-mediated conditions. In contrast to **29**, however, similar *exo-endo* isomerization of **56** to the corresponding *endo*-isomer failed. Therefore, we turned to the reduction-oxidation method. Catalytic hydrogenation of **56** under the conditions used for converting **29** to **39**

Scheme 12



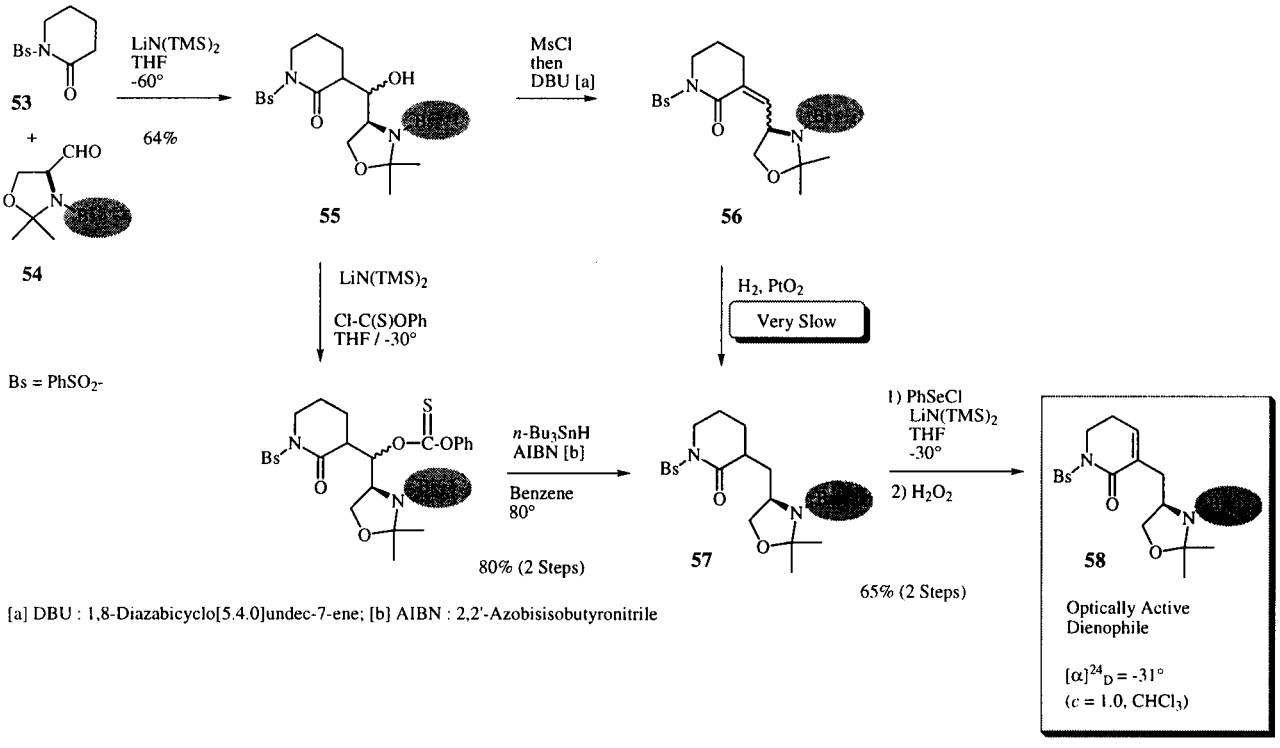
4. Total Synthesis of Ircinal A and Manzamine A

Although we anticipated that *N*-benzenesulfonyllactam would be extremely sensitive to a nucleophile under basic conditions, to our delight, a key reaction of **53** with serinal **54** using lithium bis(trimethylsilyl)amide worked well at -60° to provide **55** as a mixture of diastereomers (Scheme 13).

was very slow. Therefore, we applied the radical deoxygenation conditions using phenoxythiocarbonyl ester for **55** [17], and **57** was obtained in 80% yield (2 steps).

Conversion of **57** to the desired enantiomerically pure dienophiles **58** was achieved by base-induced phenylselenylation at the 3-position of **57** followed by oxidative elimination using previously described methods.

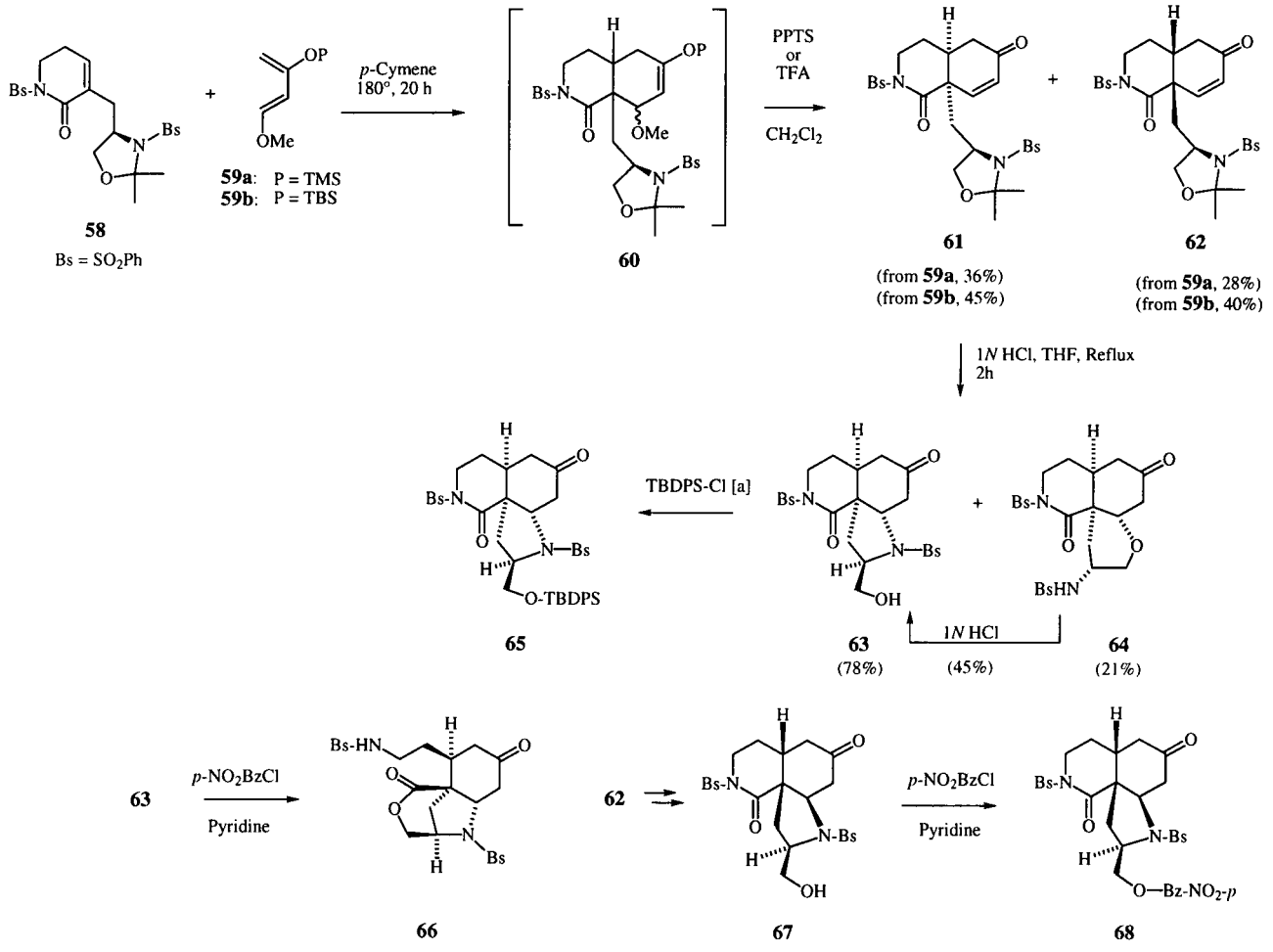
Scheme 13



[a] DBU : 1,8-Diazabicyclo[5.4.0]undec-7-ene; [b] AIBN : 2,2'-Azobisisobutyronitrile

With an efficient route to the dienophile **58** established, we turned our attention to the Diels-Alder reaction of **58** with Danishefsky diene **59**. The reaction of refluxing **58** and excess (8 equivalents) **59a** in *p*-cymene at 180° for 20 hours proceeded smoothly to give regioselective cycloaddition. Without isolation, the cycloadduct was readily transformed into the corresponding enones, slightly favoring the desired isomer **61** after deprotection with PPTS or TFA (Scheme 14).

Scheme 14



[a] TBDPS-Cl : *t*-Butyldiphenylsilyl chloride

Similar reaction of **58** with TBS-diene **59b** gave the corresponding enones (**61** and **62**) in 85% yield. Subsequently, the acetonide **61** was treated with 1 *N* hydrochloric acid in tetrahydrofuran to give a tricyclic alcohol **63** together with **64**, which could be readily converted to **63** with 1 *N* hydrochloric acid. The desired stereochemistry of **63** was secured through chemical transformation and ^{1}H nmr spectral data. When **63** was treated with *p*-nitrobenzoyl chloride in pyridine, the lactone **66** was newly formed, whereas isomer **67**, obtained from **62** in an analogous manner, gave the corresponding *p*-nitrobenzoate **68**, selectively. The unexpected formation of **66** supported the *cis* relationship of the hydroxymethyl group and ring A in **63**. The alcohol **63** was then protected with *t*-butyldiphenylsilyl (TBDPS) to give the TBDPS ether **65**, which was converted into the ketal **70**. Deprotection of two benzenesulfonyl groups of **70** followed by reprotection with a BOC group gave **71**.

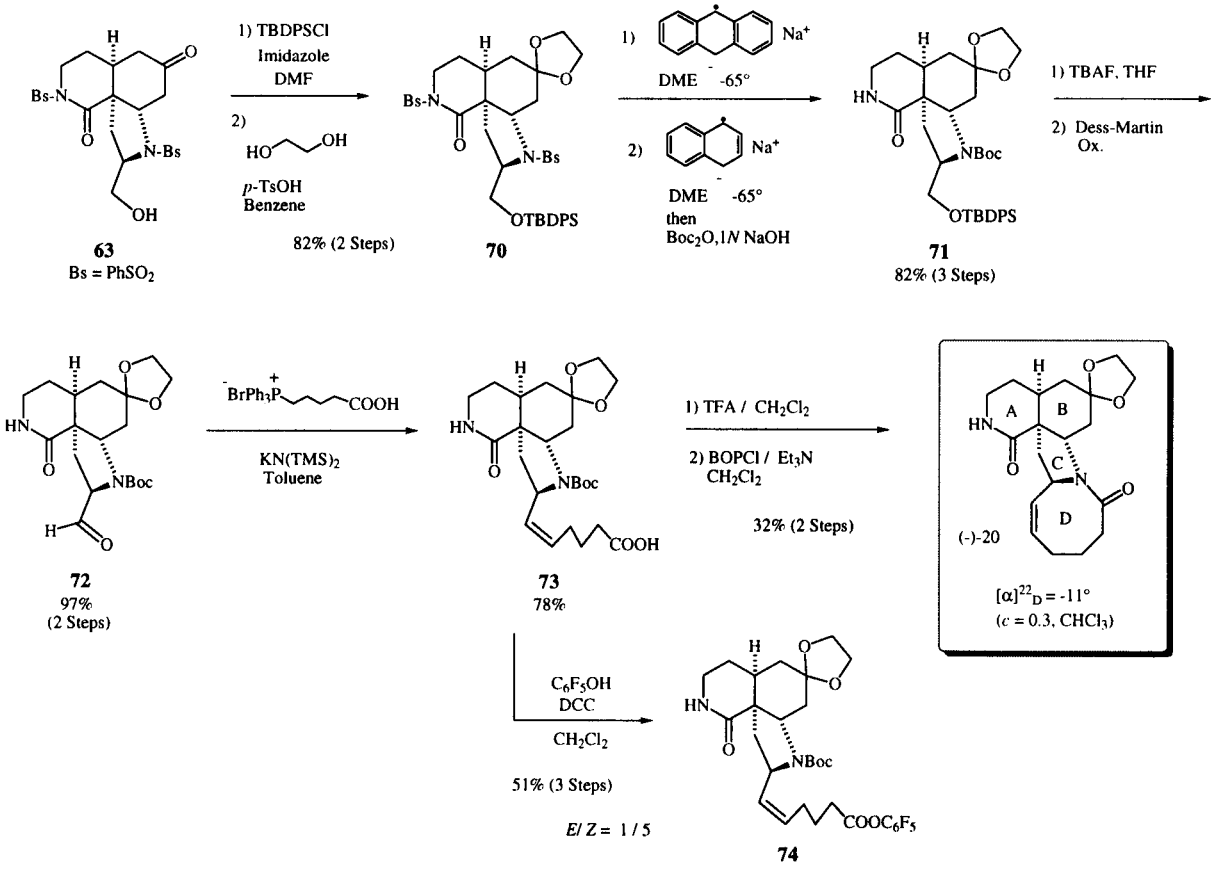
The remaining task was elongation of the side chain to construct the azocine ring system. Deprotection of the primary TBDPS ether was followed by Dess-Martin periodinane oxidation of the derived primary alcohol to give the labile aldehyde **72**. Homologation of the resulting aldehyde **72** using the Wittig reagent **41** gave the olefin **73**

(*E*/*Z* ratio 1:5) as the key cyclization substrate. A 1:5 ratio of the *E* and *Z* isomers was determined by ^{1}H nmr spectroscopy of the resultant mixture of the pentafluorophenyl ester **74**. At this stage, we chose bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) for the final cyclization [18]. Thus, a BOC group was first deprotected and the amino acid was treated with BOP-Cl to give the desired tetracyclic key compound **20** [$[\alpha]_D^{22} = -11$ (c = 0.3, chloroform)]. Its spectroscopic properties were identical in all respects to those of (±)-**20** [12,19] (Scheme 15).

was then converted to the α,β-unsaturated ester (**78**) by reduction-dehydration (Scheme 16).

Oxidation of **78** to enone **79** was examined under variety of reaction conditions, and **79** was formed in the best yield of 62% using the Salmond protocol employed by Martin [21]. Sequential reduction of **79** with sodium borohydride•cerium(III) chloride and diisobutylaluminium hydride (DIBAH) followed by acylation and oxidation gave **80**, which was reacted with 8-lithio-5-octyne-1-ol MOM ether (**81**) to produce **82** (Scheme 17).

Scheme 15

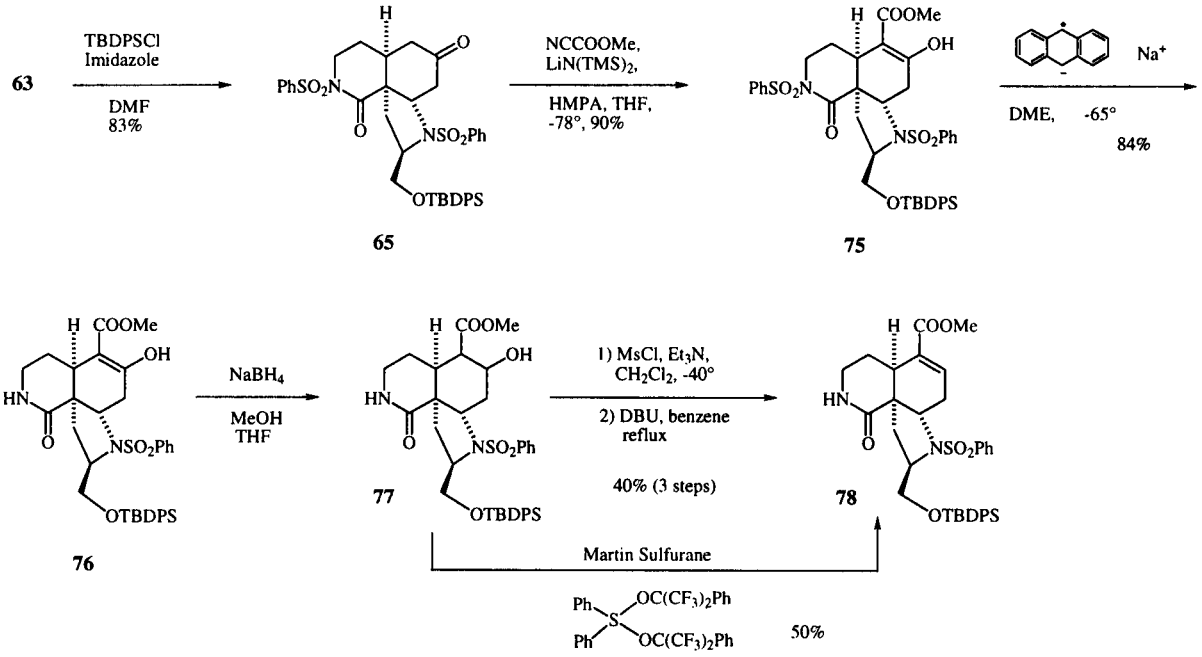


The next step in the synthesis involved introduction of the C1 unit to the B ring and functionalization of the B ring to construct the E ring system. Although this transformation appeared to be fairly straightforward, it proved to be rather difficult. Treatment of **65**, which was obtained by silylation of **63** with chloromethyl methyl ether provided a 1:1 mixture of *O*-MOM derivative and *C*-MOM derivative. Reaction of **65** with methyl chloroformate gave *O*-methoxycarbonylated product selectively. In contrast, exclusive formation of the desired ketoester **75** was achieved in 90% yield by treatment of **65** with Mander's reagent, methyl cyanoformate [20]. Deprotection of a benzenesulfonyl group of **75** provided lactam **76**, which

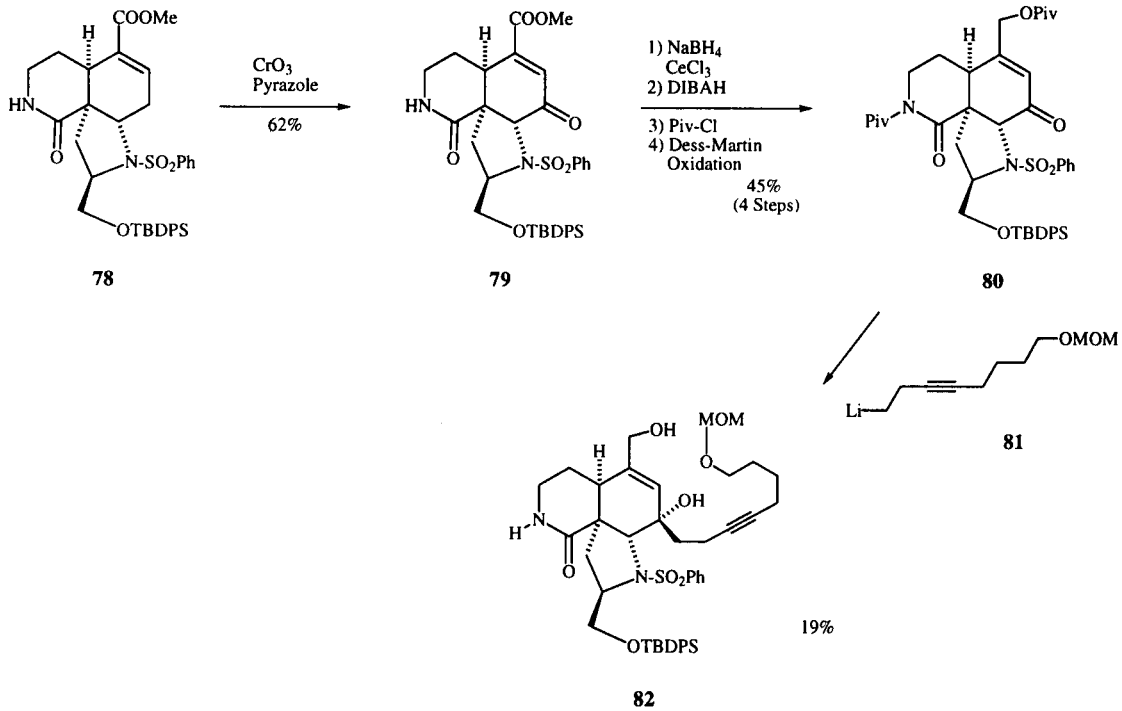
On the other hand, replacement of a benzenesulfonyl group of **76** with a BOC group gave **84** *via* **83**. The subjection of **84** to sequential reduction, dehydration, and oxidation efficiently gave **86** (Scheme 18). Deprotection of enone **86** by hydrofluoric acid gave the corresponding alcohol. Acylation of the resulting alcohol, followed by reduction and protection provided **87**, which was converted to the aldehyde **88**. Then, Wittig reaction of **88** with **41** afforded the corresponding unsaturated carboxylic acid **89**. Cyclization of **89** to an advanced intermediate **91** is now under investigation (Scheme 19).

The acetal **91** may be transformed to ircinal A, which has been converted to manzamine A by Professor Kobayashi.

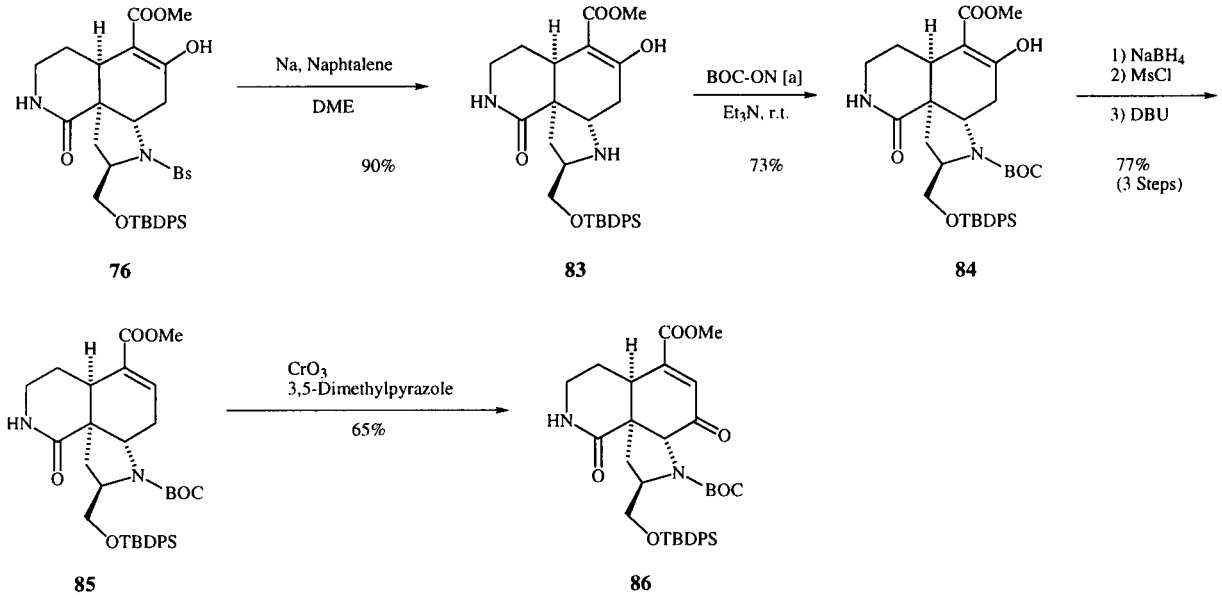
Scheme 16



Scheme 17

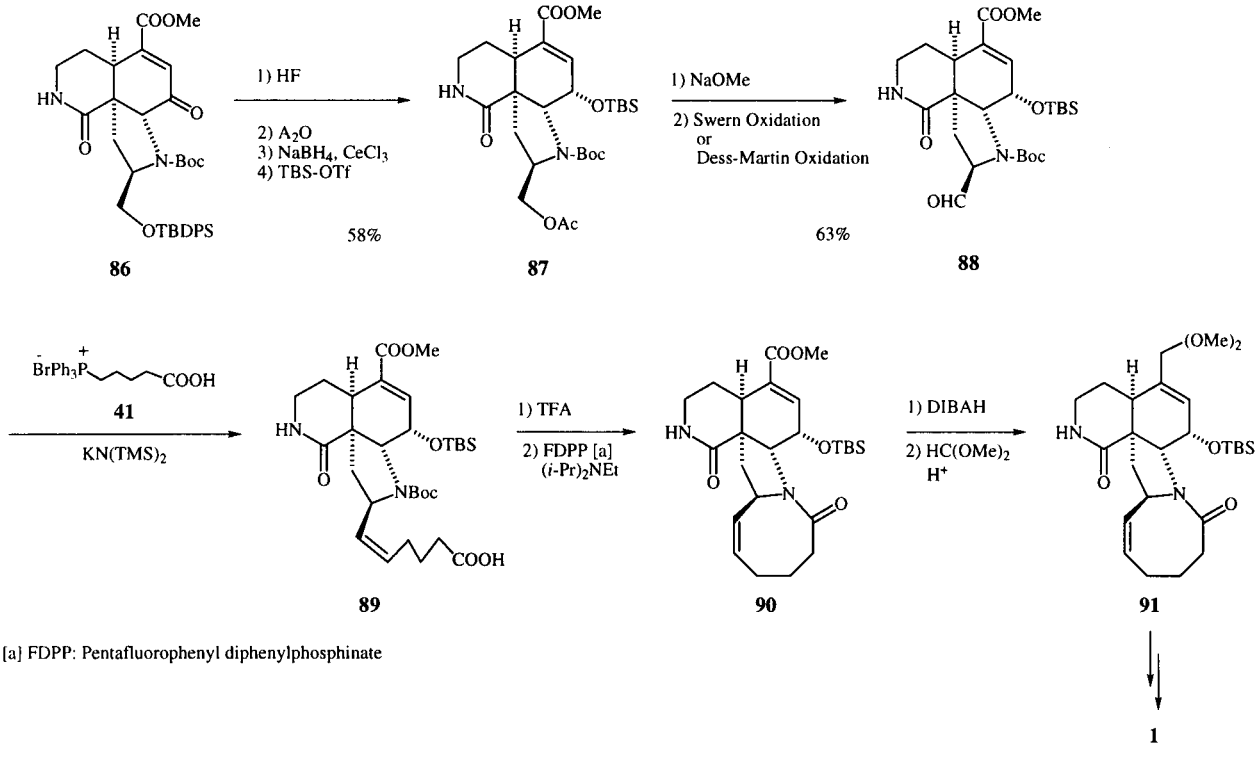


Scheme 18



[a] BOC-ON: 2-(*t*-Butoxycarbonyloxyimino)-2-phenylacetonitrile

Scheme 19



[a] FDPP: Pentafluorophenyl diphenylphosphinate

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