Synthesis of Naturally Occurring Nitrogen Heterocycles from Carbohydrates

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Carbohydrates, such as starch, are extensively used as feedstocks by the chemical industry; similarly, derivatized carbohydrates are increasingly used by organic chemists as starting materials in the synthesis of chiral heterocyclic compounds. The aim of this book is to review the recent literature dealing with the use of carbohydrates as raw materials in the synthesis of naturally occurring nitrogen heterocycles. Although carbohydrates have been used for the synthesis of other types of heterocycles, we have limited our review to their use in the synthesis of naturally occurring nitrogen heterocycles. This limitation was dictated by the extremely large number of publications that has appeared on the subject during the last two decades and our desire to give the reader as much information as possible in the confines of our book. We have not merely cited references for a given synthesis but instead have given as much detail as was possible on the experimental conditions used. The text contains six main chapters arranged according to the size and complexity of their heterocyclic rings, ranging from five- to seven-membered rings and from single to multiple fused rings. The book gives enough information on the synthesis of the compounds to enable a chemist to design a multistep synthesis. It cites the different approaches to the synthesis of naturally occurring nitrogen heterocycles in a format that enables the reader to make comparisons with other methods and make decisions on whether to use a certain procedure, modify it or devise a new synthetic methodology. In summary, the book is not a mere list of the conversion methods cited in the literature, but rather a rational discussion of these methods. Of course, the large volume of literature cited has dictated that some references be discussed in less detail than some readers would have liked, but we hope that they will understand our difficulty and forgive us. We feel that the added information in our reference book will be of greatest value to chemist in both industry and academia, and to researchers and graduate students in the fields of organic chemistry, medicinal chemistry, heterocyclic chemistry, natural product chemistry and glycochemistry.

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A. El Nemr
El Sayed H. El Ashry was born in 1942 in Elmahal Alkobra, Egypt. He studied chemistry at Alexandria University (BSc 1963, MSc 1966, PhD 1969 and DSc 1997). He has been a visiting professor at Tokyo Institute of Technology, Ohio State University, Michigan Technological University, New York State University, Darmstadt Institute of Organic Chemistry, UmAlqura University and Konstant University. He has given lectures at various universities, institutes, companies and conferences around the world. He is currently a Professor of Organic Chemistry at Alexandria University after being the head of the department for the last four years. He has supervised more than 70 MSc and PhD students and published about 300 publications and review articles in highly renowned journals in the field of carbohydrates and nucleosides, a major area of research in the series ‘Heterocycles from Carbohydrate Precursors’. He also edits various international journals. He has received many awards of recognition and distinction: in particular ‘Excellence’ and ‘1st class Ribbon of Science and Arts’ awards from the President of Egypt.

Ahmed El Nemr was born in 1962 in El Behera, Egypt. He received his bachelor’s degree in chemistry in 1984 and his master’s degree in organic chemistry from Alexandria University under the supervision of Professor E.S.H. El Ashry, after which he was awarded his PhD in Engineering in Applied Chemistry by Keio University, Yokohama, Japan. He worked for six years as a researcher at the Institute of Bioorganic Chemistry, Kawasaki, Japan, with Professor Tsutomu Tsuchiya. He is now an Associate Professor at the National Institute of Oceanography and Fisheries, Alexandria, Egypt. He is the head of Egyptian National Oceanography Data Centre (ENODC). His research interests involve carbohydrate chemistry, natural products, and organic as well as inorganic pollutants in marine environment.
## List of abbreviations and acronyms used in this book

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<td>AIBN</td>
<td>azobis(isobutronitrile)</td>
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<td>All</td>
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<td>PASE</td>
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Introduction

Carbohydrates are widely distributed in nature and constitute the largest renewable biomasses available. As such, they are considered by many as one of the most promising feedstock for the industrial preparation of many organic chemical compounds. Carbohydrates, resembling the largest class of resources, have attracted the attention to be used as substitutes for the crude oil, natural gas or coal in developing materials for trendsetting technologies. Moreover, many pharmaceutical agents incorporate nitrogen heterocyclic rings, which has attracted attention toward their synthesis. The use of carbohydrates as starting materials for the synthesis of heterocyclic compounds has long been a subject of interest in our laboratory, where significant efforts were devoted to the exploration of novel routes for the synthesis of nitrogen heterocyclic compounds from nitrogen derivatives of carbohydrates. The skeleton and functionalities in the hydrazones and bishydrazone derived from carbohydrates have been found to be of high synthetic potential, particularly as precursors for acyclic nucleosides and heterocyclic compounds. Thus, a great deal of work has been done on the transformations of hydrazones and bishydrazone into heterocyclic compounds. Since the subject of the book is naturally occurring nitrogen heterocycles, only a quick information on the role of hydrazones and osazones as precursors for heterocyclic compounds will be given herein, which could be of potential value in using such approaches in the synthesis of naturally occurring nitrogen heterocycles. This can be exemplified by the synthesis of the important starting material, acetonide of L-glyceraldehyde, which has utilized the readily available dehydro-L-ascorbic acid monophenylhydrazone. Much attention has been drawn to the synthesis of pyrazoles and pyrazolines via various routes. Isoxazolines, 1,2,3-triazoles, 1,2,4-triazoles, oxadiazoles, and thia-diazoles as well as dioxalanes, tetrazoles, pyridazines, 1,2,4-triazines, pyrrolotriazines, triazolotriazinoindoles, pyrazolopyrazoles, fused pyridazines, pyrimidines, quinoxalines, and pyridopyrazines as well as condensed triazolo ring systems and condensed diazines and condensed quinoxalines have been synthesized. Moreover, resulting periodate oxidation of the polyol residues linked to heterocycles followed by using the aldehyde or carboxylic acid functionalities for building heterocycles led to the synthesis of various types of biheterocycles.

Rationale and arrangement of the topics

The naturally occurring nitrogen heterocycles possess a wide range of biological and medicinal properties. Consequently, the design of synthetic schemes for naturally occurring heterocycles is highly desirable. Among the useful features of carbohydrates
is the ability of their nitrogen derivatives to incorporate part or all of the nitrogen atoms into the heterocyclic rings they form. Another useful feature is the availability of their multiple chiral centers in nearly all the possible configurations and their ability to retain most of their configuration during conversion to heterocycles. The resulting chirons (optically active synthons) can readily be used as versatile intermediates in the synthesis of naturally occurring heterocycles. Consequently, some monographs and reviews related to the topic became available.\textsuperscript{258–262} However, as a result of the tremendous achievement in the field we have found that the topic needs a comprehensive review to help the reader in getting ready information on the topic. The synthetic approaches described in this book are discussed in six chapters arranged according to the size of the heterocyclic rings and the number of heteroatoms in the ring. Accordingly, the chapters are arranged into (1) five-membered nitrogen heterocycles, (2) five-membered heterocycles with two heteroatoms, (3) six-membered nitrogen heterocycles, (4) seven-membered nitrogen heterocycles, (5) fused nitrogen heterocycles and (6) multifused heterocycles. Three- and four-membered nitrogen heterocycles are not treated in separate chapters but are included in the appropriate fused heterocycles.

References

INTRODUCTION

INTRODUCTION

1 Five-membered nitrogen heterocycles

As the title denotes, this chapter deals with the conversion of carbohydrate derivatives into five-membered heterocyclic compounds containing nitrogen. The types of target compounds are (1) hydroxymethylpyrrolidines, (2) carboxypyrrolidines, (3) aralkyl pyrrolidines and (4) aryl pyrrolidines, as well as other heterocycles that are grouped under the title miscellaneous (5). Although many of these naturally occurring compounds and their stereoisomers and analogues have been synthesized from noncarbohydrates, the synthesis of the naturally occurring five-membered nitrogen heterocycles from only carbohydrate will be discussed in this chapter.

1.1 Hydroxymethylpyrrolidines

Because of their ‘sugar-like’ structure it is not surprising that most syntheses of the naturally occurring hydroxymethylpyrrolidines utilize carbohydrates as starting materials. Pentoses, hexoses and their derivatives are often used; three chiral centers are usually required. Nitrogen is introduced in the synthetic sequence as azide, followed by reduction to the respective amine that can be intramolecularly cyclized. This part contains three groups of compounds: 2-hydroxymethylpyrrolidines, dihydro-2-hydroxymethyl pyrrole (nectrisine) and 2,5-dihydroxymethylpyrrolidines. Each of the first and third groups contains five natural compounds isolated from different sources and characterized by having glycosidase inhibition properties.

1.1.1 2-Hydroxymethylpyrrolidines

1,4-Dideoxy-1,4-imino-D-arabinitol [(2R,3R,4R)-2-hydroxymethyl pyrrolidine-3,4-diol, DAB1, 1] has been found in both Arachniodes standishii\(^1\,^2\) and Angylocalyx boutiqueanus\(^3\) and it is a potent inhibitor of yeast \(\alpha\)-glucosidase (50% inhibition at \(1.8 \times 10^{-7}\) M)\(^4\,^7\) and mouse gut disaccharidases to different degrees.\(^8\) Compound 1 inhibits the hydrolysis of sinigrin and progoitrin from mustard and cabbage aphid Brevicoryne brassicae.\(^9\) It also inhibits phloem unloading and/or utilization of sucrose, resulting in insufficient sucrose transport from cotyledons to roots and hypocotyls.\(^10\) The mechanism of insect antifeedant activity of 1 has been studied\(^11\) and it was found that it may be carcinogenic to rodents.\(^12\) The enantiomer 1,4-dideoxy-1,4-imino-L-arabinitol [(2S,3S,4S)-2-hydroxymethyl pyrrolidine-3,4-diol, LAB1, 2] occurs as a component of bacterial lipopolysaccharides\(^13\,^14\) but it shows a weaker inhibition of \(\alpha\)-glucosidase (50% inhibition at \(1.0 \times 10^{-5}\) M)\(^15\,^16\) and exhibits several biological activities.\(^17\,^19\) 1,4-Dideoxy-1,4-imino-D-ribitol [(2R,3R, 4S-2-hydroxymethyl pyrrolidine-3,4-diol, 3] has been isolated from Morus spp.\(^21\,^22\) 1,4-Dideoxy-1,4-imino-L-xyliotol [(2S,3R,4R)-2-hydroxymethyl pyrrolidine-3,4-diol, 4] was isolated from diatom cell walls\(^23\) and Amanita vitosa mushrooms.\(^24\) 2-Hydroxymethyl-3-hydroxypyrrrolidine [(2R,3S)-2-hydroxymethyl pyrrolidin-3-ol, CYB3, 5] was isolated from legume Castanospermum australe and it has no significant biological activity.\(^25\)
Syntheses of natural polyhydroxypyrrolidines from noncarbohydrate and their unnatural analogues from carbohydrate and noncarbohydrate have been reported.\textsuperscript{26–86} Herein, the synthesis of the natural analogues from carbohydrate building blocks will be reviewed.

\subsection*{1.1.1.1 Synthesis from \textit{d}-glucose}

A stereoselective synthesis of \textit{DAB1} (1) from \textit{d}-glucose has been reported (Scheme 1).\textsuperscript{87} Diacetone \textit{d}-glucose (6) was benzylated to give the fully protected furanose, which underwent acid hydrolysis of the terminal isopropylidene group followed by periodate oxidation, sodium borohydride reduction, mesylation and then

\begin{align*}
\text{(a) 1. THF, NaH, \text{Bu}_4\text{NI}, 0{}^\circ\text{C}, \text{BnBr}, \text{rt to 50}{}^\circ\text{C}, 2 \text{ h, 97\%}; 2. \text{CH}_3\text{OH–AcOH–H}_2\text{O (1:1:1), 50}{}^\circ\text{C, 16 h, 87\%; 3. NaIO}_4, 10\% \text{aqueous EtOH, 3 h, CH}_2\text{Cl}_2; then 20\% \text{aqueous EtOH, NaBH}_4, 8 \text{ h at rt, 88\%; 4. Py, 0{}^\circ\text{C, MsCl, rt, 2 h, 94\%; 5. NaN}_3, \text{DMF, 70}{}^\circ\text{C for 12 h, 97\%.}})}
\end{align*}

\begin{align*}
\text{(b) 1. AcCl, \text{CH}_3\text{OH, 0}{}^\circ\text{C, 36 h, 38\%}, 1. \text{Py, Tf}_2\text{O, –50 to –30}{}^\circ\text{C, 1 h, 92\%}, \text{Py, 0}{}^\circ\text{C, 36 h, 38\%}; 2. \text{Py, Tf}_2\text{O, –50 to –30}{}^\circ\text{C, 1 h, 92\%).}}
\end{align*}

\begin{align*}
\text{(c) 1. EtOAc, rt, 5\%, Pd on C, H}_2, 95\%; 2. \text{3:2 mixture of ether and aqueous NaHCO}_3, \text{CbzCl, rt, 12 h, 90\%).}}
\end{align*}

\begin{align*}
\text{(d) 1:1 mixture of TFA and H}_2\text{O, 92\%;}}
\end{align*}

\begin{align*}
\text{(e) 1. EtOH, NaBH}_4, 15 \text{ min, 98\%;}}
\end{align*}

\begin{align*}
\text{2. AcOH, H}_2, \text{Pd black, 18 h, 97.6\%).}}
\end{align*}
replacement of the mesyloxy group with azide ion to afford the azide 7. Compound 7 was treated with methanolic hydrogen chloride, followed by triflation of C-2 hydroxyl group to give the corresponding triflate 8. Hydrogenation of 8 followed by protection of the resulting bicyclic compound with benzyl chloroformate afforded the carbamate 9. Subsequent hydrolysis with TFA gave the key intermediate 10. Reduction of 10 with sodium borohydride followed by removal of the carbamate and O-benzyl protecting groups by hydrogenolysis in acetic acid gave DAB1 (1) in 33% from 6.

Synthesis of 1,4-dideoxy-1,4-imino-L-xylitol (4) has been achieved from D-glucose (Scheme 2). Borane-reductive ring opening of the benzylidene ring in compound 11, obtained from D-glucose, afforded 12 (90%). Reduction of 12 with sodium borohydride produced the corresponding triol 13 (73%), which was subjected to periodate oxidation to give the cyclic hemiacetal 14 (92%). Hydrogenation of 14 over palladium led to the formation of 3,4-dihydroxypyrrolidine 4-HCl.

**Scheme 2**  (a) BH₃, THF, 15 mol% V(O)(OTf)₂, CH₂Cl₂, rt, 3 h, 90%. (b) NaBH₄, CH₃OH, 73%. (c) NaIO₄, CH₃OH, 92%. (d) 10% Pd on C, H₂, EtOH, 1 N HCl, 94%.

1.1.1.2  **Synthesis from D-mannose**  A stereoselective synthesis of 1,4-dideoxy-1,4-imino-L-xylitol (4) from D-mannose has been reported (Scheme 3). A pyridine solution of D-mannose containing iron(III) triflate or iron(III) chloride was irradiated with a high-pressure mercury lamp in a Pyrex vessel, while oxygen gas was bubbled through to afford after acetylation the aldopentose derivative 15, which was treated with aluminum chloride in aqueous methanol to afford 1,2,3-tri-O-acetyl-D-arabinopyranose 16 in 24% overall yield from D-mannose. Triflation of 16 followed by treatment with sodium azide gave 1,2,3-tri-O-acetyl-4-azido-4-deoxy-L-xylopyranose (17) in 55% yield. Deacetylation of 17 with potassium carbonate in methanol followed by catalytic hydrogenation gave 4 in 77% yield.

1.1.1.3  **Synthesis from L-arabinose**  Synthesis of 1,4-dideoxy-1,4-imino-L-arabinitol (2) from methyl β-L-arabinopyranoside has been reported (Scheme 4). The double inversion involving the introduction of the azide function at C-4 has been effected in
Scheme 3  (a) Py, FeTf₃, hv, 8 h, O₂; then Ac₂O, rt, 14 h. (b) AlCl₃, CH₃OH, H₂O, rt, 36 h, 24% from D-mannose. (c) 1. Tf₂O, CH₂Cl₂, Py, 0° C, 1 h; 2. NaN₃, DMF, 15-crown-5, rt, 24 h, 55%. (d) 1. 10% aqueous CH₃OH, K₂CO₃, 0° C, 15 min, AcOH; 2. 10% Pd on C, H₂, 3 days; then Dowex 50X8-100 (H⁺) resin, 77%.

two steps by reacting methyl 2,3-di-O-benzoyl-β-L-arabinoside (18) with triphenylphosphine and 2,4,5-tribromoimidazole to form methyl 2,3-di-O-benzoyl-4-bromo-4-deoxy-α-D-xylopyranoside (19). This bromide was reacted with sodium azide to give 4-azido-4-deoxy-L-arabinoside (20). Dephenylation with methanolic sodium methoxide gave methyl 4-azido-4-deoxy-β-L-arabinopyranoside (21), whose acid hydrolysis and catalytic hydrogenation gave 2.

Scheme 4  (a) Ph₃P, 2,4,5-tribromoimidazole. (b) NaN₃, DMF. (c) NaOCH₃, CH₃OH. (d) 1. H₃O⁺; 2. H₂, Pd, Amberlite CG-400 (OH⁻) resin.

1.1.1.4 Synthesis from D-xylose  The synthesis of 1,4-dideoxy-1,4-imino-L-arabinitol (2) can also be achieved from D-xylose (Scheme 5). Thus, methyl β-D-xylopyranoside (22) has been treated with 2-methoxypropene followed by triflation with trifluoromethane sulfonic anhydride to afford the triflate 23. The latter underwent S_N2 displacement with sodium
azide followed by acid hydrolysis to produce the azide 24. Reduction of 24 afforded 2, via the intermediates 25–27, in 21% overall yield from 22.

Scheme 5  
(a) 1. DMF, 4 M HCl in CH₃OH, 2-methoxypropene, 60°C, 2 h; then rt, overnight, 72%; 2. CH₂Cl₂, Py, –50°C, Tf₂O, 45 min at –25°C. (b) 1. DMF, NaN₃, rt, 2 h, 45% for two steps; 2. AcOH, 2 M H₂SO₄, 95°C, 3 h; then NaHCO₃, pH 4, 65%. (c) 0.1 M aqueous HCl, 10% Pd on C, H₂, rt, 6 h, 100%.

DAB1 (1) and LAB1 (2) can be alternatively synthesized from D-xylose (Scheme 6). The acetonide 28, obtained from D-xylose, was triflated, followed by S_N2 displacement with azide ion and subsequent removal of the isopropylidene group to give 29. Selective

Scheme 6  
(a) 1. Tf₂O, Py, CH₂Cl₂; 2. NaN₃, DMF, 100°C, 12 h, 76% for two steps; 3. Dowex 50W8X resin, CH₃OH, rt, 4 h, 83%. (b) 1. p-TsCl, Py, 0°C; 2. H₂, Pd black, EtOH, NaOAc, 50°C; CbzCl, ether, H₂O containing NaHCO₃, 36% for three steps. (c) 1. TFA–H₂O (4:1); 2. NaBH₄, EtOH; 3. H₂, Pd black, AcOH, 65%. (d) 1. BnBr, NaH; 2. Dowex 50W8X (H⁺) resin; 3. BnBr, NaH, t-Bu₄NI, THF, 45% for three steps. (e) 1. TFA, H₂O; 2. NaBH₄, EtOH, rt, 1 h, 87%; 3. MsCl, Py, 90%; 4. NaN₃, DMF, 66%. (f) 1. H₂, Pd black, EtOH; 2. ion-exchange chromatography, 48%. 
tosylation of the primary hydroxyl group in 29 followed by azide reduction and subsequent cyclization with sodium acetate and protection with benzyl chloroformate afforded the carbamate 30. Hydrolysis of 30 by aqueous TFA followed by reduction of the resulting aldehyde, removal of the carbamate protecting group and purification by ion-exchange chromatography gave 1 in 15% overall yield from 28.

On the other hand, the xylofuranoside 28 was benzylated, followed by removal of the isopropylidene group and subsequent benzylation to give the tribenzylated derivative 31. Acid hydrolysis of 31 followed by sodium borohydride reduction of the resulting lactol and subsequent mesylation and then selective nucleophilic displacement of the primary mesylate by sodium azide in DMF afforded the azido mesylate 32. Reduction of the azide was accompanied by cyclization and deprotection to afford 2 in 11% overall yield from 28.

1.1.1.5 Synthesis from D-threose  Synthesis of DAB1 (1) has been carried out by conversion of the D-threose derivative 33,94 readily available from D-(−)-diethyl tartrate, to the aminonitrile 34 as an inseparable diastereomeric mixture (Scheme 7).95 Subsequent deprotection with TBAF gave the alcohol 35 (quantitative). Esterification of 35 with p-toluenesulfonyl chloride afforded 36 (84%), which was treated with TFA–H2O–THF

Scheme 7  (a) 1. TBSCI, imidazole, CH2Cl2; 2. p-(CH3O)C6H4CH2NH2, (EtO)2P(O)CN, THF, 86.7%. (b) TBAF, THF, quantitative. (c) p-TsCl, Py, 84%. (d) TFA–H2O–THF (5:1:1), 70–75°C. (e) NaOCH3, CH3OH; then 2 N HCl, 87%. (f) Same as (e), 65–70°C, 2 h; then 2 N HCl, 78%. (g) NaBH4, EtOH, 89%. (h) 1. H2, 20%, Pd(OH)2 on C, HCO2H, EtOH; 2. conc. HCl, 94%.
to afford the cyclized isomeric mixture 37 and 38 in a ratio of 4:1 (74%). Subsequent treatment with sodium methoxide in methanol gave a chromatographically separable mixture of the methyl esters 39 (21%) and 40 (28%) in addition to recovery of the starting material (48.7%), which could be recycled. Treatment of 39 with sodium methoxide in methanol afforded a 1:1 mixture of 39 and 40. Reduction of 40 with sodium borohydride gave the alcohol 41 (89%). Removal of the PMB group from 41 by catalytic hydrogenolysis provided 1, which was conveniently isolated as its crystalline hydrochloride by treatment with conc. HCl (94%). Its enantiomer LAB1 (2) was synthesized from L-(+) -diethyl tartrate following the same set of reactions previously described for 1.

1.1.1.6 Synthesis from D-lyxonolactone A synthesis of 1,4-dideoxy-1,4-imino-L-arabinitol (2) from D-lyxonolactone (42) (Scheme 8)\(^{17}\) was achieved by benzylidation, followed by mesylation to afford 43 in 80% yield from 42. Lithium borohydride reduction of 43 followed by treatment with potassium carbonate afforded the epoxide 44 (72%), which underwent triflation of the free hydroxyl group followed by S\(_2\)N displacement with azide ion to furnish the azidoepoxide 45 (92%). Hydrogenation of 45 followed by ring closure of the resulting amine using tetrabutylammonium iodide, via the intermediate iodoalcohol, afforded the pyrrolidine 46. Finally, removal of the benzylidene group with H\(_2\)SO\(_4\) afforded 2, which was isolated as the hydrochloride salt in 21% overall yield from 42.

![Scheme 8](image)

1.1.1.7 Synthesis from D-gulonolactone Synthesis of 1,4-dideoxy-1,4-imino-D-ribitol (3) from D-gulonolactone has been reported (Scheme 9).\(^{96}\) D-Gulonolactone was treated with DMP to produce diacetone D-gulonolactone (47), which underwent LiAlH\(_4\) reduction followed by mesylation to furnish 48 in 74% yield from D-gulonolactone. Heating of 48 with benzylamine afforded the protected pyrrolidine 49. Treatment of 49 with aqueous acetic acid followed by periodate oxidation of the terminal diol and subsequent borohydride reduction afforded the pyrrolidine 50. Compound 50 was debenzylated and then deacetonated to produce 3 in 29% overall yield from D-gulonolactone.
d-Gulonolactone

Scheme 9  
(a) Acetone, DMP, p-TsOH, rt, 2 days; then anhydrous Na$_2$CO$_3$, 85%. (b) 1. LiAlH$_4$, THF, rt, 30 min, 87%; 2. MsCl, DMAP, Py, rt, 2 h, 100%. (c) BnNH$_2$, 60–70$^\circ$C, 60 h, 77%. (d) 1. 80% aqueous AcOH, 50$^\circ$C, 48 h, 93%; 2. NaIO$_4$, EtOH–H$_2$O (5:1), rt, 20 min; then NaBH$_4$, 0$^\circ$C, 30 min, 71%. (e) EtOH, H$_2$, 10% Pd on C, rt, 2 h; then 50% aqueous TFA, rt, 24 h, 78%.

References