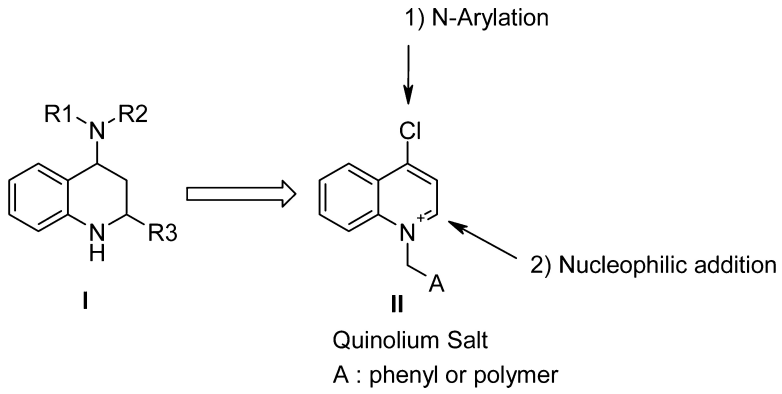
JOURNAL OF combinatorial CHEMISTRY

Article

Use of Quinolinium Salts in Parallel Synthesis for the Preparation of 4-Amino-2-alkyl-1,2,3,4-tetrahydroquinoline

Marc Bazin, and Cyrille Kuhn

J. Comb. Chem., **2005**, 7 (2), 302-308• DOI: 10.1021/cc0498534 • Publication Date (Web): 14 January 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 1 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Journal of Combinatorial Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Use of Quinolinium Salts in Parallel Synthesis for the Preparation of 4-Amino-2-alkyl-1,2,3,4-tetrahydroquinoline

Marc Bazin and Cyrille Kuhn*

Department of Chemistry, Pfizer Global Research & Development, Research Technology Center, 620 Memorial Drive, Cambridge, Massachusetts 02139

Received September 15, 2004

Compounds of pharmacological interest containing a 4-amino-2-alkyl-1,2,3,4-tetrahydroquinoline core structure were prepared starting from 4-chloroquinoline. This has been executed both in solution with a 1-benzyl-4-chloroquinolinium salt and on a solid support with a 1-(4-benzyloxybenzyl-PS)-4-chloroquinolinium resin as key intermediates. Diversification of such intermediates was accomplished through N-arylation of position 4 and subsequent nucleophilic addition of Grignard reagents of position 2 to deliver the expected 4-amino-2-alkyl-1,2,3,4-tetrahydroquinolines in 20−60% yields. The methods described within clearly demonstrate that the quinolinium salts are very efficient intermediates for parallel synthesis.

Introduction

4-Amino-2-alkyl-1,2,3,4-tetrahydroquinoline **I** is a particularly interesting core structure due to its growing use in compounds of therapeutic importance. Compounds of such structure have shown various pharmacological activities such as CETP inhibition,[1] CRTH2 antagonism,[2] Ecdysone receptor antagonism,[3] β-amyloid precursor protein secretion promotion,[4] STAT 6 modulation,[5] androgen agonism and antagonism,[6] apolipoprotein A−I formation promotion,[7] and NMDA receptor antagonism.[8] This core structure is also present in natural products such as Martinellic acid, a potent bradykinin antagonist.[9] Synthesis of this natural product has extensively been described in the past few years.[10]

The main synthetic method to prepare 4-aminotetrahydroquinoline is based on a (4 + 2) cycloaddition generally known as the imino-Diels−Alder reaction (IDA), between an *N*-arylimine and a dienophile that is promoted by Lewis acids such as Rh(I),[11] Ti(III),[12] BF_3-Et_2O,[13] $Yb(Otf)_3$,[14] $Dy(Otf)_3$,[15] and InCl.[16] An efficient version of this reaction has also been described using benzotriazoles in solution[17] or on a polymer support[18] to promote condensation of aldehydes and aromatic amines.

Another method of synthesis has been described involving an intramolecular cyclization of an *N*-aryl-β-amino ester to give the corresponding 4-oxoquinoline, which can be converted to a 4-amino-2-alkyl-1,2,3,4-tetrahydroquinoline by reductive amination.[19] This same type of reaction has been applied in one step starting from an *N*-aryl-β-amino imide.[20]

This type of structure can also be obtained by a Reissert reaction from 4-aminoquinoline followed by the reduction of the resulting enamine.[21]

In this paper we describe an efficient method to prepare 4-amino-2-alkyl-1,2,3,4-tetrahydroquinoline **I** (Figure 1) from the 4-chloroquinoline via the quinolinium salt **II** as its activated form.[22] The interest in this unique synthesis consists of realizing successively an N-arylation[23] in position 4 and a nucleophilic addition of a Grignard reagent in position 2 of an alkylquinolinium salt.[24] Indeed, in contrast to other known methods of activation of quinoline, such as carbamoylation[25] or acylation,[26] these species are stable and allow this sequence of reactions. Two different methodologies have been studied in parallel using both benzyl bromide and its polymer-supported version to make the corresponding quinolinium salt (Figure 1). Benefits and disadvantages of both methods, solution synthesis and solid-phase synthesis, will be discussed.

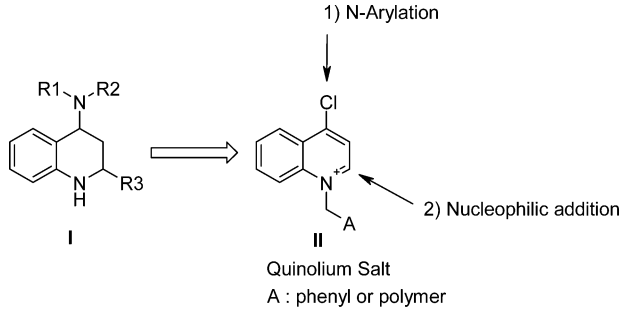


Figure 1. Retrosynthetic pathway.

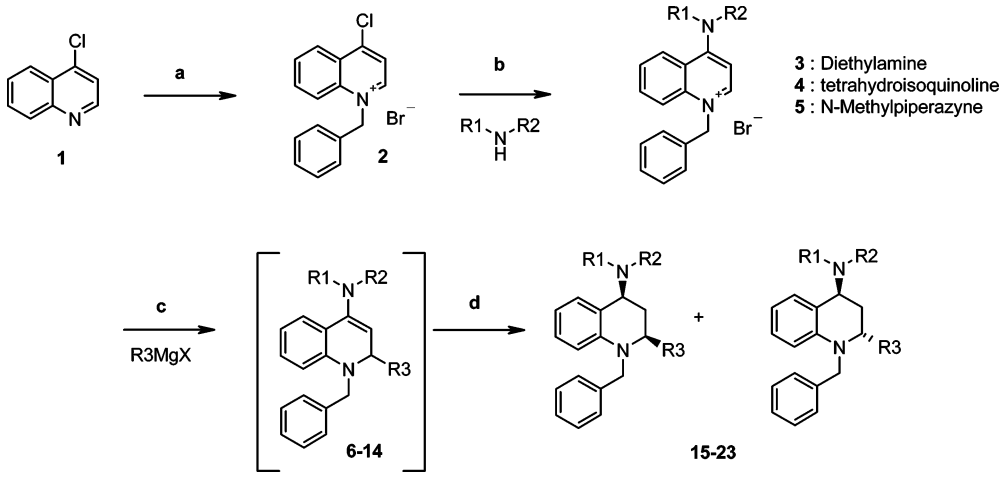
Results and Discussion

Solution Synthesis. The general synthesis of 4-amino-2-alkyl-1,2,3,4-tetrahydroquinoline is shown in Scheme 1. 4-Chloroquinoline (**1**) was alkylated with benzyl bromide at 80 °C in dimethylformamide overnight. The resulting benzyl-4-chloroquinolinium salt **2** was obtained in 68% yield by simple filtration to give the expected compound in its crystalline form, stable at room temperature. This compound was then treated with diethylamine, tetrahydroisoquinoline, or methylpiperazine in suspension in dimethylformamide at 80 °C to give the corresponding 4-amino-*N*-benzylquinolinium salts **3**−**5**. These compounds were obtained in very good yields again by simple filtration (see Table 1).

* To whom correspondence should be addressed. E-mail: Cyrille_F_Kuhn@groton.pfizer.com. Phone: (617) 551-3014.

10.1021/cc0498534 CCC: $30.25
Published on Web 01/14/2005

Scheme 1. Solution Synthesis of 4-Amino-2-alkyl-1,2,3,4-tetrahydroquinoline[a]



[a] Reagents and conditions: (a) BzBr, DMF, 80 °C; (b) amine, DMF, 100 °C; (c) Grignard reagent, THF, room temperature; (d) $NaBH(OAc)_3$, DMF, AcOH, 0 °C.

Table 1. N-Arylation of the Benzyl-4-chloroquinolinium Salt **2**

compd no.	amine	solvent	temp, °C	yield, %
3	diethylamine	DMF	80	95
4	tetrahydroisoquinoline	DMF	80	98
5	methylpiperazine	DMF	80	80

The reaction of nucleophilic addition in position 2 of 1-benzyl-4-*N*,*N*-diethylaminoquinolinium salt **3** was performed by treating this compound with methylmagnesium bromide in tetrahydrofuran at room temperature. Completion of the reaction requires 2 equiv of Grignard reagent and was achieved when the reaction mixture became homogeneous. After hydrolysis, the expected enamine **6** was isolated in quantitative yield and directly used in the next step.

The reduction of 1-benzyl-4-diethylamino-2-methyl-1,2-dihydroquinoline (**6**) was carried out using sodium triacetoxyborohydride in dimethylformamide in the presence of acetic acid at room temperature, to give **15** as a 65/35 mixture of cis/trans isomers. When this experiment is run at 0 °C, the cis isomer is obtained exclusively.[27]

The conditions of these reactions being optimized, we then applied them in a one-pot protocol to allow parallel synthesis. To validate this process, we made a small array of 4-amino-2-alkyl-1,2,3,4-tetrahydroquinoline starting from the 4-amino-1-benzylquinolinium salts **3**−**5**. These compounds in tetrahydrofuran suspension were treated by 2 equiv of alkylmagnesium chloride or bromide at room temperature and then hydrolyzed by methanol. The resulting intermediate enamines **6**−**14** were directly reduced by addition of 4 equiv of triacetoxyborohydride and acetic acid at 0 °C. HPLC analyses of the mixtures showed that all reactions went to completion. Using this technique, cis/trans ratios were determined (see Table 2). Despite the very good stereoselectivity obtained for compound **15**, most of the other examples gave mixtures of both cis and trans isomers. The purities of the expected cis/trans compounds together were greater than 85% by UV detection at 215 nm. After aqueous workup these mixtures were purified by flash chromatography to yield *cis*- and *trans*-4-amino-2-alkyl-1,2,3,4-tetrahydroquinolines **15**−**23**. Relative configurations of these compounds were determined by NMR spectrometry.[28] All the expected compounds were obtained in 20−60% overall yield for the two steps.

Table 2. Yields and cis/trans Ratios for the One-Pot Procedure

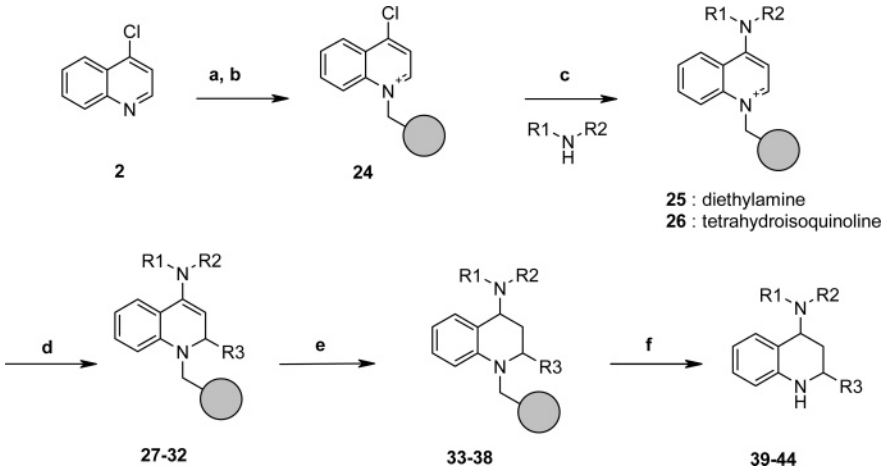
compd no.	R1−NH−R2	R3	cis/trans ratio	global yield, %
15	diethylamine	Me	100/0	30
16	diethylamine	Et	20/80	31
17	diethylamine	^{i}Pr	20/80	50
18	tetrahydroisoquinoline	Me	80/20	35
19	tetrahydroisoquinoline	Et	80/20	37
20	tetrahydroisoquinoline	^{i}Pr	40/60	20
21	methylpiperazine	Me	67/33	62
22	methylpiperazine	Et	74/26	31
23	methylpiperazine	^{i}Pr	73/26	27

We have developed a facile synthetic route to 4-amino-2-alkyl-1,2,3,4-tetrahydroquinolines from 4-chloroquinoline. Because all of the intermediates are isolated by simple filtration, only a single flash chromatography is needed to obtain the final compounds as pure diastereoisomers. This efficient process is highly amenable to parallel synthesis.

Solid-Phase Synthesis. A method for forming the quinolinium salt on a solid support and subsequent conversion to the 4-amino-2-alkyl-1,2,3,4-tetrahydroquinoline has also been developed (see Scheme 2).

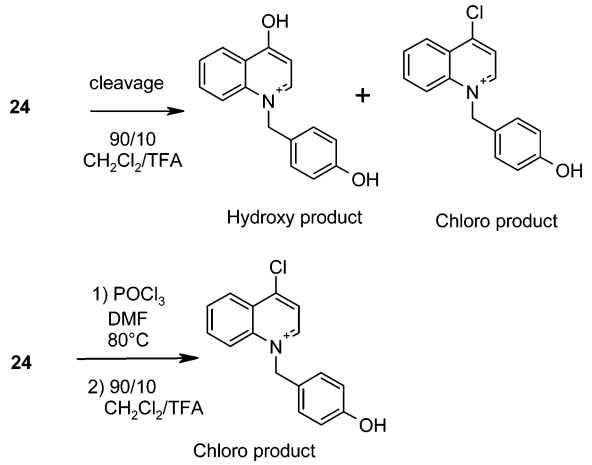
Freshly prepared bromo-Wang resin[29] was treated at 80 °C overnight with an excess of 4-chloroquinoline (**1**) as a suspension in dimethylformamide. The resulting resin was filtered and washed with methanol and dichloromethane and dried in an oven at 50 °C. An analysis of the resulting cleavage solution from treatment with 90/10 CH_2Cl_2/TFA solution showed the presence of a mixture of 4-chloroquinolinium salt and 4-hydroxyquinolinium salt bearing a methylenephenoxy fragment resulting from the cleavage of the Wang linker, which confirmed the anchorage of the quinoline on the resin (see Scheme 3). Consequently, resin **24** treated with $POCl_3$ in dimethylformamide allowed us to obtain only the bound resin 4-chloroquinolinium salt. An analysis of the solution cleavage confirmed the sole presence of 4-chloro-

Scheme 2. Solid-Phase Synthesis of 4-Amino-2-alkyl-1,2,3,4-tetrahydroquinoline[a]



[a] Reagents and conditions: (a) bromo-Wang resin, DMF, 80 °C, overnight; (b) $POCl_3$, DMF, 80 °C, 1 h; (c) amine, DMF, 80 °C, 2 h; (d) 2 equiv of Grignard reagent, THF, room temperature; (e) $NaBH(OAc)_3$, DMF, AcOH, room temperature; (f) 90/10 CH_2Cl_2/TFA.

Scheme 3. Cleavage Procedure and Regeneration of Resin **24**



quinolinium. Also on the basis of the remaining 4-chloroquinoline from the first step, the loading can be evaluated at 0.5 mmol/g.

Resin **24** was then treated by diethylamine or tetrahydroisoquinoline in dimethylformamide at 80 °C to obtain the corresponding resins **25** and **26**. For this reaction, complete conversion was obtained on the basis of the quantification of the cleavage product. Both resins were then treated with three different Grignard reagents (methylmagnesium bromide, ethylmagnesium bromide, and isopropylmagnesium chloride) in tetrahydrofuran at room temperature. During this reaction, a swelling of the resins was observed. This phenomenon can be explained by a loss of the positive charge bound to resins **25** and **26**. Samples of resins **27**−**32** were cleaved under acidic conditions (see Scheme 4).

In each case, LC/MS analysis indicated that the expected enamine **B** was the minor product and instead the major product was ketone **A** (see Table 3). Apparently, enamine **B** is readily hydrolyzed under the acidic cleavage conditions. Also, the absence of starting material demonstrates the reaction was completed.

These resulting resins **27**−**32** were reduced by successive addition of sodium triacetoxyborohydride and acetic acid. The suspensions were stirred at room temperature overnight

Scheme 4. Cleavage of Enamine Resins **27**−**32**

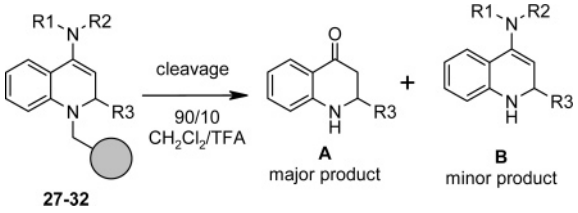


Table 3. LC/MS Analyses of the Cleavage Solution of Resins **27**−**32**

compd no.	Grignard reagent	MS^+ of A, *m/z*	t_r of A, min	MS^+ of B, *m/z*	t_r of B, min
27	MeMgCl	162	6.1	217	3.4
28	EtMgBr	176	7.1	231	4.3
29	^{i}PrMgCl	190	7.9	245	4.3
30	MeMgCl	162	6.1	277	5.8
31	EtMgBr	176	7.1	291	6.3
32	^{i}PrMgCl	190	7.9	305	7.1

Table 4. LC/MS Analyses of the Final Compounds **39**−**44**

compd no.	R1−NH−R2	R3	molar mass, g/mol	MS^+, *m/z*	global yield, %	global purity (isomers 1 + 2), %
39	tetrahydroisoquinoline	Me	278	279	12	55
40	tetrahydroisoquinoline	Et	292	293	20	66
41	tetrahydroisoquinoline	^{i}Pr	306			
42	diethylamine	Me	218	219	8	45
43	diethylamine	Et	232	233	6	68
44	diethylamine	^{i}Pr	246	247	5	56

and then washed successively by methanol and methylene chloride to obtain the desired tetrahydroquinoline-bound resins **33**−**38**. Cleavage of these resins under acidic conditions gave the expected final products **39**−**44** as diastereoisomeric mixtures (see the results in Table 4) with medium purity levels (45−68%). This can be explained by the presence of starting secondary amine (tetrahydroquinoline or diethylamine) obtained by degradation of the expected final products in the acidic conditions of the final cleavage step. However, apart from 2-isopropyl-4-(*N*-tetrahydroisoquinolin-1-yl)-1,2,3,4-tetrahydroquinoline (**41**), which wasnot observed, all the compounds were obtained in yields of 5−20% over four steps.

Despite the low yields obtained, we have demonstrated that quinolines can be activated as quinolinium salts using a bromo-Wang resin as an alkylating agent. Supported quinolinium salts can then be diversified in positions 2 and 4 to obtain 4-amino-2-alkyl-1,2,3,4-tetrahydroquinolines. Further studies to define the scope of this reaction pathway and to optimize the linking resin to improve the cleavage conditions are ongoing.

Conclusion

To summarize, we have developed a novel synthesis of 4-amino-2-alkyl-1,2,3,4-tetrahydroquinolines from a quinolinium salt. In the solution phase, subsequent reactions of N-arylation in position 4 and nucleophilic addition in position 2 on 4-chloro-*N*-benzylquinolinium salt delivered the desired products in 20−60% yield. This sequence of reactions has also been performed on a solid support with the 1-(4-benzyloxybenzyl-PS)-4-chloroquinolinium resin. Even though the solid supported synthesis gave a low yield, the use of alkyl salts of pyridinium derivatives, in a general manner, is a very powerful method for parallel synthesis.

Experimental Section

A parallel procedure has been realized with a Mettler "Miniblock" with 6 and 12 positions. Materials were from commercial suppliers and were used as received. Solvents used in the synthesis were reagent grade. ^{1}H NMR spectra were measured on DPX (Bruker) 400 MHz and AVANCE (Bruker) 500 MHz spectrometers. Chemical shifts are given in δ values (ppm) using tetramethylsilane as the internal standard. HPLC analyses have been realized on a DIONEX system UV diode array detector: UVD 340S.

HPLC Methods Used. Method 1: eluant A, water, 0.1% formic acid; eluant B, acetonitrile, 0.1% formic acid; debit, 0.25 mL/min; gradient, 5−95, 13 min; column, Kromasil C18, 2.1 × 50 mm. Method 2: eluant A, water, 0.1% TFA; eluant B, acetonitrile/2-propanol (1/1), 0.1% TFA; debit, 0.25 mL/min; gradient, 85−10, 13 min; column, Hypercarb, 2.1 × 50 mm. Method 3: eluant A, water, 0.1% formic acid; eluant B, acetonitrile, 0.1% formic acid; debit, 0.25 mL/min; gradient, 25−50, 13 min; column, X Terra, 2.1 × 50 mm. Method 4: eluant A, water, 0.1% formic acid; eluant B, acetonitrile, 0.1% formic acid; debit, 0.25 mL/min; gradient, 5−95, 13 min; column: X Terra, 2.1 × 50 mm. Method 5: eluant A, water 0.1%, formic acid; eluant B, acetonitrile, 0.1% formic acid; debit, 0.25 mL/min; gradient, isocratic at 25, 18 min; column, X Terra, 2.1 × 50 mm.

The LC/MS instrument used was a Waters-Micromass electrospray (+ and −) UV detector: 214 nm mobile phase, H_2O/CH_3CN (0.1% HCO_2H); debit, 0.25 mL/min; gradient, 5−95, 8 min; column type, Kromasil C18.

1-Benzyl-4-chloroquinolinium Bromide (2). Benzyl bromide (14.5 mL, 4 equiv) was added to a solution of 4-chloroquinoline (5 g, 30.56 mmol) in DMF (300 mL), and then the resulting solution was heated at 80 °C. After one night, solvent was removed under vacuum, and then the crude was crystallized in CH_3CN. After filtration, the solid was dried under high vacuum to obtain compound **18** (6.9 g, 20.6 mmol). Yield: 68%. ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) 6.35 (s, 2H), 7.35 (m, 5H), 8.1 (t, 1H), 8.25 (t, 1H), 8.6 (m, 3H), 9.8 (d, 1H).

General Synthesis of 1-Benzyl-4-aminoquinolinium Salts. A suspension of **2** (1 g, 3 mmol) and an appropriate amine (2 equiv) in DMF (30 mL) was stirred at 100 °C for 1−5 h and then filtered at room temperature. The product was crystallized in CH_3CN in the presence of Et_3N to obtain compounds **3**−**5**. The results are given in the following paragraphs.

1-Benzyl-4-(*N*,*N*-diethylamino)quinolinium Salt 3. Yield: 83%. ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) 8.8 (d, 1H), 8.2 (d, 1H), 8,0 (d, 1H), 7.9 (t, 1H), 7.65 (t, 1H), 7.4−7.25 (m, 5H), 7.15 (d, 1H), 3.8 (q, 4H), 1.4 (t, 6H). HPLC method 1: t_r = 6.7 min. UV: λ_{max} 222, 251, 360 nm. ES LC/MS: *m*/*z* (M^+) 291.

1-Benzyl-4-(*N*-tetrahydroisoquinolin-1-yl)quinolinium Salt 4. Yield: 95%. ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) 8.95 (d, 1H), 8.4 (d, 1H), 8.05 (d, 1H), 7.95 (t, 1H), 7.7 (t, 1H), 7.4−7.2 (m, 10H), 5.9 (s, 2H), 5.1 (s, 2H), 4.1 (t, 2H), 3.2 (t, 2H). HPLC method 1: t_r = 7.8 min; UV: λ_{max} 222, 244, 362 nm. ES LC/MS: *m*/*z* (M^+) 351.

1-Benzyl-4-(*N*-methylpiperaz-4-yl)quinolinium Salt 5. Yield: 83%. ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) 9.05 (d, 1H), 8.2 (d, 1H), 8.1 (d, 1H), 8.0 (t, 1H), 7.7 (t, 1H), 7.45−7.3 (m, 6H), 6.0 (s, 2H), 3.9 (m, 4H), 2.6 (m, 4H), 2.3 (s, 3H). HPLC method 1: t_r = 3.3 min. UV: λ_{max} 222, 240, 355 nm. ES LC/MS: *m*/*z* (M^+) 318.

General Procedure of One-Pot Nuclephilic Addition−Reduction. An appropriate Grignard reagent (3 equiv) was added to a suspension of a 1-benzyl-4-*N*,*N*-dialkylquinolinium salt (1 mmol) in THF (10 mL) at room temperature. After 1 h, the mixture was hydrolyzed by 2.5 mL of MeOH at 0 °C. A sample was analyzed by NMR. $NaBH(OAc)_3$ (4 equiv) and then 1 mL of acetic acid were added to the solution at 0 °C. $NaBH(OAc)_3$ (4 equiv) was added again 1 h later. After 1 h, 1.5 mL of concentrated NaOH, 10 mL of saturated $NaHCO_3$, and then 50 mL of water were added. The resulting solution was extracted two times by 50 mL of AcOEt. The organic layer was dried over Na_2SO_4 and then evaporated under vacuum to an oil. The crude was purified by chromatography on silica gel with 90/10 cyclohexane/AcOEt as eluant.

Results. (1) Grignard Reagent MeMgBr/THF (3 M) on Compound 3. Intermediate Compound 1-Benzyl-4-(*N*,*N*-diethylamino)-2-methyl-1,2-dihydroquinoline (6). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) 7.35−7.2 (m, 6H), 6.9 (m, 1H), 6.6 (t, 1H), 6.4 (d, 1H), 5.15 (d, 1H), 4.4 (dd, 2H), 4.0 (m, 1H), 2.9 (q, 4H), 1.0 (m, 9H). HPLC method 1: t_r = 6.9 min. Global yield: 30%. cis/trans ratio: 99/1.

***cis*-1-Benzyl-4-(*N*,*N*-diethylamino)-2-methylquinoline (*cis*-15).** ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.55 (d, 1H), 7.25 (m, 4H), 7,15 (m, 1H), 6,9 (t, 1H), 6.6 (t, 1H), 6.35 (d, 1H), 4.35 (dd, 2H), 4.05 (dd, J = 3.8 and 12 Hz, 1H), 3.45 (m, 1H), 2,6 (m, 2H), 2,35 (m, 2H), 2,0 (dt, J = 12.6 and 3.8 Hz, 1H), 1,7 (q, J = 12 Hz, 1H), 1,1 (d, 3H), 1,0 (t, 6H). HPLC method 4: t_r = 7.6 min. UV: λ_{max} 208, 256, 314 nm.

(2) Grignard Reagent EtMgBr/THF (1 M) on Compound 3. Intermediate Compound 1-Benzyl-4-(*N*,*N*-di-

ethylamino)-2-ethyl-1,2-dihydroquinoline (7). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) 7.4−7.2 (m, 6H), 6.95 (t, 1H), 6.6 (t, 1H), 6.45 (d, 1H), 5.15 (d, 1H), 4.45 (dd, 2H), 3.8 (m, 1H), 2.95 (m, 4H), 1.55 (m, 2H), 1.05 (t, 6H), 0.8 (t, 3H). HPLC method 1: t_r = 7.9 min. Global yield: 31%. cis/trans ratio: 20/80.

***trans*-1-Benzyl-4-(*N*,*N*-diethylamino)-2-ethylquinoline (*trans*-16).** ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.6 (d, 1H), 7.3−7.2 (m, 5H), 6.95 (t, 1H), 6.6 (t, 1H), 6.35 (d, 1H), 4.5 (dd, 2H), 4.05 (dd, J = 12 and 4.5 Hz, 1H), 3.35 (m, 1H), 2.65 (m, 2H), 2.4 (m, 2H), 2.05 (dt, 1H), 1.8 (td, J = 12.3 and 4.7 Hz, 1H), 1.7 (m, 1H), 1.5 (m, 1H), 1.1 (t, 6H), 0.9 (t, 3H). HPLC method 4: t_r = 7.6 min. UV: λ_{max} 213, 259, 318 nm.

(3) Grignard Reagent ^{i}PrMgCl/THF (2 M) on Compound 3. Intermediate Compound 1-Benzyl-4-(*N*,*N*-diethylamino)-2-isopropyl-1,2-dihydroquinoline (8). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) 7.3−7.1 (m, 6H), 6.85 (t, 1H), 6.5 (t, 1H), 6.4 (d, 1H), 5.0 (d, 1H), 4.45 (dd, 2H), 3.7 (m, 1H), 2.85 (m, 4H), 1.85 (m, 1H), 1.0 (t, 6H), 0.7 (dd, 6H). HPLC method 1: t_r = 8.4 min. Global yield: 50%. cis/trans ratio: 20/80.

***trans*-1-Benzyl-4-(*N*,*N*-diethylamino)-2-isopropylquinoline (*trans*-17).** ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.55 (d, 1H), 7.2−7.1 (m, 5H), 6.85 (t, 1H), 6.55 (t, 1H), 6.4 (d, 1H), 4.5 (dd, 2H), 3.95 (dd, J = 11.7 and 5.4 Hz, 1H), 3.0 (m, 1H), 2.5 (m, 2H), 2.35 (m, 2H), 2.0 (dt, 1H), 1.85 (m, 1H), 1.7 (td, J = 12.3 and 4.4 Hz, 1H), 1.0 (t, 6H), 0.9 (d, 3H), 0.8 (d, 3H). HPLC method 4: t_r = 8.0 min. UV: λ_{max} 213, 260, 318 nm.

(4) Grignard Reagent MeMgBr/THF (3 M) on Compound 4. Intermediate Compound 1-Benzyl-4-(*N*-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-methyl-1,2-dihydroquinoline (9). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) 7.4−7.1 (m, 10H), 7.0 (m, 1H), 6.65 (t, 1H), 6.55 (d, 1H), 5.25 (d, 1H), 4.4 (dd, 2H), 4.1 (d, 1H), 3.85 (d, 1H), 3.6 (m, 1H), 3.2 (m, 1H), 3.0 (m, 1H), 2.9 (m, 2H), 1.0 (d, 3H). HPLC method 1: t_r = 9.2 min. Global yield: 35%. cis/trans ratio: 80/20.

***cis*-1-Benzyl-4-(*N*-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-methyltetrahydroquinoline (*cis*-18).** ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.6 (d, 1H), 7.35 (m, 4H), 7.25 (m, 1H), 7.15 (m, 3H), 7.1 (d, 1H), 7.05 (t, 1H), 6.7 (t, 1H), 6.55 (d, 1H), 4.55 (dd, 2H), 4.25 (dd, J = 3.8 and 11.7 Hz, 1H), 3.9 (dd, 2H), 3.6 (m, 1H), 3.05 (m, 2H), 2.95 (m, 1H), 2.7 (m, 1H), 2.5 (dt, J = 12.6 and 3.8 Hz, 1H), 1.95 (q, J = 12 Hz, 1H), 1.3 (d, 3H). HPLC method 1: t_r = 7.7 min. UV: λ_{max} 212, 259, 317 nm.

(5) Grignard Reagent EtMgBr/THF (1 M) on Compound 4. Intermediate Compound 1-Benzyl-4-(*N*-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-ethyl-1,2-dihydroquinoline (10). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) 7.4−7.0 (m, 11H), 6.65 (t, 1H), 6.55 (d, 1H), 5.25 (d, 1H), 4.4 (dd, 2H), 4.15 (d, 1H), 3.85 (d, 1H), 3.7 (m, 1H), 3.3 (m, 1H), 3.0 (m, 1H), 2.9 (m, 2H), 1.5 (m, 2H), 0.75 (t, 3H). HPLC method 1: t_r = 9.4 min. Global yield: 37%; cis/trans ratio: 80/20.

***cis*-1-Benzyl-4-(*N*-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-ethylquinoline (*cis*-19).** ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.55 (d, 1H), 7.3 (m, 4H), 7.25 (m, 1H), 7.15 (m, 3H), 7.05 (d, 1H), 7.0 (t, 1H), 6.65 (t, 1H), 6.5 (d, 1H), 4.5 (dd, 2H), 4.1 (dd, J = 2.8 and 11.4 Hz, 1H), 3.9 (dd, 2H), 3.3 (m, 1H), 3.05 (m, 2H), 2.9 (m, 1H), 2.65 (m, 1H), 2.3 (dt, J = 12.6 and 3.8 Hz, 1H), 1.8 (q, J = 11.7 Hz, 1H), 1.75 (m, 1H), 1.5 (m, 1H), 0.9 (t, 3H). HPLC method 2: t_r = 4.4 min. UV: λ_{max} 207, 260, 320 nm.

***trans*-1-Benzyl-4-(*N*-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-ethylquinoline (*trans*-19).** ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.55 (d, 1H), 7.2 (m, 4H), 7.2 (m, 1H), 7.15 (m, 3H), 7.05 (d, 1H), 7.0 (t, 1H), 6.6 (t, 1H), 6.4 (d, 1H), 4.5 (dd, 2H), 4.0 (dd, J = 4.4 and 11 Hz, 1H), 3.85 (dd, 2H), 3.45 (m, 1H), 2.95 (m, 2H), 2.85 (m, 1H), 2.7 (m, 1H), 2.1 (dt, J = 12.9 and 4.4 Hz, 1H), 1.8 (td, J = 4.1 and 11.5 Hz, 1H), 1.75 (m, 1H), 1.55 (m, 1H), 0.9 (t, 3H). HPLC method 2: t_r = 14.6 min. UV: λ_{max} 207, 260, 320 nm.

(6) Grignard Reagent ^{i}PrMgCl/THF (2 M) on Compound 4. Intermediate Compound 1-Benzyl-4-(*N*-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-isopropyl-1,2-dihydroquinoline (11). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) 7.4−7.1 (m, 10H), 7.0 (m, 1H), 6.65 (t, 1H), 6.55 (d, 1H), 5.3 (d, 1H), 4.55 (dd, 2H), 4.2 (d, 1H), 3.85 (d, 1H), 3.6 (m, 1H), 3.2 (m, 1H), 3.0 (m, 1H), 2.9 (m, 2H), 1.85 (m, 1H), 1.0 (t, 3H), 0.75 (m, 3H). HPLC method 1: t_r = 9.4 min. Global yield: 20%. cis/trans ratio: 40/60.

***cis*-1-Benzyl-4-(*N*-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-isopropylquinoline (*cis*-20).** ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.45 (d, 1H), 7.25−7.15 (m, 6H), 7.05 (m, 2H), 6.95 (t, 2H), 6.6 (t, 2H), 4.4 (dd, 2H), 4.0 (dd, 1H), 3.7 (dd, 2H), 3.25 (d, J = 11 Hz, 1H), 3.0 (m, 2H), 2.8 (m, 1H), 2.6 (m, 1H), 2.05 (m, 2H), 1.65 (q, J = 11.8 Hz, 1H), 0.8 (d, 3H), 0.65 (d, 3H). HPLC method 2: t_r = 2.4 min. UV: λ_{max} 209, 261, 312 nm.

***trans*-1-Benzyl-4-(*N*-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-isopropylquinoline (*trans*-20).** ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.35 (d, 1H), 7.2 (m, 2H), 7.15−7.05 (m, 6H), 6.95 (t, 2H), 6.5 (q, 2H), 4.5 (dd, 2H), 3.85 (t, 1H), 3.7 (dd, 2H), 3.15 (q, J = 5.4 Hz, 1H), 2.8 (m, 3H), 2.6 (m, 1H), 1.95 (m, 2H), 0.85 (d, 3H), 0.8 (d, 3H). HPLC method 2: t_r = 12.1 min. UV: λ_{max} 209, 261, 312 nm.

(7) Grignard Reagent MeMgBr/THF (3 M) on Compound 5. Global yield: 62%. cis/trans ratio: 67/33.

***cis*-1-Benzyl-4-(*N*-methylpiperaz-4-yl)-2-methylquinoline (*cis*-21).** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.45 (d, 1H), 7.25−7.15 (m, 5H), 6.95 (t, 1H), 6.65 (t, 1H), 6.4 (d, 1H), 4.5 (dd, 2H), 3.95 (dd, 1H), 3.5 (m, 1H), 2.8 (m, 2H), 2.5 (m, 6H), 2.3 (s, 3H), 2.1 (dt, 1H), 1.85 (q, 1H), 1.2 (d, 3H). HPLC method 4: t_r = 8.1 min. UV: λ_{max} 208, 256, 307 nm.

***trans*-1-Benzyl-4-(*N*-methylpiperaz-4-yl)-2-methylquinoline (*trans*-21).** HPLC method 4: t_r = 7.7 min. UV: λ_{max} 208, 256, 307 nm.

(8) Grignard Reagent EtMgBr/THF (1 M) on Compound 5. Intermediate Compound 1-Benzyl-4-(*N*-methylpiperaz-4-yl)-2-ethyl-1,2-dihydroquinoline (13). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) 7.3−7.15 (m, 6H), 6.9 (t, 1H), 6.55 (t, 1H), 6.4 (d, 1H), 5.05 (d, 1H), 4.35 (dd, 2H), 3.7 (m, 1H), 3.05 (m, 2H), 2.55 (m, 4H), 2.3 (s, 3H), 1.8

(m, 2H), 1.4 (m, 2H), 0.7 (t, 3H). HPLC method 1: t_r = 9.44 min. Global yield: 31%. cis/trans ratio: 74/26.

***cis*-1-Benzyl-4-(*N*-methylpiperaz-4-yl)-2-ethylquinoline (*cis*-22).** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.45 (d, 1H), 7.3−7.2 (m, 5H), 7.0 (t, 1H), 6.65 (t, 1H), 6.5 (d, 1H), 4.5 (dd, 2H), 3.9 (dd, 1H), 3.3 (m, 1H), 2.8 (m, 2H), 2.5 (m, 6H), 2.3 (s, 3H), 2.2 (dt, 1H), 1.8 (q, 1H), 1.75 (m, 1H), 1.5 (m, 1H), 0.8 (t, 3H). HPLC method 3: t_r = 6.8 min. UV: λ_{max} 210, 257, 309 nm.

***trans*-1-Benzyl-4-(*N*-methylpiperaz-4-yl)-2-ethylquinoline (*trans*-22).** HPLC method 3: t_r = 6.2 min. UV: λ_{max} 210, 257, 309 nm.

(9) Grignard Reagent ^{i}PrMgCl/THF (2 M) on Compound 5. Intermediate Compound 1-Benzyl-4-(*N*-methylpiperaz-4-yl)-2-isopropyl-1,2-dihydroquinoline (14). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) 7.2−7.1 (m, 6H), 6.9 (t, 1H), 6.5 (t, 1H), 6.4 (d, 1H), 5.0 (d, 1H), 4.45 (dd, 2H), 3.7 (q, 1H), 3.0 (m, 2H), 2.55 (m, 4H), 2.3 (s, 3H), 1.8 (m, 2H), 1.2 (m, 1H), 0.75 (d, 3H), 0.7 (d, 3H). HPLC method 1: t_r = 8.82 min. Global yield: 27%. cis/trans ratio: 74/26.

***cis*-1-Benzyl-4-(*N*-methylpiperaz-4-yl)-2-isopropylquinoline (*cis*-23).** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.45 (d, 1H), 7.3−7.2 (m, 5H), 7.0 (t, 1H), 6.65 (t, 1H), 6.5 (d, 1H), 4.5 (dd, 2H), 3.9 (dd, 1H), 3.3 (m, 1H), 2.8 (m, 2H), 2.5 (m, 6H), 2.3 (s, 3H), 2.2 (dt, 1H), 1.8 (q, 1H), 1.85 (m, 1H), 0.9 (d, 3H), 0.8 (d, 3H). HPLC method 5: t_r = 4.9 min. UV: λ_{max} 208, 259, 299 nm.

***trans*-1-Benzyl-4-(*N*-methylpiperaz-4-yl)-2-isopropyquinoline (*trans*-23).** HPLC method 5: t_r = 6.9 min. UV: λ_{max} 208, 259, 299 nm.

Bromo-Wang Resin. Triphenylphosphine (424 mg, 3 equiv) and carbon tetrabromide (536 mg, 3 equiv) were added successively to a suspension of TG-HMP resin (2 g, 0.27 mmol/g) (Novasyn) in CH_2Cl_2 (20 mL), and then the resulting solution was stirred for 3 h. The resin was filtered and washed three times by successively DMF and CH_2Cl_2. Then the resin was dried in an oven at 50 °C under vacuum to obtain 2.1 g. ^{13}C NMR (500 MHz, $CDCl_3$): δ (ppm) 130 (s), 114 (s), 67 (s), 33 (s).

1-Wang-PS-4-chloroquinolinium Resin 24. The suspension of 6.53 g of bromo-Wang resin and 4-chloroquinoline (**1**) (22.51 g, 15.5 mmol) in DMF (20 mL) was stirred at 80 °C overnight. The resin was filtered and washed three times by successively DMF and CH_2Cl_2. Then resin **24** was dried in an oven at 50 °C under vacuum to obtain 7.2 g compared to 7.9 g expected. This resin was treated in a solution of 10% $POCl_3$ in DMF (72 mL) for 1 h at 80 °C. The resin was filtered and washed three times by successively DMF and CH_2Cl_2. Then resin **24** was dried in an oven at 50 °C under vacuum to obtain 7.2 g again.

Amination of Resin 24. The appropriate amine (1 mmo1) was added to a suspension of 1 g of resin **24** (0.5 mmol) in DMF (10 mL), and the resulting solution was stirred for 2 h at 80 °C. The resulting resin was filtered and washed three times by successively DMF and CH_2Cl_2 and then dried in an oven at 50 °C under vacuum.

Resin 25. Yield: 0.95 g obtained. CH_2Cl_2/TFA (90/10) cleavage solution analysis. ES LC/MS: *m*/*z* (MH^+) 307.60 HPLC: t_r = 6.3 min.

Resin 26. Yield: 0.95 g obtained. CH_2Cl_2/TFA (90/10) cleavage solution analysis. ES LC/MS: *m*/*z* (MH^+) 367.69. HPLC: t_r = 6.6 min.

General Procedure of One-Pot Alkylation−Reduction. The appropriate Grignard reagent solution (0.750 mmo1) was added to a suspension of 0.5 g of resin **25** or **26** in THF (3 mL) at room temperature. Then 0.750 mmol of Grignard reagent solution was added again. After 2 h, the resulting resin was filtered and washed three times by successively MeOH and CH_2Cl_2. Each resulting resin on suspension in DMF (3 mL) was treated by 500 mg of $NaBH(OAc)_3$ and then 0.5 mL of acetic acid. Each resulting suspension was stirred at room temperature overnight and then filtered. Each resin was filtered and washed three times by successively MeOH and CH_2Cl_2. The resins were cleaved by 90/10 CH_2Cl_2/TFA solution and analyzed.

Compound 39. Yield: 8.3 mg, 12%. ES LC/MS (55%): *m*/*z* (MH^+) 279. HPLC: t_r = 6.05 and 6.50 min.

Compound 40. Yield: 14.6 mg, 20%. ES LC/MS (66%): *m*/*z* (MH^+) 293. HPLC: t_r = 5.6 and 6.0 min.

Compound 42. Yield: 4.4 mg, 8%. ES LC/MS (45%): *m*/*z* (MH^+) 219. HPLC: t_r = 2.3 and 3.65 min.

Compound 43. Yield: 3.5 mg, 6%. ES LC/MS (68%): *m*/*z* (MH^+) 233. HPLC: t_r = 4.05 and 4.70 min.

Compound 44. Yield: 3.1 mg, 5%. ES LC/MS (56%): *m*/*z* (MH^+) 247. HPLC: t_r = 5.40 min.

Acknowledgment. We gratefully acknowledge Dr. Laurence Philippe and Ms. Melanie Habert for analytical experiments and Dr. Bridget Cole for proofreading.

References and Notes

(1) (a) Deninno, M. P.; Mularski, C. J.; Ruggeri, R. B.; Wester, R. T. PCT Int. Appl. WO 2000017166, 2000; 108 pp. (b) Deninno, M. P.; Magnus-Aryitey, G. T.; Ruggeri, R. B.; Wester, R. T. PCT Int. Appl. WO 2000017165, 2000; 129 pp. (c) Deninno, M. P.; Magnus-Aryitey, G. T.; Ruggeri, R. B.; Wester, R. T. PCT Int. Appl. WO 2000017164, 2000; 136 pp.

(2) (a) Awad, M. M. A.; Bazin, M.; Feru, F.; Goldstein, S. W.; Kuhn, C. F. PCT Int. Appl. WO 2004035543, 2004; 124 pp. (b) Ghosh, S.; Elder, A. M.; Carson, K. G.; Sprott, K.; Harrison, S. PCT Int. Appl. WO 2004032848, 2004; 257 pp.

(3) Smith, H. C.; Cavanaugh, C. K.; Friz, J. L.; Thompson, C. S.; Saggers, J. A.; Michelotti, E. L.; Garcia, J.; Tice, C. M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1943−1946.

(4) Kakihana, M.; Kato, K.; Mori, M.; Yamashita, T. PCT Int. Appl. WO 2002088087, 2002; 233 pp.

(5) Bladh, H.; Hansson, T.; Nikitidis, G.; Norden, C.; Pettersson, L.; Varga, M. PCT Int. Appl. WO 2002079165, 2002; 57 pp.

(6) Miyakawa, M.; Amano, S.; Kamei, M.; Hanada, K.; Furuya, K.; Yamamoto, N. PCT Int. Appl. WO 2002022585, 2002; 65 pp.

(7) Abe, H.; Nagata, M.; Hata, T. Jpn. Kokai Tokkyo Koho JP 2002053557, 2002; 73 pp.

(8) Leeson, P. D.; Carling, R. W.; Moore, K. W.; Moseley, A. M.; Smith, J. D.; Stevenson, G.; Chan, T.; Baker, R.; Foster, A. C. *J. Med. Chem.* **1992**, *35*, 1954−68.

(9) Ma, D.; Xia, C.; Jiang, J.; Zhang, J. *Org. Lett.* **2001**, *3*, 2189−2191.
(10) Xia, C.; Heng, L.; Ma, D. *Tetrahedron Lett*. **2002**, *43*, 9405−9409 and references therein.
(11) Aresta, M.; Quaranta, E.; Treglia, S.; Ibers, J. A. *Organometallics* **1988**, *7*, 577−583.
(12) Clerici, A.; Porta, O. *Tetrahedron Lett.* **1990**, *31*, 2069−2072.
(13) (a) Stevenson, G., I.; Leeson, P. D.; Rowley, M. *Bioorg. Med. Chem. Lett.* **1992**, *2*(5), 371−374. (b) Malassene, R.; Sanchez-Bajo, L.; Toupet, L.; Hurvois, J.-P.; Moinet, C. *Synlett* **2002**, *9*, 1500−1504.
(14) Stevenson, P. J.; Graham, I. *ARKIVOC* **2003**, *vii*, 139−144.
(15) Batey, R. A.; Simoncic, P. D.; Lin, D.; Smyj, R. P.; Lought, A. *J. Chem. Commun.* **1999**, 651−652.
(16) (a) Stevenson, P. J.; Hadden, M. *Tetrahedron Lett.* **1999**, *40*, 1215−1218. (b) Hadden, M.; Nieuwenhuyzen; O. D.; Stevenson, P. J.; Thompson, N. *Tetrahedron* **2001**, *57*, 5615−5624. (c) Hadden, M.; Nieuwenhuyzen, O. D.; Potts, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron Lett.* **2001**, *42*, 6417−6419.
(17) (a) Katritzky, A. R.; Rachwal, B.; Rachwal, S. *J. Org. Chem.* **1995**, *60*, 7631−7640. (b) Talukdar, S.; Chen, C.-T.; Fang, J.-M. *J. Org. Chem.* **2000**, *65*, 3148−3153.
(18) Talukdar, S.; Chen, R.-J.; Chen, C.-T.; Lo, L.-C.; Fang, J.-M. *J. Comb. Chem.* **2001**, *3*, 341−345.
(19) Ma, D.; Xia, C.; Jiang, J.; Zhang, J.; Tang, W. *J. Org. Chem.* **2003**, *68*, 442−451.
(20) Damon, D. B.; Dugger, R. W.; Scott, R. W. PCT Int. Appl. WO 2002088085, 2002; 29 pp.
(21) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 6801−6808.
(22) Zincke, T. H.; Heuser, G.; Möller, W. *Ann. Chim.* **1904**, 296.
(23) (a) Surrey, A. R.; Lesher, G. Y. *J. Am. Chem. Soc.* **1959**, *81*, 2894−2897. (b) Andrus, A.; Partridge, B.; Heck, J. V. *Tetrahedron Lett.* **1984**, *25*, 911−914.
(24) Holm, T. *Acta Chem. Scand.* **1991**, *45*, 276−279.
(25) Chen, C.; McDonald, I. A.; Munoz, B. *Tetrahedron Lett.* **1998**, *39*, 217−220.
(26) Chen, C.; Munoz, B. *Tetrahedron Lett.* **1998**, *39*, 6781−6784.
(27) (a) Carey, F. A.; Sundberg, R. J. *Chimie organique avancée*, 3rd ed.; Plenum Press: New York, 1990; Part B, pp 241−243. (b) Dauben, W. G.; Fonken, G. J.; Noyce, S. D. *J. Am. Chem. Soc.* **1956**, *78*, 2579−2582.
(28) Funabashi, M.; Iwakawa, M.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2885−2894.
(29) Ngu, K.; Patel, D. V. *Tetrahedron Lett.* **1997**, *38*, 973−976.

CC0498534