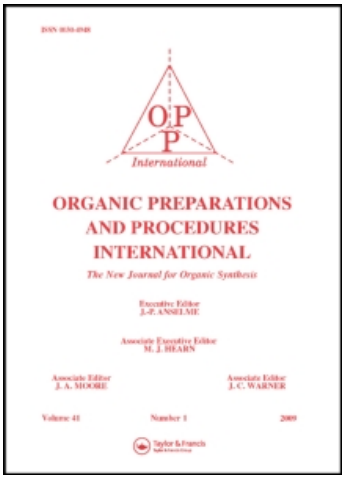


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

THE ZINCKE REACTION. A REVIEW

Wei-Chieh Cheng[a]; Mark J. Kurth[a]
[a] Department of Chemistry, University of California, Davis, CA

To cite this Article Cheng, Wei-Chieh and Kurth, Mark J.(2002) 'THE ZINCKE REACTION. A REVIEW', Organic Preparations and Procedures International, 34: 6, 585 — 608
To link to this Article: DOI: 10.1080/00304940209355784
URL: http://dx.doi.org/10.1080/00304940209355784

ORGANIC PREPARATIONS AND PROCEDURES INT., 34 (6), 585-608 (2002)

THE ZINCKE REACTION. A REVIEW

Wei-Chieh Cheng and Mark J. Kurth*

Department of Chemistry, University of California
One Shields Avenue, Davis, CA 95616-5295

THE ZINCKE REACTION. A REVIEW

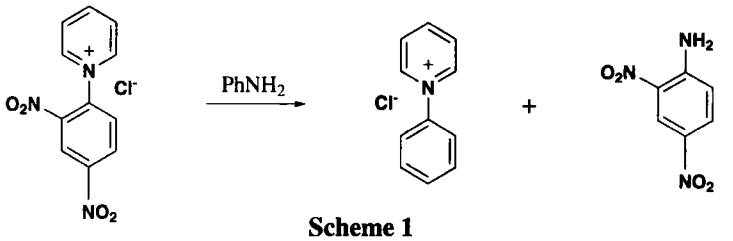
Wei-Chieh Cheng and Mark J. Kurth*

Department of Chemistry, University of California
One Shields Avenue, Davis, CA 95616-5295

INTRODUCTION

Pyridine derivatives play very significant roles in heterocyclic chemistry due to their abundance in nature, versatility in chemical transformations, and broadly-based biological activities.[1-3] Among these pyridine derivatives, quaternary pyridinium compounds have received a great deal of attention — especially in drug discovery, organic chemistry, and natural products synthesis.[4,5] The most general and straightforward method for the preparation of quaternary pyridinium compounds is to use the pyridine as a nucleophile in the displacement of the halide ion from alkyl or acyl halides. Unfortunately, with aryl halides this reaction is difficult unless there are electron- withdrawing groups on the aromatic ring or harsh reaction conditions are employed. With secondary and tertiary alkyl halides, alkylation of pyridine generally results in low yield because dehydrohalogenation is a major reaction path.[6,7] Moreover, when the displacement occurs at an asymmetric carbon atom in the alkyl halide, racemization by competing S_N1 and S_N2 processes may occur. Obviously, this approach to the preparation of *N*-alkylpyridinium salts has limitations, especially in asymmetric synthesis.

In 1903, Zincke reported that 1-(2,4-dinitrophenyl)pyridinium chloride undergoes ring opening with aniline followed by cyclization to deliver 1-phenylpyridinium chloride[8], which would be difficult to be prepared by arylation of pyridine with chlorobenzene (*Scheme 1*). This method known



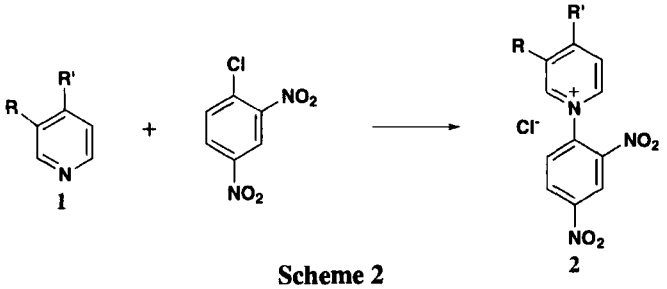
Scheme 1

as the Zincke reaction, provides an efficient and elegant approach to the preparation of *N*-aryl or *N*-alkylpyridinium salts where the alkyl groups can be primary, secondary, or tertiary. Optical activity is retained when stereogenic primary amines are used as the nucleophile. Here, we survey the literature from the original publication by Zincke in 1903 until 2001. Historical and mechanistic information on

the Zincke reaction are briefly discussed, and then synthetic applications and chemical transformations from the last two decades are emphasized.

I. PREPARATION OF ZINCKE SALTS

N-(2,4-Dinitrophenyl)pyridinium chloride salts (Zincke salts) are prerequisites for the Zincke reaction. In generally, they are derived from the reaction of 1-chloro-2,4-dinitrobenzene with various pyridines; their preparation has been discussed by Vompe *et al.*[9] and others.[10-12] The important aspects of this chemistry, summarized in *Scheme 2*, are: (i) Hindered pyridines (2 or 6-substituted) do



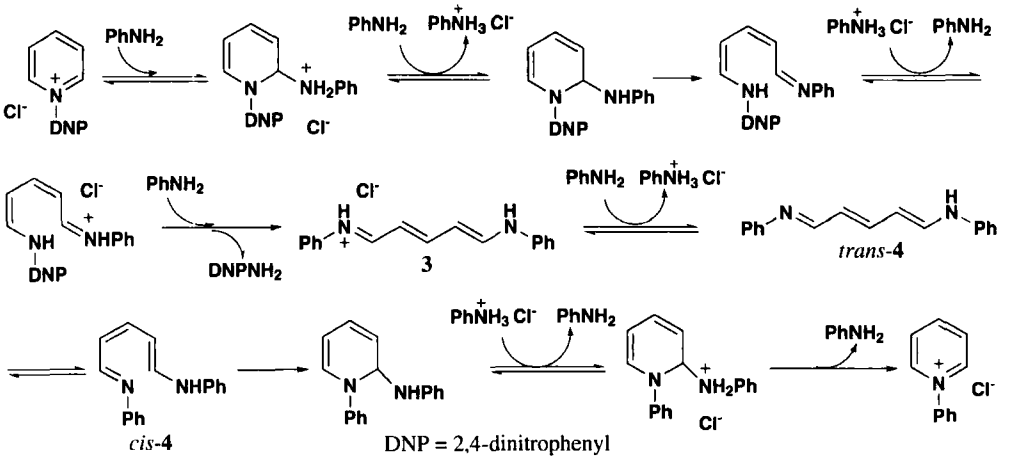
Scheme 2

not generally provide Zincke salts (**2**) because of unfavorable steric effects. (ii) When R = Cl, F, CN, NO_2, COOH; or R' = Cl, Br, CN, NO_2, the pyridines (**1**) are too electron-deficient for Zincke salts to be obtained. (iii) Zincke salts **2** are readily obtained if R = Me, I, OH, OMe, NHAc, NMe_2, $CONEt_2$, $CONH_2$; or R' = NHAc, NHPh, OMe. (iv) When R = Br, or either R or R' = COOEt, the reaction proceeds only at high temperature.[9-12]

II. HISTORICAL INFORMATION

1. Mechanism

The key steps in the mechanism of the Zincke reaction[13-15] may be divided into three stages: (i) ring opening, (ii) *cis-trans* interconversions, and (iii) ring closure (*Scheme 3*). The ring opening



Scheme 3

reaction of 2,4-dinitrophenylpyridinium chloride with aniline gives 5-anilino-*N*-phenyl-2,4-pentadienylideniminium chloride (**3**, glutaconic dialdehyde derivative) as a deep red crystalline salt. According to ultraviolet spectroscopy, structures **3** and **4** are in equilibrium.[16] But, in the presence of excess triethylamine, **3** is driven to **4**. This interconversion process of *trans*-**4** to *cis*-**4** is clearly required prior to the ring-closure step. Through a series of protonation, conjugation, and deprotonation steps, the rapid equilibrium between *cis* and *trans* conformations of **4** is allowed even though the *trans* conformation is more stable.[17] Investigation of solvent effects suggests that the ring closure of *cis*-**4** takes place *via* a non-polar transition state; that is electrophilic cyclization predominates over nucleophilic addition.[17]

Recently, Kurth and co-workers have extended the Zincke reaction to solid-supported organic synthesis and also investigated the mechanism on solid-phase.[18] Although the Zincke products synthesized on solid-phase are indistinguishable from solution-phase products, the mechanism is probably different because the intermediate amino-pentadienylideniminium **5**, which would be formed from covalent bond site-site interactions, would be difficult to form on solid-phase (*Figure 1*).

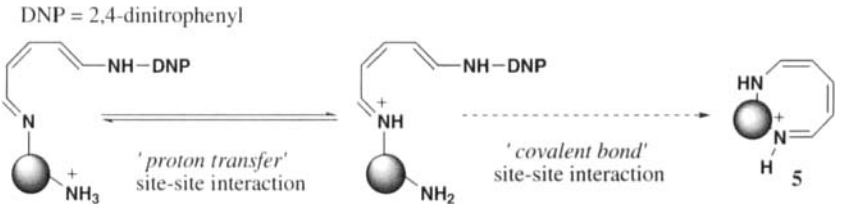
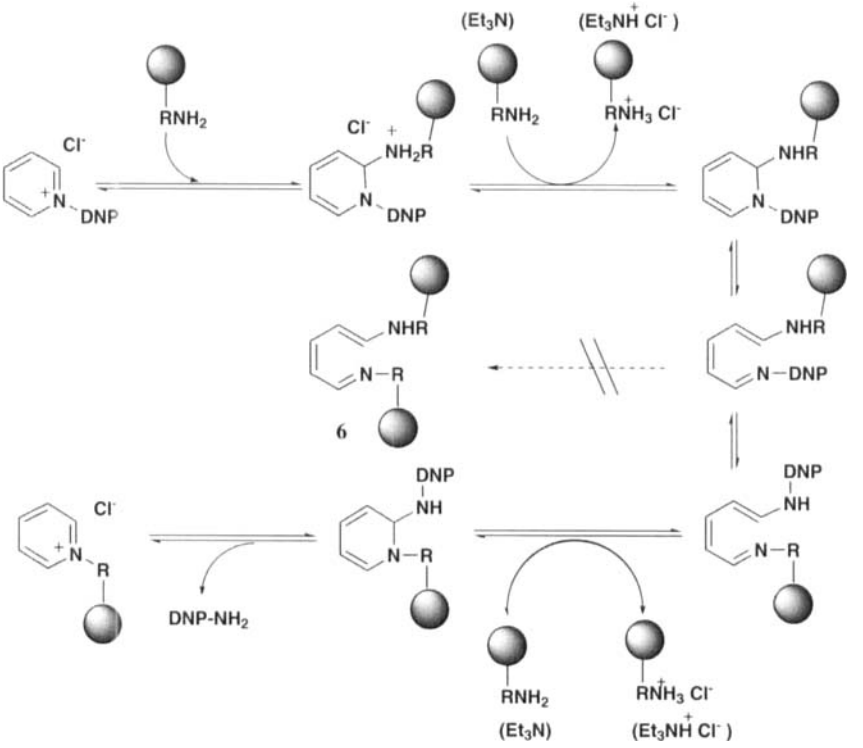


Fig. 1

Based on Ise's solution phase mechanism,[15] the solid-phase Zincke reaction would require two types of resin-bound amine interactions; namely, 'proton transfer site-site interactions' and 'covalent bond site-site interactions'. However, the latter interaction would be difficult because this interaction would generate new cross-linkage which would reduce resin mobility (*e.g.* **6** in *Scheme 4*).[18] To study the details of the Zincke reaction on solid-phase, three crucial factors have been investigated including (i) the degree of resin crosslinking, (ii) the degree of functional group loading, and (iii) the nature of the solvent. In reactions without TEA, yield improvement was observed with loadings greater than 0.3 mmol per gram of resin. This result which means that effective site-site interactions occur at loadings of more than 0.3 mmol per gram of resin is in agreement with Patchornik's report that 0.1-0.3 mmol per gram of resin loadings can be employed successfully in syntheses requiring effective site-isolation.[19] The fact that solid-phase Zincke reactions proceed in good yield at resin loadings of ≤ 0.3 mmol per gram of resin (even at considerably lower loadings such as 0.09 mmol per gram of resin) in the presence of TEA indicates that the addition of triethylamine greatly facilitates several key proton transfer steps.



Scheme 4

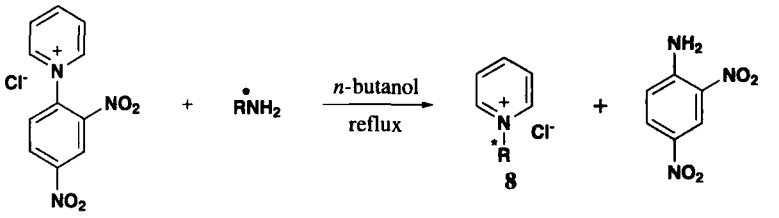
2. Influence of Substituents on Zincke Salts

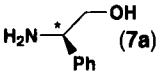
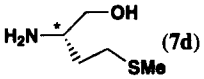
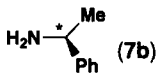
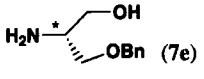
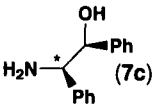
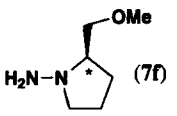
Because of the complicated series of nucleophilic ring opening, proton transfer, *cis-trans* interconversion, and electrophilic ring closure steps, substituents on the Zincke salt affect the course of the reaction dramatically. Due to the strong electron acceptor effect of the dinitrophenyl group and depending on the substitution on the pyridinium ring of the Zincke salts, the nucleophilic amine may cleave the endocyclic C-N bond to open the ring or cleave the exocyclic C-N bond to generate the substituted pyridinium species (thence to the ylide) *via* an *N*-substitution reaction.[20] In general, electron-withdrawing groups on the pyridinium ring of Zincke salts increase the electron deficiency and thus the rate of ring opening. In contrast, electron-donating groups on the ring retard the rate of the ring opening. Raising the reaction temperature or changing the solvent are two usual methods used to increase reaction rates. Interestingly, changing the counteranion (*e.g.* from chloride anion to dodecyl sulfate) is another alternative.[21] Presumably, the chloride anion is sufficiently nucleophilic to compete with the amine and the lipophilic dodecyl sulfate is sometimes chosen to replace choride because it is a less nucleophilic anion. Moreover, the dodecyl sulfate provides salts with better solubility in organic solvents.

III. SYNTHETIC APPLICATIONS

1. Zincke Salts with Amines

The reaction of *N*-2,4-dinitrophenylpyridinium chloride with amines has been studied extensively.[8-12] However, stereogenic amines have not been appropriately applied to the Zincke reaction until recently.[22-24] In 1992, Marazano and co-workers demonstrated that the preparation of asymmetric pyridinium salts (Zincke products) was feasible by employing various stereogenic primary amines [*i.e.*, (R)-(-)-amino-2-phenylethanol (**7a**) and (S)-(-)-1-phenylethylamine (**7b**)] to couple with *N*-2,4-dinitrophenylpyridinium chloride in refluxing *n*-butanol to furnish stereogenic *N*-alkyl pyridinium salts **8a-f** (*Scheme 5*).[25] The chirality of the nucleophilic amine was retained in the Zincke product

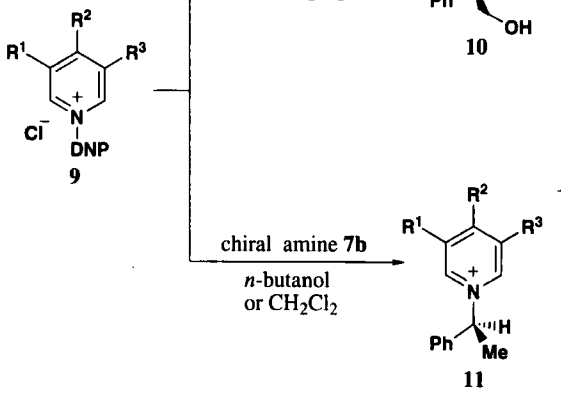


Chiral primary amines	Product (%)	Chiral primary amines	Product (%)
 (**7a**)	89 (**8a**)	 (**7d**)	70 (**8d**)
 (**7b**)	90 (**8b**)	 (**7e**)	70 (**8e**)
 (**7c**)	70 (**8c**)	 (**7f**)	70 (**8f**)

Scheme 5

with no racemization or inversion. Coupling amines **7a** or **7b** in MeOH at room temperature with pyridinium salts **9** mono- or disubstituted at positions 3, 4, or 5 did not proceed well. After variation of solvents and conditions, the yields of Zincke products **10** and **11** were enhanced to 63-95% for monosubstituted Zincke salts **9** (R = methyl, ethyl, phenyl, *t*-butyl, or ethylene ketal) by using refluxing protic solvent such as *n*-butanol. In contrast, for dialkyl substituted Zincke salts **9**, a non-protic solvent (CH_2Cl_2) was more suitable and the yields of Zincke product **11c-e** were in the 52-95% range (*Scheme 6*). Presumably, electron-donating effects of dialkyl substituted groups on the Zincke salts retard primary amines from opening the pyridine ring. With non-protic dichloromethane as solvent, the ring opening of dialkyl substituted Zincke salts became less difficult than when protic *n*-butanol was employed as solvent.

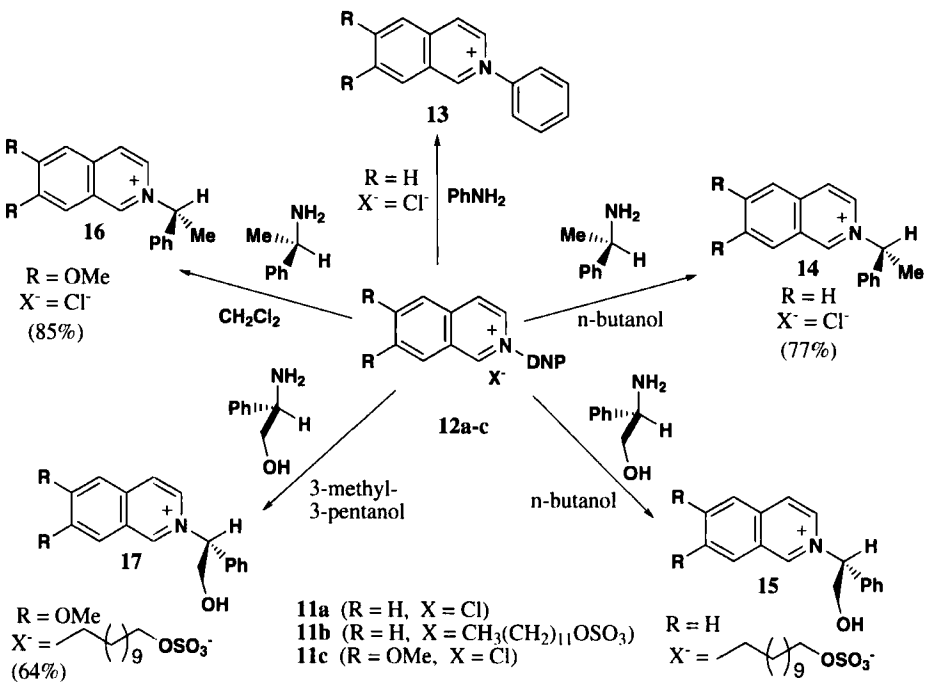
In addition, isoquinoline derivatives also form Zincke salts with 1-chloro-2,4-dinitrobenzene in the same way as pyridine.[26,27] Coupling of Zincke salt **12a** (R = H, X = Cl) with aniline or (R)-(+)-1-phenylethylamine gave *N*-phenylisoquinolinium chloride salt **13**[28] or stereogenic *N*-alkyl isoquinolinium chloride salt **14**,[29] respectively (*Scheme 7*). Unfortunately, without anion-exchange from chloride



Product	R^1	R^2	R^3	Yield(%)
10a	Me	**H**	H	81
10b	H	***t*-Bu**	H	64
10c	H	**Me**	H	63
10d	H	**Ph**	H	79
10e	H		H	95

Product	R^1	R^2	R^3	Yield(%)
11a	**Et**	**H**	H	86
11b	**H**	***t*-Bu**	H	95
11c	**Me**	**Me**	H	92
11d	**Me**	**H**	Me	87
11e	-$(CH_2)_4$-		H	52

Scheme 6



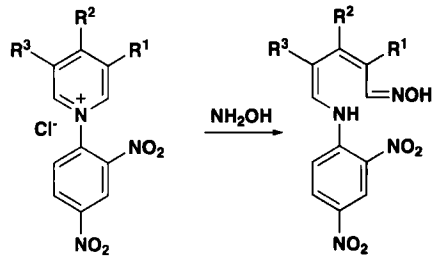
Scheme 7

to dodecyl sulfate, the Zincke reaction between **12a** and (R)-(-)-phenylglycinol produced a low yield. After anion exchange from chloride to dodecyl sulfate, 2-(2,4-dinitrophenyl)isoquinolinium dodecyl

sulfate salt **12b** (R = H, X = $CH_3(CH_2)_{11}OSO_3$) reacted with (R)-(-)-phenylglycinol in refluxing *n*-butanol to deliver **15** in a satisfactory 75% yield. However, the donor effect of methoxy groups on Zincke salt **12c** (R = OCH_3) resulted in the Zincke reaction proceeding slowly with (R)-(+)-1-phenylethylamine and (R)-(-)-phenylglycinol. Modifying conditions of the Zincke reaction (*i.e.*, solvent change to CH_2Cl_2 or anion exchange to dodecyl sulfate) improved the yields of **16** and **17** to 85% and 64%, respectively.

2. Zincke Salts with Hydroxylamine, Hydrazines and Carboxylic Acid Hydrazides

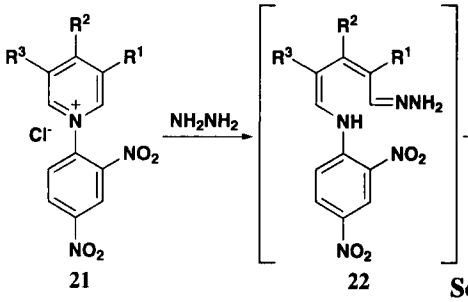
The Zincke reaction not only refers to amines condensing with *N*-(2,4-dinitrophenyl)pyridinium chlorides, but also to hydroxylamine, hydrazine and carboxylic acid hydrazides.[30,31] Tamura and co-workers developed a new synthetic route for the preparation of pyridine *N*-oxides,[32] *N*-iminopyridinium ylides or *N*-aminopyridinium salts by coupling hydroxylamine, benzhydrazide or hydrazine with 2,4-dinitrophenylpyridinium chloride *via* the Zincke reaction.[30-32] Treatment of unsubstituted or mono alkyl *N*-(2,4-dinitrophenyl)pyridinium chlorides **18** with hydroxylamine in methanol at room temperature gives **19** in high yields (*e.g.* 97% yield for **19a**). Subsequent refluxing of 5-(2,4-dinitroanilino)-2,4-pentadienal oxime **19** in dioxane-water (4:1) generates pyridine *N*-oxides **20** in 32-88% yield from the pyridine substrate used to prepare **18** (*Scheme 8*). Treatment of solutions of *N*-(2,4-dinitrophenyl)pyridinium chloride **21** in water with hydrazine effected ring opening. After



Product	R^1	R^2	R^3	Yield(%)
20a	H	H	H	88.3
20b	Me	H	H	53.5
20c	H	Me	H	65.5
20d	Me	H	H	32.5

Scheme 8

addition of dioxane and reflux for 10-15 h, the corresponding *N*-aminopyridinium salts (**23a-c**) were obtained in 34-50% yields (*Scheme 9*).[32] By a similar protocol, benzhydrazide was condensed with 3-substituted *N*-(2,4-dinitrophenyl)pyridinium chloride **24** in the presence of triethylamine to generate

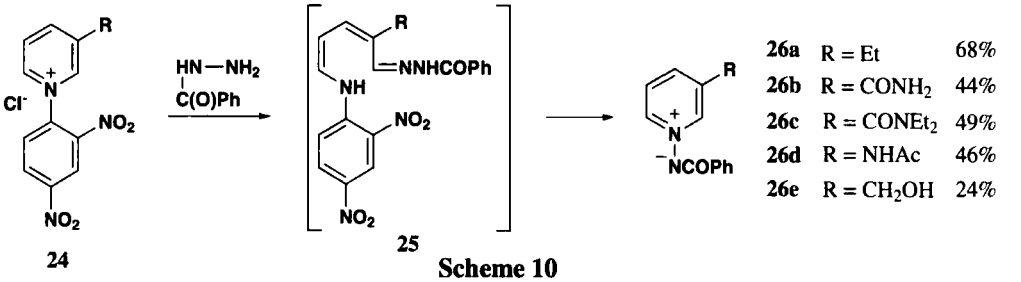


Product	R^1	R^2	R^3	Yield(%)
23a	H	H	H	50
23b	Me	H	H	34
23c	Me	H	Me	47

Scheme 9

N-benzoylimino derivatives **26a-e** in 24-68% yield (*Scheme 10*).[31] In a related study, Redda and co-

workers accomplished a similar result (**24** → **26e**; 62% yield) by treating **24** with benzoylhydrazine and triethylamine in methanol to give intermediate **25**, which was then hydrolysed by dioxane/H_2O treatment to yield **26e**.[33]



24 **25**

Scheme 10

One synthetic application is the preparation of *N*-amino-1,2,3,6-tetrahydropyridine analogs. Various precursors such as *N*-alkyl hydropyridines and *N*-iminohydropyridines have received much attention due to the pharmacological activity of derivatives of 1,2,3,6-tetrahydropyridine (THP, **27**),[34] 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, **28**),[34] and *N*-amino-1,2,3,6-tetrahydropyridines **29**[35,36] (*Figure 2*). This procedure has been applied extensively by Knaus and Redda (*Scheme 11*).[37-39]

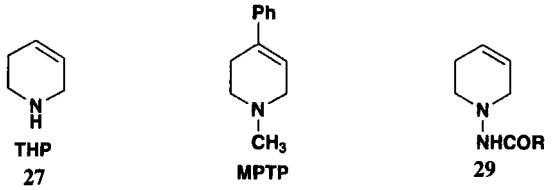
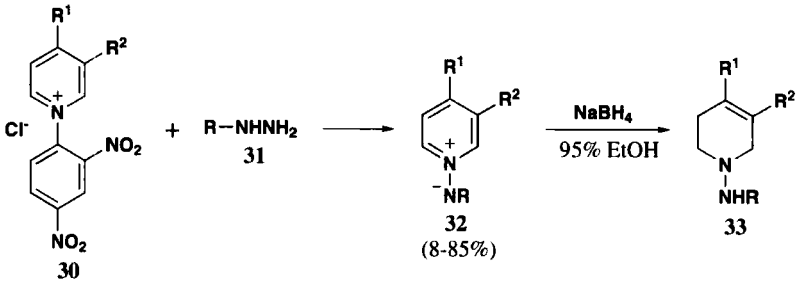


Fig. 2

Thus, treatment of various arylsulfonyl-, pyridylcarbonyl- and arylalkylhydrazines **31** with Zincke salt **30** afforded *N*-iminopyridinium ylides **32** in yields ranging from 8% to 85%.[35-39] Reduction of **32** with



$R^1 = R^2$ = H, Hydroxymethyl, 3-Hydroxypropyl, Benzyl, Alkyl

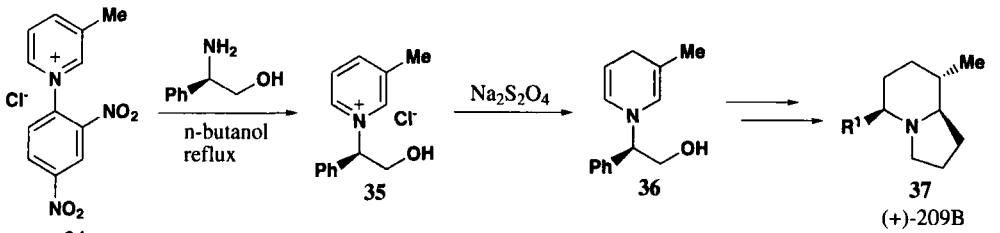
R = $C_6H_5SO_2$-, CH_3SO_2-, C_6H_5CO-, CH_3CO-, 2-Pyridyl-CO-, 3-Pyridyl-, 4-Pyridyl-CO-

Scheme 11

sodium borohydride in ethanol provided several *N*-imino-1,2,3,6-tetrahydropyridine derivatives **27** for pharmacological studies.

3. Zincke Reactions in Natural Product Synthesis

Natural products containing six-membered nitrogen heterocycles are plentiful and many exhibit interesting biological activity. The Zincke reaction provides an efficient and practical alternative for the generation of stereogenic and non-stereogenic quaternary pyridinium salts. Even though the Zincke reaction is but one step in these synthetic sequences, it often plays a significant and pivotal role. Among the natural product syntheses described below, the quaternary pyridinium salts from the Zincke reaction can be used to provide either the target molecules or important precursors. New types of alkaloids, including indolizidine 209B (**37**), were discovered from the skin extracts of neotropical dart-poison frogs.[40,41] The Zincke reaction was employed in the synthesis of indolizidine (+)-209B and derivatives to build the skeleton as well as orchestrate the stereogenic centers. In this short and effective strategy (*Scheme 12*),[42] 3-picoline was treated with 1-chloro-2,4-dinitrobenzene in acetone to

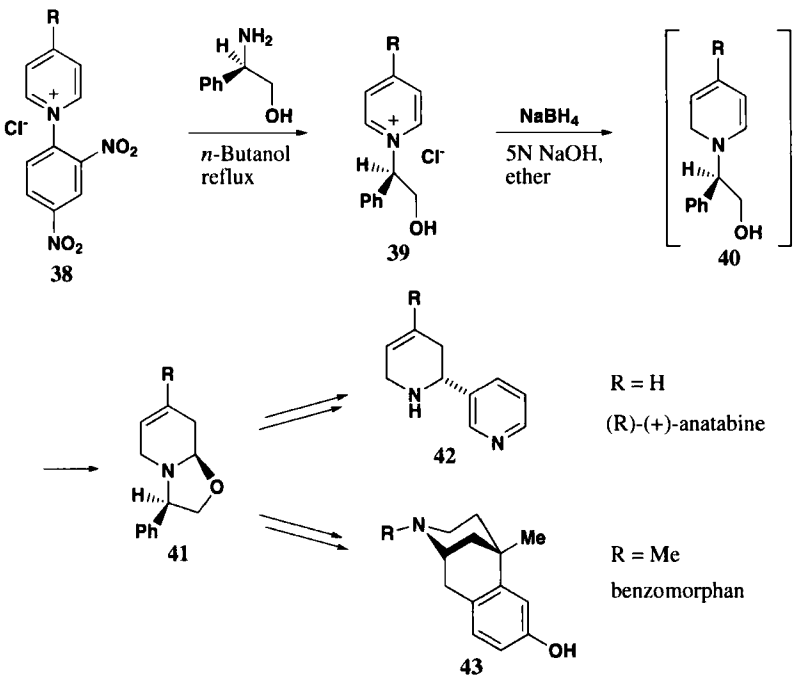


Scheme 12

afford crystalline Zincke salt **34**. Reflux with (R)-(-)-phenyglycinol in *n*-butanol converted **34** to chiral pyridinium Zincke product **35**. Reduction of **35** by sodium dithionite ($Na_2S_2O_4$) containing K_2CO_3 in a two-phase (Et_2O/H_2O) solution delivered chiral 1,4-dihydropyridine **36** (1,4-DHP).[43] Upon subsequent alkylation, hydrogenation, and cyclization, 5,8-disubstituted indolizidine alkaloid (+)-209B (**37**) was obatined in 10% overall yield from 3-picoline.

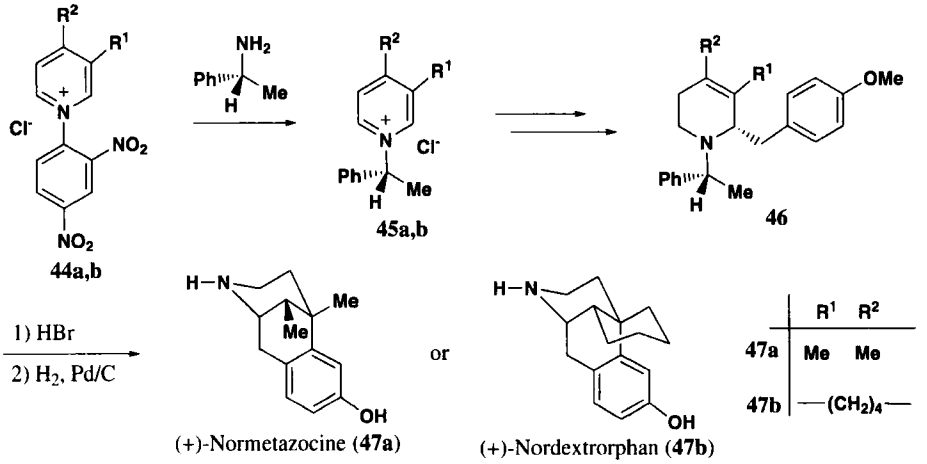
Another application of the Zincke reaction is the synthesis of tobacco alkaloid (+)-anatabine (**42**, R = H) and (+)-benzomorphan (**43**, R = Me) (*Scheme 13*).[44] Treatment of Zincke salts **38** with (R)-(-)-phenylglycinol in refluxing *n*-butanol furnished chiral pyridinium salts **39**. These salts were reduced by $NaBH_4$ in the presence of NaOH in a two-phase (Et_2O/H_2O) solution to generate 1,2-dihydropyridine **40**. Interestingly, this intermediate cyclized spontaneously to tetrahydro-5H-oxazolo[3,2-a]pyridines **41**.[45] After alkylation and removal of the phenylethanol auxiliary, tobacco alkaloid (R)-(+)-anatabine (**42**) was obtained in 55% overall yield. By use of a similar synthetic approach, (+)-benzomorphan (**43**) was successfully obtained from **41** *via* a three-step procedure (alkylation, removal of phenyl ethanol auxiliary, and cyclization).

Likewise, (+)-normetazocine (**47a**) and (+)-nordextrorphan (**47b**), precursors of benzomorphan and morphinan analgesics or antitussive drugs, were successfully synthesized employing the



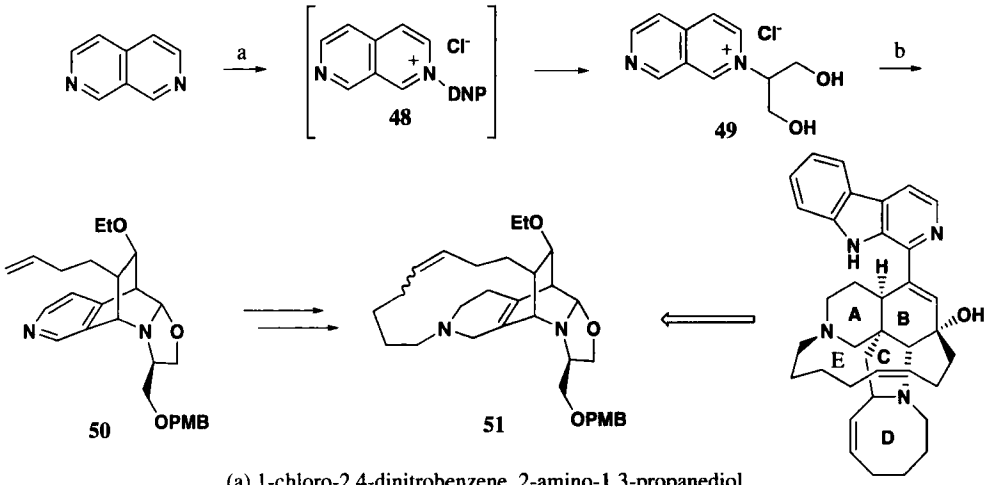
Scheme 13

Zincke reaction as the key transformation (*Scheme 14*).[21] When (R)-(+)-1-phenylethylamine was employed instead of (R)-(-)-phenylglycinol in the Zincke reaction with 3,4-dialkyl-substituted Zincke salts **44a** and **44b**, Zincke products **45a** and **45b** were obtained in 92% and 58% yield, respectively. After a series of transformations including alkylation, reduction, Grewe's cyclization, and hydrogenation, (+)-normetazocine (**47a**) and (+)-nordextrorphan (**47b**) were obtained in 9% and 13% overall yield, respectively.



Scheme 14

Recently, the cytotoxic activity and original framework of the manzamine alkaloids, particularly manzamine A, led organic and medicinal chemists to target syntheses of these alkaloids. Langlois and co-workers successfully utilized the Zincke reaction for the synthesis of the ABE tricyclic core of manzamine A.[46] Initial attempts to prepare *N*-alkylnaphthyridinium salt **49** by direct alkylation of 2,7-naphthyridine with 2-chloro- or 2-iodo-1,3-propanediol failed even under high pressure (CH_2Cl_2, 15 kbar, 65 oC, 7d). To circumvent this problem, the authors modified the synthetic route and employed a Zincke reaction as the key step to achieve and demonstrate the facility of their synthetic approach (*Scheme 15*). First, 2,7-naphthyridine was treated with 1-chloro-2,4-dinitrobenzene in butanol or water to prepare Zincke salt **48** which, followed by direct coupling with 2-amino-1,3-propanediol, gave Zincke product **49** in one pot.[47] Naphthyridinium intermediate **49** was subjected

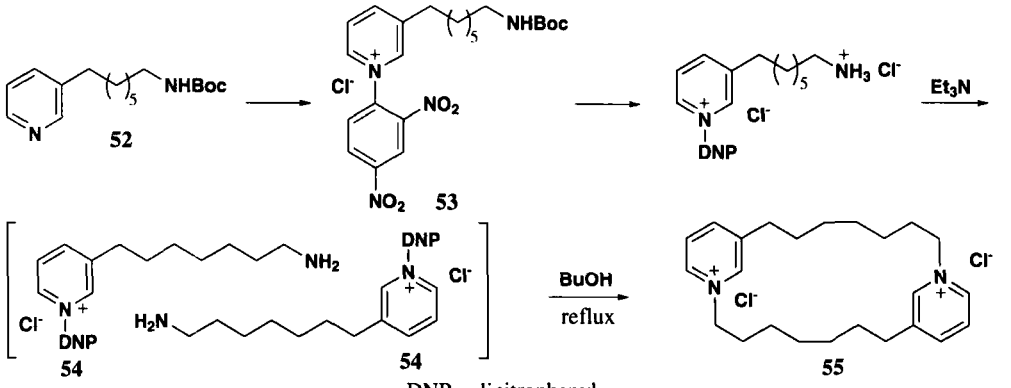


(a) 1-chloro-2,4-dinitrobenzene, 2-amino-1,3-propanediol, H_2O, reflux. (b) (z)-EtOCH=CH$(CH_2)_2$CH=CH_2, $CaCO_3$.
DNP = dinitrophenyl; PMB = para-methoxybenzyl

Scheme 15

to a Bradsher cycloaddition with dienophiles followed by spontaneous oxazolidine formation and subsequent protection of ROH (as ROPMB) to generate adduct **50**. Subsequent *N*-alkylation to the 5-hexenyl pyridinium salt and intramolecular metathesis with Grubbs catalyst gave, after reduction, the anticipated tetrahydropyridine **51** in 18% overall yield from 2,7-naphthyridine.

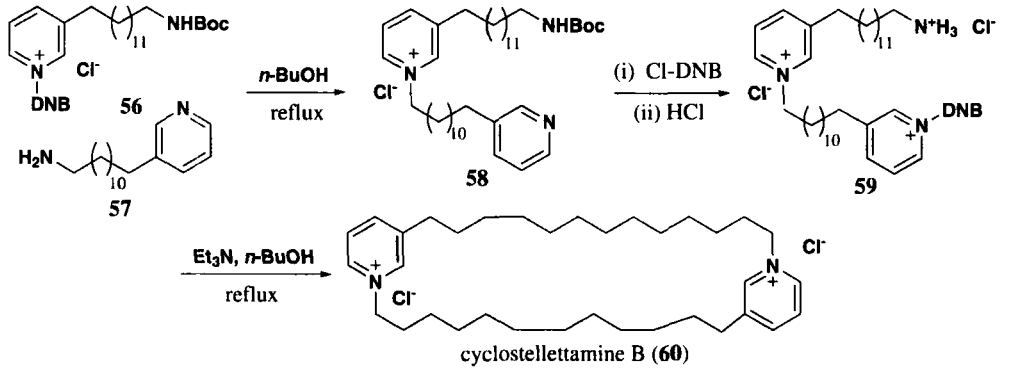
Another example of natural product synthesis is the dimeric or oligomeric pyridinium macrocycles. These macrocycles employ 3-alkylpyridinium as a unit to build dimers or oligomers *via* a head-to-tail type connection. Interestingly, pyridinium formation *via* the Zincke reaction provides a new and efficient route for the synthesis of these pyridinium macrocycles, especially for unsymmetric macrocyclic dimers (two different lengths of alkyl chains in the dimeric pyridinium macrocycle). Marazano and coworkers elegantly employed the Zincke reaction to accomplish this type of cyclization (*Scheme 16*).[48] Thus, 3-(aminoalkyl)-pyridines **52**, derived from 3-picoline, were coupled with 1-chloro-2,4-dinitrobenzene (ClDNB) to give Zincke salt **53**. Sequential removal of the Boc protecting



DNP = dinitrophenyl

Scheme 16

group in acidic medium and addition of triethylamine in butanol delivered pyridinium salt **54**. Refluxing **54** in *n*-butanol effected the Zincke reaction and resulted in the formation of the symmetric bispyridinium dimer **55** in 43% yield. As for the synthesis of unsymmetrical macrocyclic dimers such as cyclostellettamine B, two 3-(aminoalkyl)pyridine units (**56**, **57**; different length side-chains) were prepared individually from 3-picoline (*Scheme 17*). After two sequential Zincke reactions including

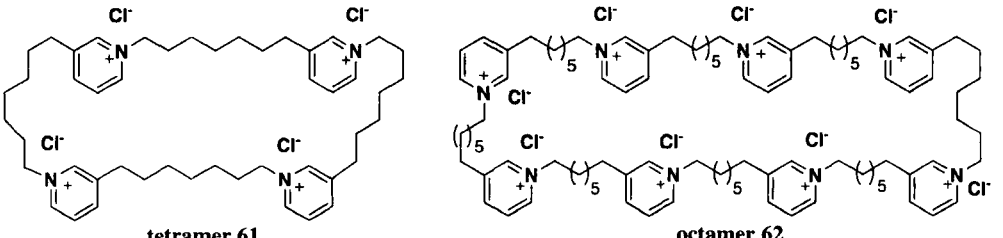


cyclostellettamine B (**60**)

DNP = dinitrophenyl
Cl-DNB = 1-chloro-2,4-dinitrobenzene

Scheme 17

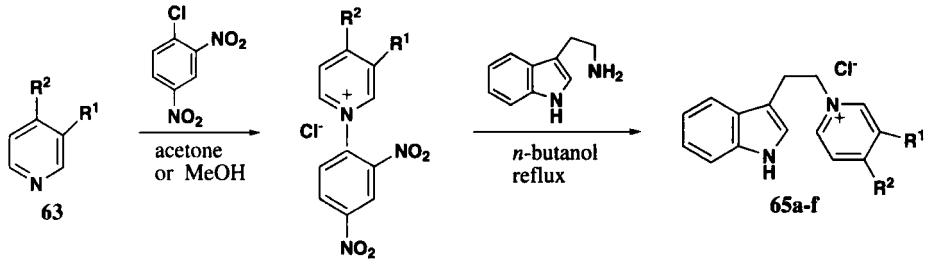
the intramolecular macrocylization, unsymmetrical dimeric pyridinium macrocycle **60** (cyclostelletta-mine B) was obtained in 20-25% overall yield from 3-picoline. Under similar conditions, tetramer **61** and octamer **62** were successfully synthesized *via* the Zincke reactions in modest to good yields (*Figure 3*).



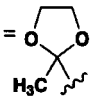
tetramer **61** octamer **62**

Fig. 3

A final application of the Zincke reaction in natural product synthesis is the preparation of 1-[2-(3-indol)ethyl]pyridinium chloride derivatives, which are important intermediates in the synthesis of alkloids.[49] First, Zincke salts **64** were prepared by treating various 3,4-disubstituted pyridines **63** with 1-chloro-2,4-dinitrobenzene (ClDNB) in acetone or methanol (*Scheme 18*). Treatment of the resulting Zincke salts **64** with tryptamine in *n*-butanol afforded the desired 1-[2-(3-indol)ethyl]alkyl pyridinium chloride derivatives **65a-f** in 80-85% yield. These compounds can be used for the preparation of the corresponding 1,2- and 1,4-dihydropyridines or 2-pyridones.[48]



63 **64** **65a-f**

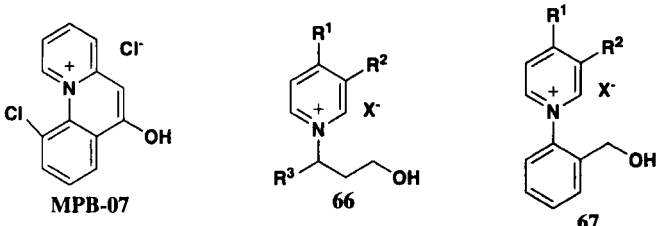
Product	Yield (%)	Product	Yield (%)
65a $R^1 = H$, $R^2 = H$	85	**65e** $R^1 = CH_3$, $R^2 = CH_3$	80
65b $R^1 = H$, $R^2 = CH_3$	85	**65f** R^1 =  $R^2 = H$	85
65c $R^1 = CH_3$, $R^2 = H$	80		
65d $R^1 = CH_2CH_3$, $R^2 = H$	85		

Scheme 18

4. The Zincke Reactions in Solid-Phase Organic Synthesis

Fueled by a rapidly growing interest in combinatorial chemistry, solid-phase organic synthesis (SPOS) is under intensive application and research.[50,51] SPOS enjoys several advantages over solution-phase synthesis: for example, reactions can be driven to completion by the use of excess reagent and product isolation by simple filtration is operationally simple and time efficient. In addition, solid-supported reactions are readily automated. These advantages offer the opportunity for rapid synthesis of libraries of heterocyclic compounds for pharmaceutical and agrochemical discovery.

Kurth and co-workers succeeded in applying the Zincke reaction on solid-phase to efficiently synthesize different libraries of interesting compounds. The first application was to prepare 3-hydroxyalkyl- or 3-hydroxyarylpyridinium salts in the search for CFTR (CF transmembrane conductance regulator) activation.[52] It has been reported that the benzo[c]quinolizinium derivative MPB-07 (*Figure 4*) activates wild-type CFTR in a variety of cell systems.[53] By utilizing solid-phase synthesis



MPB-07 **66** **67**

Fig. 4

techniques, MPB-07-like derivatives were prepared *via* the Zincke reaction for the construction of pyridinium salts like those found in **66** or **67** (*Figure 4*). For the solid-phase strategy,[54] Wang resin and NovaSyn TGA resin (polymer-bound poly(ethyleneglycol)hydroxymethylphenyl resin) were selected and various polymer-bound amino ethers (**68a-d**) were generated (*Figure 5*). Screening

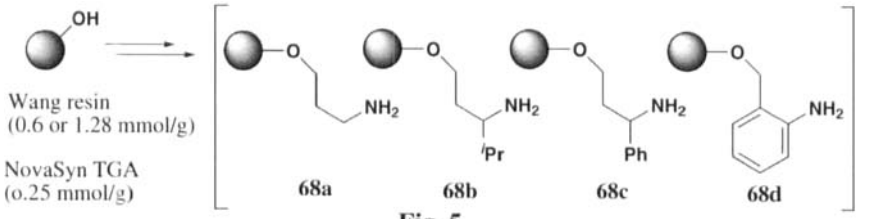
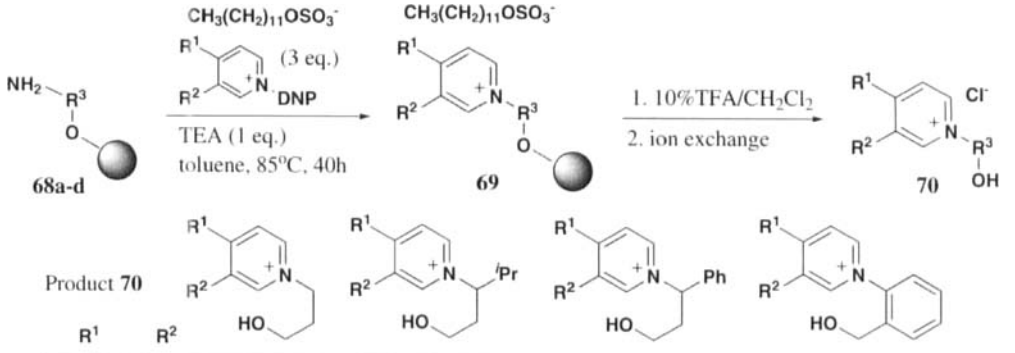


Fig. 5

various conditions led to the optimized protocol for the solid-phase Zincke reaction which requires higher temperature (>80°), longer reaction time (40 h), the dodecyl sulfate anion, and an efficient resin swelling solvent (toluene) instead of *n*-butanol or methanol. In addition, a significant improvement was noticed upon addition of one equivalent of triethylamine to the solid-phase Zincke reaction. Presumably, triethylamine plays the role of a proton transfer medium which facilitated several steps in the solid-phase Zincke reaction. After release from resin and anion exchange from dodecyl sulfate to chloride, the Zincke products, 3-hydroxyalkyl- or 3-hydroxyarylpyridinium salts **70**, (*Scheme 19*) were obtained in good yield and high purity for CFTR screening.



R1	R2				
H	H	51	76	61	89
H	OMe	61	80	81	89
Ph	H	43	74	63	75
-(CH=CH)2-		52	70	74	----

Scheme 19

Another application of the Zincke reaction on solid-phase is the synthesis of vesamicol analogs as inhibitor of vesicular acetylchlorine transporter (VAChT).[55] Previous approaches to vesamicol analogs indicated that (+)-R,R-*trans*-2-(4-phenylpiperidino)cyclohexanol (**71**) was 25-fold more potent than its enantiomer.[56] Benzovesamicol (**72**) exhibited a 40-fold higher affinty for VAChT than **71**.[57] In addition, flexible vesamicol analog **73**, which lacks the cyclohexyl moiety of **71**, is equipotent

with **71** (*Figure 6*).[58] Based on these structural studies, optical active and flexible vesamicol analogs (**77-79**) were designed and synthesized *via* a combinatorial solid-phase method in order to develop

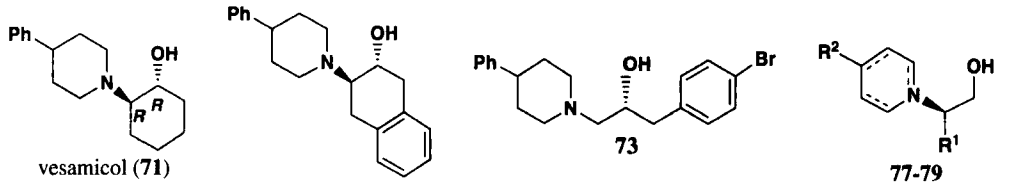
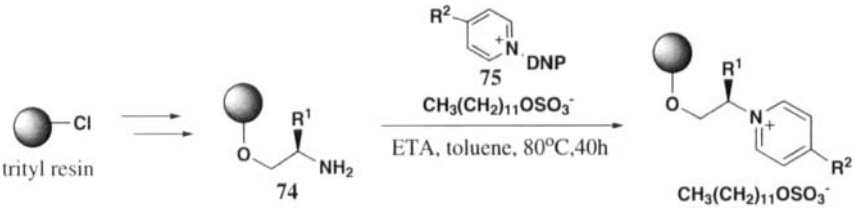


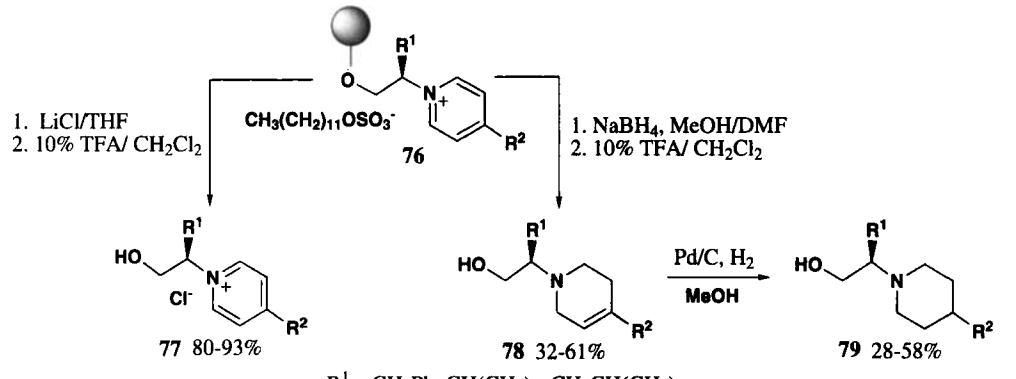
Fig. 6

more potent and selective ligands for VAChT. For this solid-phase synthetic method,[59] the most important step was the Zincke reaction of resin-bound (trityl linker) amino ether **74** with 2,4-dinitrophenylpyridinium salt **75** to deliver polymer-bound stereogenic Zincke product **76** (*Scheme 20*). After anion exchange with lithium chloride, Zincke product **77** could be liberated in high yield from the



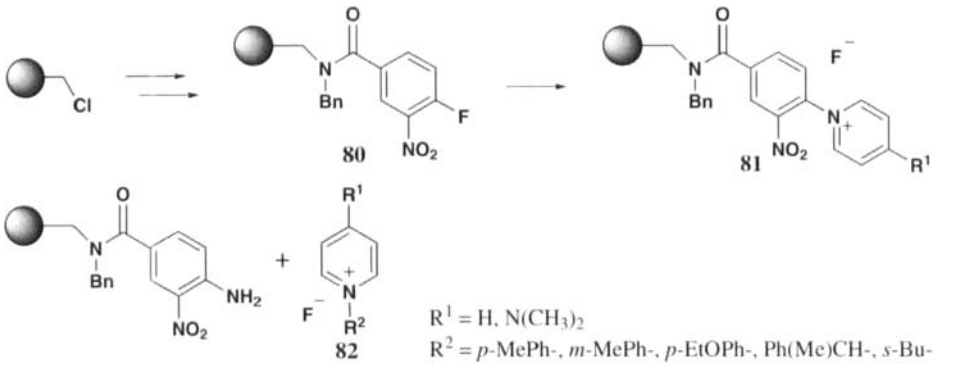
Scheme 20

resin employing TFA. When $NaBH_4$ reduction preceded TFA treatment, tetrahydropyridine derivative **78** could be cleaved from the resin. Subsequent solution-phase reduction (H_2/Pd) of **78** gave substituted piperidines **79** (*Scheme 21*).



Scheme 21

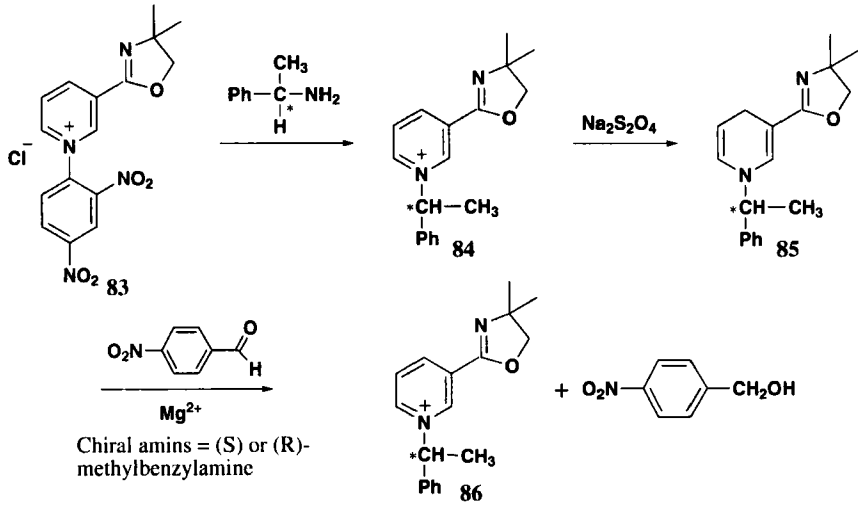
The Zincke reaction can also be employed in a traceless linker SPOS approach.[60] Merrifield resin was subject to *N*-alkylation and amide formation to prepare intermediate resin **80** (*Scheme 22*). The resin-bound Zincke salts **81** were generated by condensing resin **80** with various pyridines in toluene at 80° for 24h. Coupling this resin-bound Zincke salt with anilines in toluene at 80° for 40h, liberated Zincke product **82** from the initial Merrifield resin in 10-20% overall yield without any residual element of linker attached.



Scheme 22

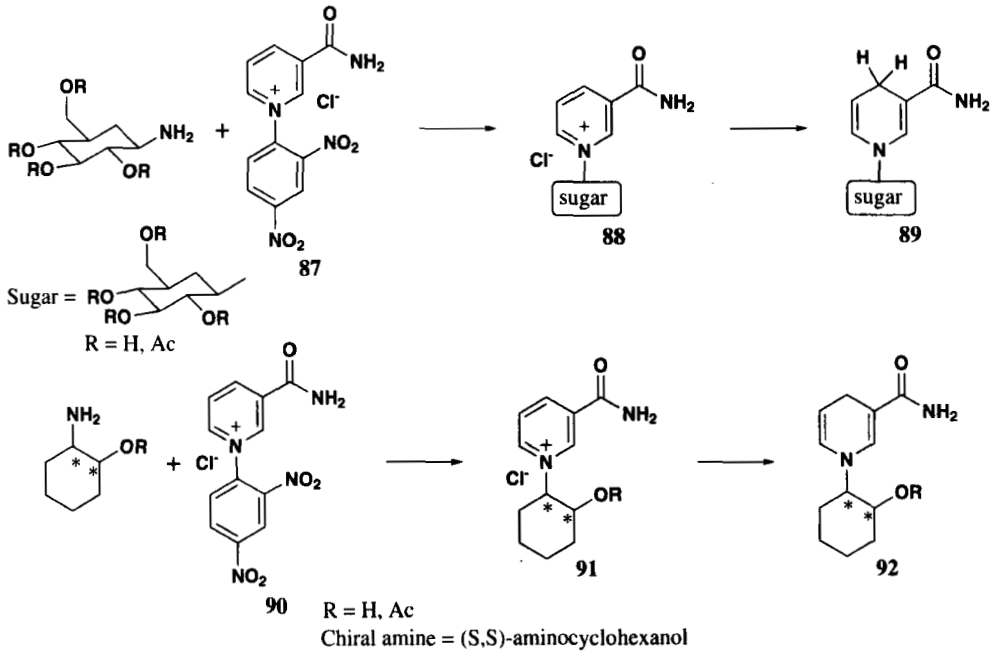
5. Miscellaneous Application

To investigate the reactivity of the dihydropyridine–pyridinium salt redox system, the Zincke reaction was employed to prepare a new NADH model in which a stereogenic moiety is attached to the pyridine nitrogen. This new class of NADH model, *N*-alkyl-3-oxazolyl-1,4-dihydropyridine **85**, was synthesized *via* typical Zincke reaction and then reduced by sodium dithionite (*Scheme 23*).[61] The reactivity of this model was studied by reduction of *p*-nitrobenzaldehyde in the presence of



Scheme 23

magnesium perchlorate to give *p*-nitrobenzyl alcohol in quantitative yield (*Scheme 23*). Likewise, other new asymmetric NADH models including 1,4-dihydronicotinamide sugar pyranosides 1,*N*-(1S,2S)-2-hydroxy- and acetoxycyclohexyl-1,4-dihydronicotinamide **89** and **92** were synthesized *via* Zincke reactions and reduction in basic aqueous sodium dithionite (*Scheme 24*).[62]



Scheme 24

Nicotinamide adenine dinucleotide (NAD) is a biologically important compound incorporating adenine and nicotinamide nucleosides within one molecule. To study the structure-activity relationship in a series of NAD analogs, differently functionalized acyclic linking chains between adenine and nicotinamide moieties were targeted to form "abbreviated" NAD^+ analogs (*Figure 7*).[63-66] Thus,

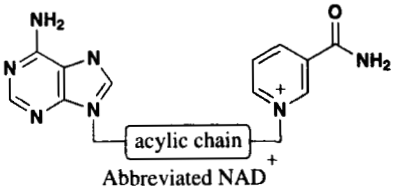
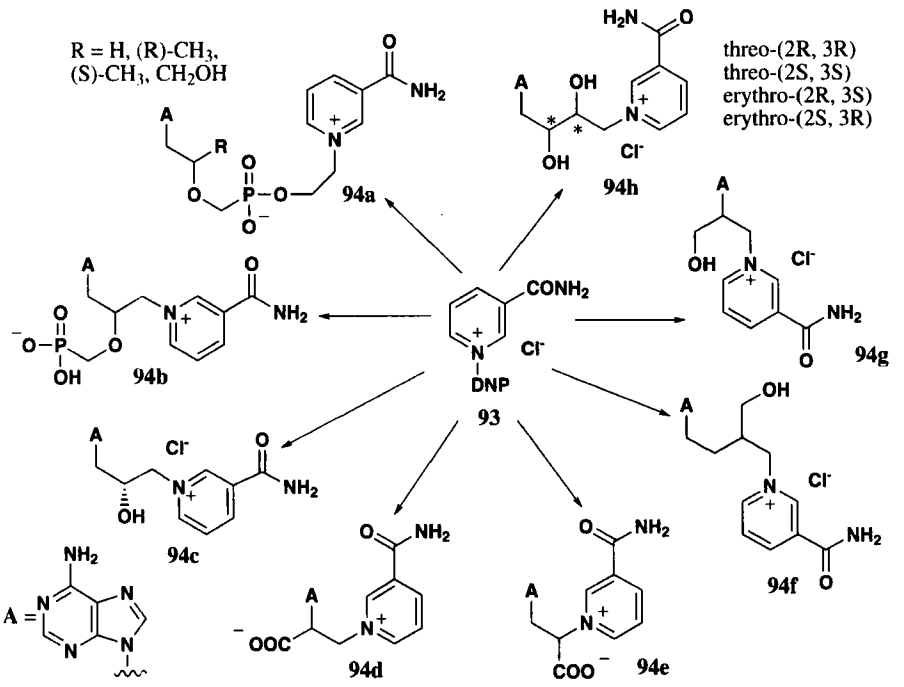


Fig. 7

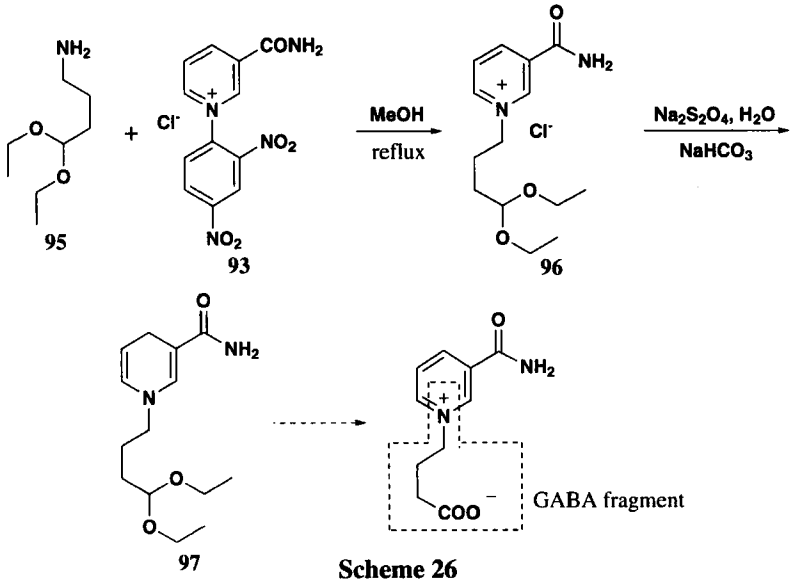
various acyclic amines containing adeninyl moiety were prepared by *N*-alkylation of adenine. These amines were then condensed with 3-carbamoyl-1-(2,4-dinitrophenyl)pyridinium chloride **93** (Zincke salt) in methanol to afford abbreviated NAD^+ analogs **94a-h** (*Scheme 25*).

The Zincke reaction can also be utilized for the synthesis of GABA+-CDS, useful to investigate membrane delivery. The dihydropyridine–pyridinium salt redox system has been extensively



Scheme 25

explored for chemical delivery systems (CDS) in drug design and delivery. To investigate the effect of this redox system in brain delivery of γ-aminobutyric acid (GABA) analogues, the GABA analogues were coupled with nicotinamide *via* the Zincke reaction to form quaternary pyridinium salts.[67] Diethyl acetal **95** was chosen as starting material since it would be slowly hydrolyzed to the aldehyde and then undergo oxidation to the GABA analogue (*Scheme 26*). The acetal pyridinium salt **96** was prepared in



Scheme 26

75% yield by treatment of Zincke salt **93** (3-carbamoyl-1-(2,4-dinitrophenyl)pyridinium chloride) with 4-aminobutyraldehyde diethyl acetal (**95**) in refluxing methanol. After reduction of pyridinium salt **96** in basic aqueous sodium dithionite, the 1,4-dihydropyridine salt **97** (GABA+-CDS) was obtained in 56% yield.

IV. CONCLUSION

This review indicates that Zincke products (*N*-alkyl- or *N*-arylpyridinium salts) are important as target molecules and as intermediates in heterocyclic chemistry and medicinal chemistry. Indeed, the Zincke reaction has evolved from primarily reports of mechanistic studies to the realm of synthetic applications. The most significant advantage of the Zincke reaction is that the resulting pyridinium salts allow the direct attachment of a stereogenic carbon atom to the nitrogen atom of the pyridine ring. As a result, the Zincke reaction has been employed frequently in asymmetric syntheses. In addition, it has recently been applied in solid-phase synthesis which sets the stage for applications in drug discovery and combinatorial chemistry.

REFERENCES

1. D. O'Hagan, *Nat. Prod. Rep.*, **17**, 435 (2000).

2. U. Eisner and J. Kuthan, *Chem. Rev.*, **72**, 1 (1972).

3. D. M. Stout and A. I. Meyers, *Chem. Rev.*, **82**, 223 (1982).

4. W. Sliwa, *Heterocycles*, **43**, 2005 (1996).

5. W. Sliwa, *ibid.*, **29**, 557 (1989).

6. J. Menschutkin, *J. Russ. Phys. Chem. Soc.*, **34**, 411 (1902).

7. A. J. de Gee, W. J. Sep, J. W. Verhoeven, and T. J. de Boer, *J. Chem. Soc., Perkin Trans. 1*, 676 (**1974**).

8. T. Zincke, *Justus Liebigs Ann. Chem.*, **330**, 361 (1903); **333**, 296 (1904); **338**, 107 (1905); **341**, 365 (1905).

9. A. F. Vompe, N. F. Turitsyna, and I. I. Levkoev, *Dokl. Akad. Nauk SSSR* **65**, 839 (1949); *Chem. Abstr.*, **43**, 6626 (1949); A. F. Vompe and N. F. Turitsyna, *Zhur. Obshch, Khim.*, **27**, 3282 (1957); *Chem. Abstr.*, **52**, 9112d (1958).

10. J. Epsztzjn, E. Lunt, and A. R. Katritzky, *Tetrahedron*, **26**, 746 (1970).

11. H. Lettre, W. Haede, and E. Rubhum, *Justus Liebigs Ann. Chem.*, **579**, 123 (1953).

12. F. N. Stepanov, N. A. Aldanova, A. G. Yurchenko, and N. L. Doygan, *Chem. Abstr.*, **60**, 15800e (1964).

13. E. N. Marvell, G. Caple, and I. Shahidi, *ibid.*, **92**, 5646 (1970).

14. N. Ise, T. Okubo, H. Kitano, and S. Kunugi, *ibid.*, **97**, 2882 (1975).

15. S. Kunugi, T. Okubo, and N. Ise, *ibid.*, **98**, 2282 (1976).

16. E. N. Marvell, G. Caple, and I. Shahidi, *Tetrahedron Lett.*, 277 (**1967**).

17. E. N. Marvell, G. Caple, and I. Shahidi, *J. Am. Chem. Soc.*, **92**, 5641 (1970).

18. M. Eda and M. J. Kurth, *J. Chem. Soc., Chem. Commun.*, 723 (**2001**).

19. A. Patchornik and M. A. Kraus, *J. Am. Chem. Soc.*, **92**, 7587 (1970).

20. A. N. Kost, S. P. Gromov, and R. S. Sagituullin, *Tetrahedron*, **37**, 3423 (1981).

21. Y. Genisson, C. Marazano, and B. C. Das, *J. Org. Chem.*, **58**, 2052 (1993).

22. D. Gnecco, C. Marazano, R. G. Enriquez, J. L. Teran, M. del Rayo Sanchez S., and A. Galindo, *Tetrahedron: Asymmetry*, **9**, 2027 (1998).

23. M. Mehmandoust, C. Marazano, and B. C. Das, *J. Chem. Soc., Chem. Commum.*, 1185 (**1989**).

24. Y.-S. Wong, D. Gnecco, C. Marazano, A. Chiaroni, C. Riche, A. Billion, and B. C. Das, *Tetrahedron*, **54**, 9357 (1998).

25. Y. Genisson, C. Marazano, D. Gnecco, M. Mehmandoust, and B. C. Das, *Synlett*, 431 (**1992**).

26. B. Agai and K. Lempert, *Tetrahedron*, **28**, 2069 (1972).

27. D. Barbier, C. Marazano, C. Riche, B. C. Das, and P. Potier, *J. Org. Chem.*, **63**, 1767 (1998).

28. T. H. Zincke and G. Weisspfenning, *Justus Liebigs Ann. Chem.*, **396**, 103 (1913).

29. D. Barbier, C. Marazano, B. C. Das, and P. Potier, *ibid.*, **61**, 9596 (1996).

30. Y. Tamura and N. Tsujimoto, *Chem. Ind.*, 926 (**1970**).

31. Y. Tamura, Y. Miki, T. Honda, and M. Lkeda, *J. Heterocyclic Chem.*, **9**, 865 (1972).

32. Y. Tamura, N. Tsujimoto, and M. Mano, *Chem. Pharm. Bull.*, **19**, 130 (1971).

33. K. N. Rao, K. K. Redda, F. Y. Onayemi, H. Melles, and J. Choi, *J. Heterocyclic Chem.*, **32**, 307 (1995).

34. D. S. Fries, J. de Vries, B. Hazelhoff, and A. S. Horn, *J. Med. Chem.*, **29**, 424 (1986).

35. K. N. Rao, K. K. Redda, and F. Y. Onayemi, *J. Heterocyclic Chem.*, **32**, 307 (1995).

36. T. Wilson, U. Onubogu, R. Kode, and K. Redda, *Drugs Exptl. Clin. Res.*, **24**, 165 (1998)

37. E. E. Knaus and K. Redda, *J. Heterocyclic Chem.*, **13**, 1237 (1976).

38. J. M. Yeung, L. A. Corleto, and E. E. Knaus, *J. Med. Chem.*, **25**, 191 (1982).

39. K. K. Redda, H. Melles, and K. N. Roa, *J. Heterocyclic Chem.*, **27**, 1041 (1990).

40. J. W. Daly, C. W. Myers, and N. Whittaker, *Toxicon*, **25**, 1023 (1987).

41. T. Tokuyama, N. Nishimori, A. Shimada, M. W. Edwards, and J. W. Daly, *Tetrahedron*, **43**, 643 (1987).

42. D. Gnecco, C. Marazano, and B. C. Das, *J. Chem. Soc., Chem. Commun.*, 625 (**1991**).

43. Y.-S. Wong, C. Marazano, D. Gnecco, and B. C. Das, *Tetrahedron Lett.*, **35**, 707 (1994).

44. Y. Genisson, M. Mehmandoust, C. Marazano, and B. C. Das, *Heterocycles*, **39**, 811 (1994).

45. Y.-S. Wong, C. Marazano, D. Gnecco, Y. Genisson, A. Chiaroni, and B. C. Das, *J. Org. Chem.*, **62**, 729 (1997).

46. E. Magnier and Y. Langlois, *Tetrahedron Lett.*, **39**, 837 (1998).

47. D. Urban, E. Duval, and Y. Langlois, *ibid.*, **41**, 9251(2000).

48. A. Kaiser, X. Billot, A. Gateau-Olesker, C. Marazano, and B. C. Das, *J. Am. Chem. Soc.*, **120**, 8026 (1998).

49. D. Gnecco, J. Juarez, A. Galindo, C. Marazano, and R. G. Enriquez, *Synth. Commun.*, **29**, 281(1999).

50. R. E. Sammelson and M. J. Kurth, *Chem. Rev.*, **101**, 137 (2001).

51. B. A. Lorsbach and M. J. Kurth, *ibid.*, **99**, 1549 (1999).

52. F. S. Collins, *Science*, **256**, 774 (1992).

53. F. Becq, Y. Mettey, M. A. Gray, L. J. Galietta, R. L. Dormer, M. Merten, T. Metaye, V. Chappe, C. marvingt-Mounir, M. A. Zegarra-McPherson, C. Rogier, M. Joffre, B. E. Argetn, D. Sarrouilhe, W. Kammouni, C. Figarella, B. Verier, M. Cola, and J.-M. Verfond, *J. Biol. Chem.*, **39**, 27415 (1999).

54. M. Eda, M. J. Kurth, and M. H. Nantz, *J. Org. Chem.*, **65**, 5131 (2000).

55. I. G. Marshall and S. M. Parsons, *Trends Neurosci.*, **10**, 174 (1987).

56. G. A. Rogers, S. M. Parsons, D. C. Anderson, L. M. Nilsson, B. A. Bahr, W. D. Kornreich, R. Kaufman, R. S. Jacobs, and B. Kirtman, *J. Med. Chem.*, **32**, 1217 (1989).

57. G. A. Rogers, W. D. Kornreich, K. Hand, and S. M. Parsons, *Mol. Pharmacol.*, **44**, 633 (1993).

58. S. M. N. Efange, R. H. Michelson, A. K. Dutta, and S. M. Parsons, *J. Med. Chem.*, **34**, 2638 (1991).

59. M. Eda and M. J. Kurth, *Tetrahedron Lett.*, **42**, 2063 (2001).

60. W.-C. Cheng and M. J. Kurth, Unpublished data.

61. P. Binay, G. Dupas, J. Bourguignon, and G. Queguiner, *Can. J. Chem.*, **65**, 648 (1987).

62. N. Baba, T. Makino, J. Oda, and Y. Inouye, *ibid.*, **58**, 387 (1980).

63. D. Hockova, H. Votavova, and A. Holy, *Tetrahedron: Asymmetry*, **6**, 2375 (1995).

64. K. Juricova, S. Smrckova, and A. Holy, *Coll. Czech. Chem. Commun.*, **60**, 237 (1995).

65. D. Hockova, M. Masojidkova, and A. Holy, *ibid.*, **61**, 1538 (1996).

66. D. Hockova and A. Holy, *ibid.*, **62**, 948 (1997).

67. P. A. Woodard, D. Window, M. E. Brewster, K. S. Estes, and N. Bodor, *Drug Design and Delivery*, **6**, 15 (1990).

(Received July 9, 2001; in final form April 16, 2002)