A Facile Synthesis of Novel Acyclo-*C*-Nucleoside Analogues from L-Rhamnose via Variants of Bohlmann–Rahtz Reaction

Srinivas Kantevari,* Siddamal Reddy Putapatri

Organic Chemistry Division-II, Indian Institute of Chemical Technology, Hyderabad 500007, India
E-mail: kantevari@yahoo.com; E-mail: kantevari@gmail.com

Received 9 June 2010

Abstract: Synthesis of a series of novel acyclo-*C*-nucleoside analogues bearing substituted pyridines, dihydro-6*H*-quinolin-5-ones, dihydro-5*H*-cyclopentapyridin-5-one, tetrahydrocyclohepta[*b*] pyridine-5-one, and azafluorinone has been achieved in very good yields, through $CeCl_3 \cdot 7H_2O$-NaI-catalyzed one-pot condensation of a variant of the Bohlmann–Rahtz reaction using β-enaminones derived from L-rhamnose, acyclic and cyclic 1,3-dicarbonyls, and ammonium acetate. Ready availability of reactive β-enaminones, use of a cerium catalyst, and shorter reaction times are the advantages of this protocol over previous methodology. A plausible mechanism invoking cerium-catalyzed sequential Michael addition–cyclodehydration–elimination reactions is also presented.

Key words: Bohlmann–Rahtz reaction, acyclo-*C*-nucleosides, $CeCl_3 \cdot 7H_2O$-NaI, one-pot condensation, β-enaminone, L-rhamnose, heterocycles

Acyclo-*C*-nucleosides with an open-chain sugar moiety attached to a heterocycle through a C–C bond have gained considerable attention in recent years due to their broad spectrum of biological activity.[1] Notable among them are the natural bengazoles and synthetic carbohybrids linked to imidazoles, pyrazoles, benzimidazoles, piperidines, indolizidines, and nitrones (Figure 1), which have been shown to possess significant pharmacological activity.[2,3] We envisaged that fusing acyclic polyol units to a pyridine core would create a series of acyclo-*C*-nucleosides with similar properties.[4]

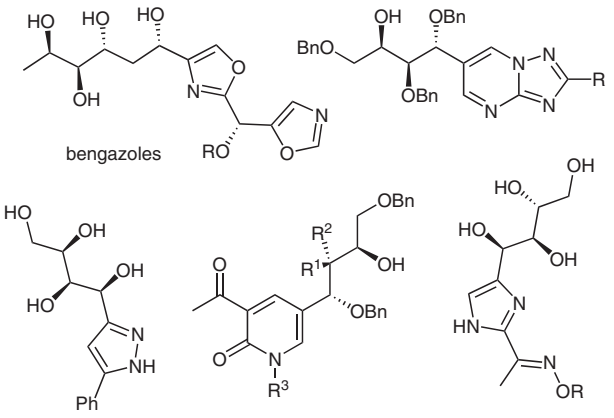


Figure 1 Representatives of natural and synthetic acyclo-*C*-nucleosides

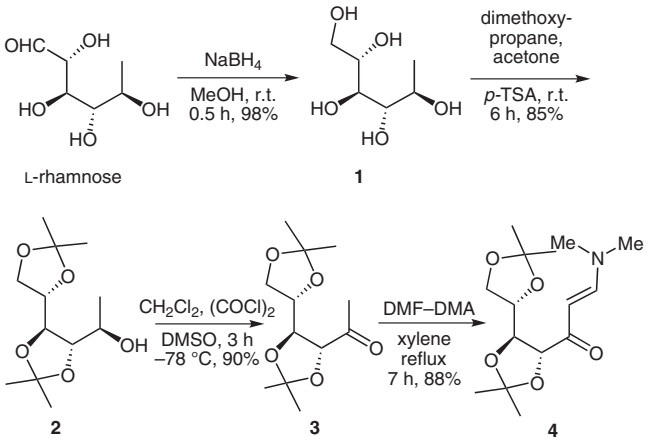
Incisive work by Bagley[5] has unveiled a remarkable variant of the classical Bohlmann–Rahtz synthesis,[6] wherein an alkynone and 3-amino alkenoate combine in refluxing solvent to afford substituted pyridines in good yields. This chemistry could deliver libraries of pyridine analogues, if it were to prove serviceable with variants of alkynones and 3-aminoalkenoates.[7] From our research[8] as well as others,[9] it is clear that β-enaminones could serve as polarized variants of alkynones in the synthesis of 2,3,6-trisubstituted pyridines. In order to obtain a suitable sugar-containing enaminone building block, the readily available deoxymonosaccharide, L-rhamnose (6-deoxymannose) was taken as the starting substrate.

Among lanthanide-based catalysts, cerium(III) chloride has emerged as a cheap, efficient, and green reagent (it shows the same toxicity level as sodium chloride) able to catalyze selective transformations and cyclizations.[10] In most cases, the activity of $CeCl_3$ can be increased in combination with NaI.[10] The successful use of cerium(III) in reactions using 1,3-dicarbonyl substrates[11] prompted us to investigate its applicability in the one-pot condensation of β-enaminones derived from L-rhamnose with 1,3-dicarbonyl compounds and ammonium acetate.

In this paper we report an efficient $CeCl_3 \cdot 7H_2O$-NaI catalyzed one-pot synthesis of acyclo-*C*-nucleoside analogues bearing 2,3,6-trisubstituted pyridines **6a–f**,**i**, dihydro-6*H*-quinolin-5-ones **6j**,**l**,**o**, dihydro-5*H*-cyclo pentapyridin-5-one **6k**, tetrahydrocyclohepta[*b*]pyridine-5-one **6m**, and azafluorinone **6n**. The one-pot condensation of (*E*)-3-(dimethylamino)-1-[(4*S*,4′*S*,5*R*)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl]-2-propenone **4** (here after referred to as enaminone **4**) derived from L-rhamnose, with acyclic and cyclic 1,3-diketones **5a–p** and ammonium acetate in the presence of $CeCl_3 \cdot 7H_2O$-NaI catalyst resulted in the title compounds with high regioselectivity.

As a starting point of the study, 1-[(4*S*,4′*S*,5*R*)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl)ethanone (**3**) required for the preparation of enaminone **4** was synthesized by improving the literature method[12] starting from L-rhamnose (Scheme 1). L-Rhamnitol (**1**) obtained after $NaBH_4$ reduction, was protected by reacting with 2,2-dimethoxypropane. Swern oxidation of **2** gave methyl ketone **3** in excellent yield. Finally, the required building block **4** was obtained in 88% yield after refluxing **3** with dimethylformamide dimethylacetal (DMF-DMA) in xylene.

SYNLETT 2010, No. 15, pp 2251–2256
Advanced online publication: 12.08.2010
DOI: 10.1055/s-0030-1258038; Art ID: D13610ST



Scheme 1 Synthesis of β-enaminone **4**

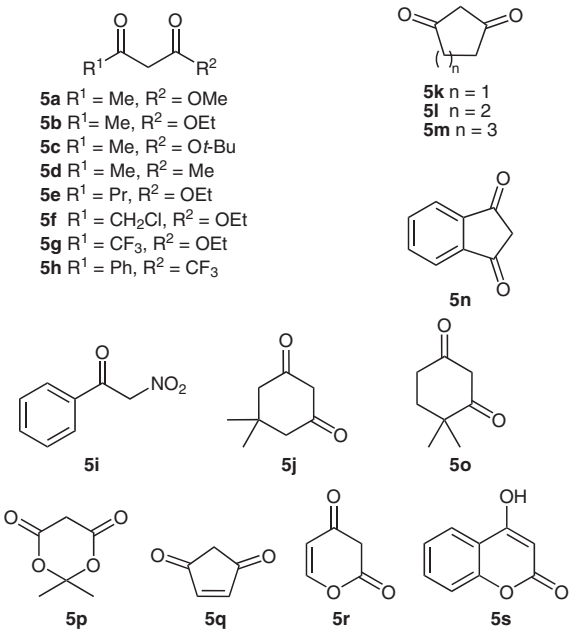


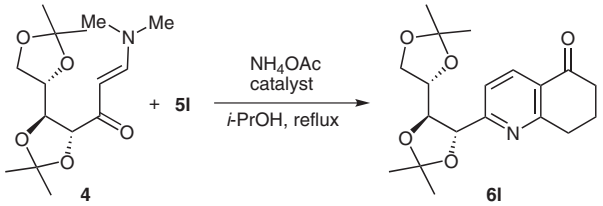
Figure 2 Acyclic and cyclic 1,3-dicarbonyl compounds examined

With the desired sugar building block **4** to hand, various catalysts and reaction conditions were screened to effect the desired reaction (Table 1). Initial efforts using AcOH as solvent[9f] in the condensation of enaminone **4** with cyclohexane-1,3-dione **5l** and ammonium acetate led to a mixture of products. After a series of experiments, the condensation of enaminone **4** with cyclohexane-1,3-dione **5l** and ammonium acetate was successful using $CeCl_3·7H_2O$-NaI (20.0 mol%) in refluxing 2-propanol for 3 hours (Table 1, entry 21) to afford quinolinone **6l** in very good yield (88%). From our results it appears that the water associated with cerium(III) salt plays a role in the ability of the $CeCl_3·7H_2O$-NaI to promote the condensation of enaminone **4** with 1,3-cyclohexanedione. When we attempted reaction in the presence of NaI without using $CeCl_3·7H_2O$ starting material was quantitatively recovered (Table 1, entry 22). It was also noted that, in the absence of NaI, the procedure with $CeCl_3·7H_2O$ required 24 hours to give product **6l** in 55% yield (Table 1, entry 4).

Here it is also noteworthy that tetrabutylammonium bromide (TBAB) and $K_5CoW_{12}O_{40}·3H_2O$ catalysts also gave product **6l** in comparable yields (84% and 76%, respectively; Table 1, entries 9 and 18) but the procedure required longer reaction times and the latter catalyst required special preparation.

Encouraged by these results, the general scope of the reaction was further investigated with various acyclic 1,3-diketones **5a–i** (Figure 2) under the optimized protocol. All the reactions except with **5g** and **5h** proceeded

Table 1 Evaluation of Potential Catalysts[a]



Entry	Catalyst (mol%)	Time (h)	Yield (%)[b]
1	AcOH (solvent)	24	sluggish
2	$HClO_4$-SiO_2 (20)	12	5
3	$Co(OAc)_2·4H_2O$ (20)	12	18
4	$CeCl_3·7H_2O$ (20)	24	55
5	$FeCl_3·H_2O$ (20)	24	15
6	$Zn(ClO_4)_2·4H_2O$ (20)	12	12
7	$SnCl_2·2H_2O$ (20)	12	15
8	$CoCl_2$ (20)	12	10
9	TBAB (20)	24	84
10	$Mg(ClO_4)_2$ (20)	24	18
11	$La(CF_3SO_3)_3$ (5)	24	12
12	$In(CF_3SO_3)_3$ (5)	24	18
13	$Sc(CF_3SO_3)_3$ (5)	24	16
14	$Cu(CF_3SO_3)_3$ (5)	24	12
15	$Yb(CF_3SO_3)_3$ (5)	24	10
16	Montmorillonite-K10 (20)	24	18
17	$Na_2WO_4·2H_2O$ (20)	24	9
18	$K_5CoW_{12}O_{40}·3H_2O$ (5)	5	76
19	$K_5CoW_{12}O_{40}·3H_2O$ (10)	5	61
20	anhyd $CeCl_3$ (20)	24	ca. 3
21	$CeCl_3·7H_2O$-NaI (20)	3	88
22	NaI (20)	24	0

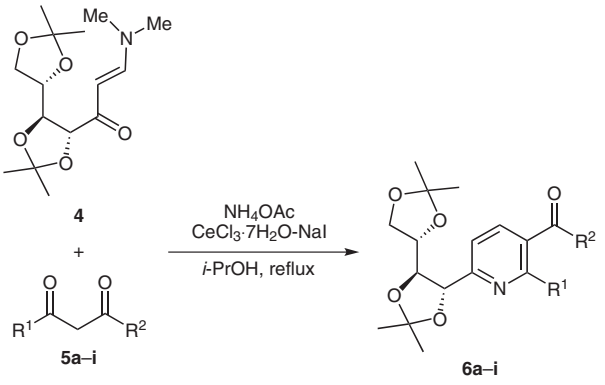
[a] All the reactions were performed with **4** (1.0 mmol), **5l** (1.2 mmol), and NH_4OAc (2.0 mmol). The progress of the reaction was monitored by TLC.
[b] Isolated yield.

smoothly to give the corresponding trisubstituted pyridines **6a–f**,**i** in good to excellent yields (Table 2). All the products obtained were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, ESI-MS, and HRMS analysis.

In the case of fluorinated acyclic 1,3-diketones **5g** and **5h**, the reaction was sluggish and did not give the desired product. In both these cases, purification of reaction mixture through silica gel column chromatography led to the recovery of starting substrate **4** in quantitative yield.

In an extension, we further tested the protocol with various cyclic 1,3-diketones **5j–s** (Figure 3). Most of the reactions proceeded well and acyclo-*C*-nucleoside analogues bearing dihydro-6*H*-quinolin-5-ones **6j**,**l**,**o**, dihydro-5*H*-cyclopentapyridin-5-one **6k**, tetrahydrocyclohepta[*b*]pyridine-5-one **6m**, and azafluorinone **6n** were isolated in moderate to very good yields. With **5o**, the condensation reaction proceeded regioselectively to give **6o** as the sole product, the regioselectivity of methyl substituents in **6o** being assessed by ^{1}H-^{13}C HMBC spectroscopic analysis.

Table 2 Synthesis of Trisubstituted Pyridines **6a–i**



Entry	1,3-Dicarbonyl			Time (h)	Product	Yield (%)
	5	R^1	R^2			
1	**5a**	Me	OMe	3.0	**6a**	82
2	**5b**	Me	OEt	3.5	**6b**	80
3	**5c**	Me	O*t*-Bu	3.0	**6c**	76
4	**5d**	Me	Me	3.0	**6d**	82
5	**5e**	Pr	OEt	4.0	**6e**	72
6	**5f**	CH_2Cl	OEt	3.5	**6f**	65
7	**5g**	CF_3	OEt	12	**6g**	<1
8	**5h**	Ph	OCF_3	12	**6h**	<1
9	**5i**	Ph	NO_2[a]	8	**6i**	32

[a] NO_2 replaces COR^2 moiety.

The low yield obtained with 1,3-cyclopentadione **5k** (Figure 3) may be due to the steric strain arising in the reaction. Reaction with olefinic 1,3-dicarbonyl compounds **5q–s** failed to give the desired products. All products **6j–o**

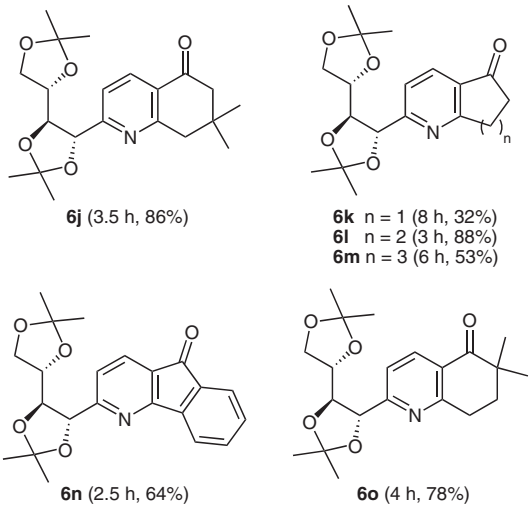
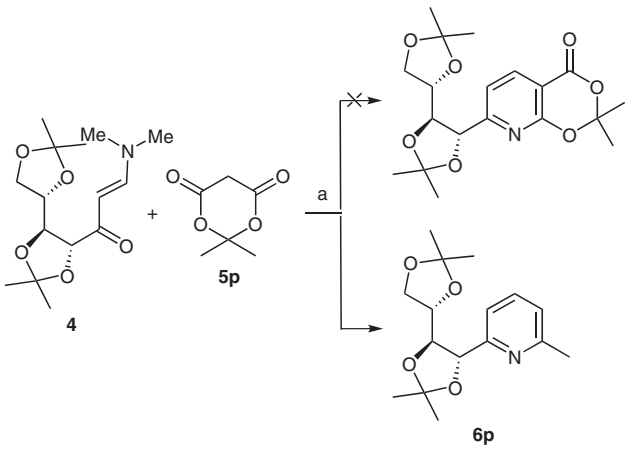


Figure 3 Synthesis of acyclo-*C*-nucleosides analogues bearing dihydro-6*H*-quinolin-5-ones **6j**,**l**,**o**, dihydro-5*H*-cyclopenta pyridin-5-one **6k**, tetrahydrocyclohepta [*b*]pyridine-5-one **6m**, and azafluorinone **6n**.

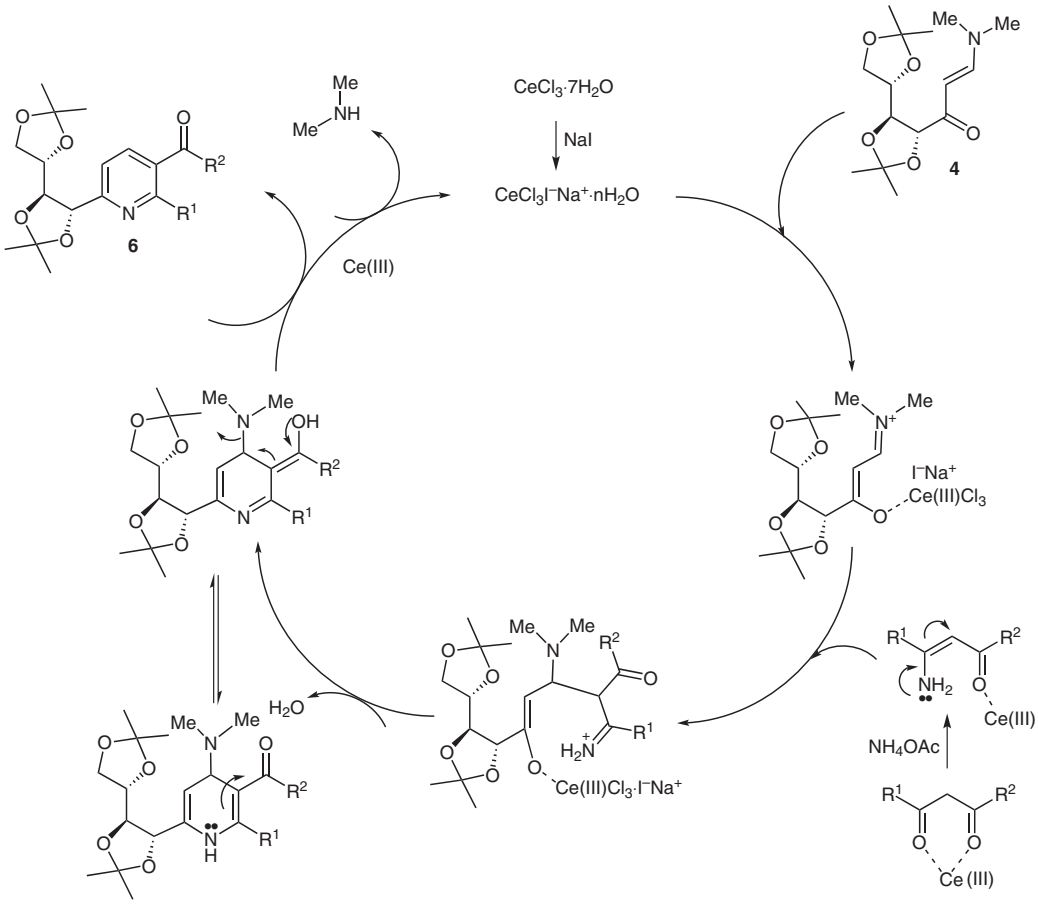
were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, ESI-MS, and HRMS analysis.

Under the reaction conditions, Meldrum's acid **5p** (Scheme 2) behaved as a masked ketone, generating acetone which condensed with ammonia and then reacted with **4** in the pyridine forming process to give 6-substituted picoline **6p** in 35% yield. Use of ammonium formate or ammonium carbonate instead of ammonium acetate did not alter the product or yield and increasing the equivalents of Meldrum's acid (2.5 equiv) was necessary to ensure maximum consumption of starting material **4** (75% yield).



Scheme 2 Formation of picoline analogue **6p**. *Reagents and conditions*: (a) NH_4OAc, $CeCl_3·7H_2O$-NaI, *i*-PrOH, reflux.

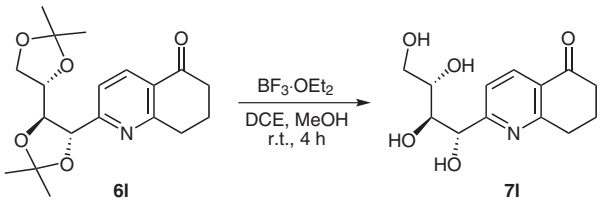
At this stage of investigation the exact mechanism of this reaction is not clear; although a plausible cerium-activated reaction sequence for the formation of **6** is presented here (Scheme 3). Based on the above results, and literature precedent on cerium-catalyzed chemical transformations,[12] both $CeCl_3·7H_2O$ and NaI are required in the



Scheme 3 CeCl3·7H2O-NaI-catalyzed plausible reaction sequence for the formation of acyclo-*C*-nucleoside analogues **6**

catalytic process. Although the enhanced catalytic activity exerted by NaI with $CeCl_3·7H_2O$ is still obscure, it is believed to be due to the formation of an activated complex $CeCl_3I^-Na^+·nH_2O$. Another unexplained aspect is the role of water as anhydrous $CeCl_3$ is found to be inactive. Mechanistically similar to the Bohlmann–Rahtz reaction the condensation is postulated proceed through a cerium-activated process[12] initially with the formation of enaminone from the corresponding 1,3-dicarbonyl compound and then Michael addition to the activated enaminone **4**. The intermediate thus formed can undergo cyclodehydration, followed by elimination of dimethylamine[13] leading to product **6**.

To test the applicability to generate a library of novel water soluble acyclo-*C*-nucleoside derivatives, **6l** was successfully deprotected with $BF_3·OEt_2$ in dichloroethane and methanol (Scheme 4). The acyclo-*C*-nucleoside derivative **7l** thus obtained was fully characterized by NMR spectroscopy and mass spectrometric analysis.



Scheme 4 Deprotection of **6l**

In conclusion, we have described an efficient method for the synthesis of a series of acyclo-*C*-nucleoside analogues bearing 2,3,6-trisubstituted pyridines **6a–f**,**i**, dihydro-6*H*-quinolin-5-ones **6j**,**l**,**o**, dihydro-5*H*-cyclopentapyridin-5-one **6k**, tetrahydrocyclohepta[*b*]pyridine-5-one **6m**, and azafluorinone **6n**. $CeCl_3·7H_2O$-NaI-catalyzed one-pot condensation of β-enaminone **4** with acyclic and cyclic 1,3-dicarbonyls **5a–p** and ammonium acetate proceeded efficiently to give the target products in very good yields. Low toxicity and ready availability of reagents and starting materials, shorter reaction times at comparatively low temperatures are advantages of this protocol. The present procedure is also readily amenable to parallel synthesis and the generation of new acyclo-*C*-nucleoside libraries and deprotection of ketal **6l** with $BF_3·OEt_2$ afforded water-soluble analogue **7l**. The complete library generation of these novel acyclo-*C*-nucleosides and associated biological evaluations will be reported in due course.

(2*S*,3*S*,4*S*,5*R*)-Hexane-1,2,3,4,5-pentanol (1)

To a solution of L-rhamnose (5.0 g, 30 mmol) in MeOH (25 mL) $NaBH_4$ (0.9 g, 25 mmol) was added in portions for 0.5 h. After vigorous stirring for another 0.5 h, the reaction mixture was neutralized with Dowex IR-120 H^+ resin (ca. 6.0 g) to remove the sodium salts. The solid resin was filtered and the MeOH solution was concentrat-

ed under vacuum to give L-rhamnitol (**1**, 4.96 g, 98%) as a viscous oil that was used in the next step without further purification.

(*R*)-1-[(4*S*,4′*S*,5*S*)-2,2,2′,2′-Tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl]ethanol (2)

To a solution of L-rhamnitol (**1**, 4.81 g, 29.0 mmol) in anhyd acetone (80 mL), 2,2-dimethoxypropane (7.54 mL, 72 mmol) and PTSA (0.4 g) were added under nitrogen and stirred at r.t. for 6 h. Triethylamine (2.0 mL) was added, and the reaction mixture was concentrated under vacuum to dryness. The residue obtained was purified by column chromatography (silica gel; hexane–EtOAc = 95:5) to afford (*R*)-1-[(4*S*,4′*S*,5*S*)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl]ethanol (**2**, 6.05 g) in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.15 (q, *J* = 6.0 Hz, 1 H), 3.93–4.05 (m, 2 H), 3.56–3.73 (m, 3 H), 3.25 (br s, 1 H), 1.43 (s, 3 H), 1.35 (s, 6 H), 1.33 (s, 3 H), 1.23 (d, *J* = 6.0 Hz, 3 H). The spectral data are in agreement with literature values.[12]

1-[(4*S*,4′*S*,5*R*)-2,2,2,2′-Tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl]ethanone (3)

To a cooled (–78 °C) solution of DMSO (4.3 mL, 60.9 mmol) in anhyd CH_2Cl_2 (20 mL) was added oxaloyl chloride (3.43 mL, 40.6 mmol) over 5 min under nitrogen. A solution of 1,2:3,4-di-*O*-isopropylidene-L-rhamnitol (**2**, 5.0 g, 20.3 mmol) in anhyd CH_2Cl_2 (15 mL) was added dropwise over 10 min, and the mixture was stirred at –78 °C for 1 h. Triethylamine (8.55 mL, 60.9 mmol) was introduced to the solution, the mixture was stirred at –78 °C for 20 min, allowed to warm up to r.t., H_2O (50 mL) was added, and the product was extracted with CH_2Cl_2 (6 × 25 mL). The organic phase was washed with brine solution and dried over anhyd Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography (silica gel; hexane–EtOAc = 97:3) to give 1-[(4*S*,4′*S*,5*R*)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl]ethanone (**3**, 4.46 g, 90%) as a colorless liquid: $[\alpha]_D^{25}$ –0.7 (*c* 1.0, $CHCl_3$); lit. $[\alpha]_D^{20}$ –0.1 (*c* 1.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.26 (d, *J* = 5.1 Hz, 1 H), 4.05–4.16 (m, 2 H), 3.91 (dd, *J* = 3.9, 4.5 Hz, 2 H), 2.28 (s, 3 H), 1.43 (s, 3 H), 1.39 (s, 3 H), 1.34 (s, 3 H), 1.32 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.0, 111.0, 109.5, 82.9, 77.8, 76.2, 66.3, 26.7, 26.4, 26.1, 25.9, 24.8. IR (neat): 2936, 1724, 1373, 1252, 1215, 1073 cm^{-1}. ESI-MS: *m/z* = 245 $[M + H]^+$, 267 $[M + Na]^+$. ESI-HRMS: *m/z* calcd for $C_{12}H_{20}O_5Na$: 267.1208 $[M + Na]^+$; found: 267.1212.

(*E*)-3-(Dimethylamino)-1-[(4S,4′*S*,5*R*)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl]-2-propenone (4)

To a solution of **3** (2.0 g, 8.19 mmol) in xylene (25 mL) was added under nitrogen *N*,*N*-dimethylformamide dimethylacetal (3.4 mL, 24.5 mmol) and the mixture refluxed for 7 h (monitored by TLC). The xylene was distilled off, and the crude residue was purified by column chromatography (silica gel; hexane–EtOAc = 3:7) to yield (*E*)-3-(dimethylamino)-1-[(4*S*,4′*S*,5*R*)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl]-2-propenone (**4**) as pale brown oil, 2.16 g (88%). $[\alpha]_D^{25}$ –27.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 12.8 Hz, 1 H), 5.42 (d, *J* = 12.8 Hz, 1 H), 4.10–4.28 (m, 3 H), 3.95–4.08 (m, 2 H), 3.13 (s, 3 H), 2.87 (s, 3 H), 1.47 (s, 3 H), 1.42 (s, 3 H), 1.36 (s, 3 H), 1.35 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.8, 154.0, 110.5, 109.4, 91.2, 81.5, 78.7, 76.3, 65.6, 44.9, 37.1, 27.1, 26.30, 26.3, 25.2. IR (neat): 2986, 2933, 1651, 1572, 1424, 1370, 1215, 1068. cm^{-1}. ESI-MS: *m/z* = 300 $[M + H]^+$, 322 $[M + Na]^+$. ESI-HRMS: *m/z* calcd for $C_{15}H_{25}NO_5Na$: 322.1630 $[M + Na]^+$; found: 322.1643.

General Procedure for the Synthesis of 2-[(4*R*,4′*S*,5*S*)-2,2,2′,2′-Tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl]-7,8-dihydroquinolin-5(6*H*)-one (6l)

To a mixture of (*E*)-3-(dimethylamino)-1-[(4*S*,4′*S*,5*R*)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl]-2-propenone (**4**, 0.3 g, 1.0 mmol), 1,3-cyclohexanedione (**5l**, 0.13 g, 1.2 mmol), NH_4OAc (0.15 g, 2.0 mmol) in *i*-PrOH (5 mL) were added $CeCl_3 \cdot 7H_2O$ (75 mg, 0.2 mmol) and NaI (30 mg, 0.2 mmol) and the mixture refluxed for 3 h (monitored by TLC). The reaction mixture was cooled to r.t., and the solid precipitate was filtered and washed with cold *i*-PrOH. The combined solvents were evaporated, and the crude residue was subjected to column chromatography (silica gel; hexane–EtOAc = 85:15) to obtain 2-[(4*R*,4′*S*,5*S*)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl]-7,8-dihydroquinolin-(6*H*)-one (**6l**, 0.306 g, 88%) as pale yellow oil. $[\alpha]_D^{25}$ –7.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.1 Hz, 1 H), 7.47 (d, *J* = 8.1 Hz, 1 H), 4.87 (d, *J* = 6.8 Hz, 1 H),4.26–4.37 (m, 2 H), 4.06–4.1 (dd, *J* = 2.8 Hz, 2 H), 3.12 (t, *J* = 6.2 Hz, 2 H), 2.66 (t, *J* = 6.0 Hz, 2 H), 2.14–2.24 (m, 2 H), 1.50 (s, 3 H) 1.44 (s, 3 H), 1.31 (s, 3 H), 1.24 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.71, 163.19, 163.26, 135.55, 127.16, 119.98, 110.8, 109.5, 81.4, 81.0, 76.2, 66.0, 38.5, 32.4, 27.1, 26.9, 26.2, 25.2, 21.8. IR (neat): 2985, 2928, 1691, 1585, 1376, 1216, 1158, 1069 cm^{-1}. ESI-MS: *m/z* 348 $[M + H]^+$. ESI-HRMS: *m/z* calcd for $C_{19}H_{25}NO_5Na$: 370.1630 $[M + Na]^+$; found: 370.1649.

6,6-Dimethyl-2-[(4*R*,4′*S*,5*S*)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl]-7,8-dihydroquinolin-5(6*H*)-one (6o)

Yield 78%; $[\alpha]_D^{25}$ –5.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 8.1 Hz, 1 H), 7.46 (d, *J* = 8.1 Hz, 1 H), 4.87 (d, *J* = 6.6 Hz, 1 H),4.26–4.37 (m, 2 H), 4.07 (d, *J* = 5.4 Hz, 2 H),3.13 (t, 6.4 Hz, 2 H), 2.02 (t, 6.4 Hz, 2 H), 1.50 (s, 3 H) 1.45 (s, 3 H), 1.30 (s, 3 H),1.25 (s, 3 H), 1.22 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.2, 163.0, 162.1, 136.4, 126.0, 120.0, 110.8, 109.5, 81.4, 81.0, 76.3, 66.0, 41.4, 35.2, 29.6, 28.8, 27.1, 26.9, 26.2, 25.2, 24.0. IR (neat): 2925, 2856, 1687, 1585, 1377, 1220, 1157, 1071 cm^{-1}. ESI-MS: *m/z* = 376 $[M + H]^+$. ESI-HRMS: *m/z* calcd for $C_{21}H_{29}NO_5Na$: 398.1943 $[M + Na]^+$; found: 398.1928.

Typical Procedure for the Deprotection of 6l

To a solution of compound **6l** (0.25 g, 0.72 mmol) in DCE–MeOH (1:1, 4 mL), $BF_3 \cdot OEt_2$ (0.6 mL, 2.6 mmol) was added and the mimxture stirred at 25 °C. After 4 h, Na_2CO_3 (0.5 g) was added, the solid residue was filtered and washed with MeOH. The organic solution was concentrated, and the crude residue was purified by column chromatography (silica gel, EtOAc–MeOH = 96:4) to give 2-[(1*S*,2*R*,3*S*)-1,2,3,4-tetrahydroxybutyl]-7,8-dihydroquinolin-5(6*H*)-one (**7l**, 0.17g) in 91% yield; mp 103–106 °C. $[\alpha]_D^{25}$ –14.3 (*c* 1.0, MeOH). ^{1}H NMR (300 MHz, D_2O): δ = 8.33 (d, *J* = 8.3 Hz, 1 H), 7.60 (d, *J* = 8.3 Hz, 1 H), 5.07 (d, *J* = 2.0 Hz, 1 H), 3.79–3.89 (m, 3 H), 3.67 (dd, *J* = 6.0 Hz, 1 H), 3.12 (t, *J* = 6.0 Hz, 2 H), 2.74 (t, *J* = 5.8 Hz, 2 H), 2.154–2.242 (m, 2 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 198.5, 168.8, 162.9, 134.7, 126.3, 120.3, 74.3, 72.8, 71.7, 63.8, 38.4, 32.2, 21.9. IR (KBr): 3348, 2946, 1699, 1587, 1384, 1095, 1046 cm^{-1}. ESI-MS: *m/z* = 268 $[M + H]^+$. ESI-HRMS: *m/z* calcd for $C_{13}H_{18}NO_5$ $[M + H]^+$: 268.1184; found: 268.1179.

Supporting Information

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are spectral data and copies of ^{1}H NMR, ^{13}C NMR, and HRMS of all novel products **3**, **4**, **6a–f**, **6i–p**,**7l**.

Acknowledgement

The authors are grateful to Dr. J. S. Yadav, Director, IICT and Dr. V. V. N. Reddy, Head, Organic Chemistry Division-II, IICT, Hyderabad for their continuous support, encouragement and financial assistance throughout the MLP projects. S.R.P. is grateful to CSIR for a fellowship (JRF).

References and Notes

(1) (a) Wellington, K. W.; Benner, S. A. *Nucleosides, Nucleotides Nucleic Acids* **2006**, *25*, 1309. (b) Wu, Q. P.; Simons, C. *Synthesis* **2004**, 1533. (c) Nasr, A. Z. *Nucleosides, Nucleotides Nucleic Acids* **2004**, *23*, 1825. (d) Belkadi, M.; Othman, A. A. *Trends Appl. Sci. Res.* **2011**, *6*, 17.

(2) (a) Alonso-Cruz, C. R.; Freire, R.; Rodriguez, M. S.; Suarez, E. *Synlett* **2007**, 2723. (b) Otero, I.; Methling, K.; Feist, H.; Michalik, M.; Quincoces, J.; Reinke, H.; Peseke, K. *J. Carbohydr. Chem.* **2005**, *24*, 809. (c) Montero, A.; Feist, H.; Michalik, M.; Quincoces, J.; Peseke, K. *J. Carbohydr. Chem.* **2002**, *21*, 305. (d) Sagar, R.; Park, S. B. *J. Org. Chem.* **2008**, *73*, 3270. (e) Montero, A.; Feist, H.; Michalik, M.; Quincoces, J.; Peseke, K. *Synthesis* **2002**, 664.

(3) For indolizidines, see: (a) Bonanni, M.; Marradi, M.; Cardona, F.; Cicchi, S.; Goti, A. *Beilstein J. Org. Chem.* **2007**, *3*, 44. For imidazoles, see: (b) Wu, W.; Yan, J.; Zhang, H. WO 2008/128041, **2008**. For benzimidazoles, see: (c) Sallam, M. A. E.; Waagen, V.; Anthonsen, T. *Carbohydr. Res.* **2008**, *343*, 388. For nitrones, see: (d) Fischer, R.; Druckova, A.; Fisera, L.; Hametner, C. *ARKIVOC* **2002**, *(viii)*, 80. For piperidines, see: (e) Boutefnouchet, S.; Moldvai, I.; Gacs-Baitz, E.; Bello, C.; Vogel, P. *Eur. J. Org. Chem.* **2007**, 3028. For other carbohybrids, see: (f) Yadav, L. D. S.; Rai, A.; Rai, V. K.; Awasthi, C. *Synlett* **2008**, 529. (g) Irmak, M.; Lahnert, T.; Boysen, M. M. K. *Tetrahedron Lett.* **2007**, *48*, 7890. (h) Roy, A. D.; Subramanian, A.; Mukhopadhyay, B.; Roy, R. *Tetrahedron Lett.* **2006**, *47*, 6857.

(4) (a) Le, G. T.; Abbenante, G.; Becker, B.; Grathwohl, G.; Halliday, J.; Tometzki, G.; Zuegg, J.; Meutermans, W. *Drug Discovery Today* **2003**, *8*, 701. (b) Rudloff, I.; Michalik, M.; Montero, A.; Peseke, K. *Synthesis* **2001**, 1686.

(5) (a) Bagley, M. C.; Dale, J. W.; Merritt, E. A.; Xiong, X. *Chem. Rev.* **2005**, *105*, 685. (b) Bagley, M. C.; Glover, G.; Merritt, E. A. *Synlett* **2007**, 2459. (c) Merritt, E. A.; Bagley, M. C. *Synlett* **2007**, 954. (d) Bagley, M. C.; Chapaneri, K.; Dale, J. W.; Xiong, X.; Bower, J. *J. Org. Chem.* **2005**, *70*, 1389. (e) Bagley, M. C.; Xiong, X. *Org. Lett.* **2004**, *6*, 3401.

(6) Bohlmann, F.; Rahtz, D. *Chem. Ber.* **1957**, *90*, 2265.

(7) Aulakh, V. S.; Ciufolini, M. A. *J. Org. Chem.* **2009**, *74*, 5750.

(8) (a) Kantevari, S.; Chary, M. V.; Vuppalapati, S. V. N. *Tetrahedron* **2007**, *63*, 13024. (b) Kantevari, S.; Chary, M. V.; Vuppalapati, S. V. N.; Lingaiah, N. *J. Heterocycl. Chem.* **2008**, 1099.

(9) (a) Lieby-Muller, F.; Allais, C.; Constantieux, T.; Rodriguez, J. *Chem Commun.* **2008**, 4207. (b) Davis, J. M.; Truong, A.; Hamilton, A. D. *Org. Lett.* **2005**, *7*, 5405. (c) Senaiar, R. S.; Young, D. D.; Deiters, A. *Chem. Commun.* **2006**, 1313. (d) Alnajjar, A.; Abdelkhalik, M. M.; Al-Enezi, A.; Elnagdi, M. H. *Molecules* **2009**, *14*, 68. (e) Riyadh, S. M.; Abdelhamid, I. A.; Al-Matar, H. M.; Hilmy, N. M.; Elnagdi, M. H. *Heterocycles* **2008**, *75*, 1849. (f) Al-Saleh, B.; Abdelkhalik, M. M.; Eltoukhy, A. M.; Elnagdi, M. H. *J. Heterocycl. Chem.* **2002**, *39*, 1035. (g) Bashford, K. E.; Burton, M. B.; Cameron, S.; Cooper, A. L.; Hogg, R. D.; Kane, P. D.; MacManus, D. A.; Matrunola, C. A.; Moody, C. J.; Robertson, A. A. B.; Warne, M. R. *Tetrahedron Lett.* **2003**, *44*, 1627. (h) Omran, F. A.; Awadi, N. A.; Khair, A. A. E.; Elnagdi, M. H. *Org. Prep. Proced. Int.* **1997**, *29*, 285. (i) Reddy, G. J.; Latha, D.; Thirupathaiah, C.; Rao, K. S. *Tetrahedron Lett.* **2005**, *46*, 301.

(10) (a) Tambade, P. J.; Patil, Y. P.; Bhanage, B. M. *Curr. Org. Chem.* **2009**, *13*, 1805. (b) Comelles, J.; Moreno-Mañas, M.; Vallribera, A. *ARKIVOC* **2005**, *(ix)*, 207.

(11) (a) Bartoli, G.; Marcantoni, E.; Sambri, L. *Synlett* **2003**, 2101. (b) Bartoli, G.; Fernandez-Bolanos, J. G.; Antonio, G. D.; Foglia, G.; Giuli, S.; Gunnella, R.; Mancinelli, M.; Marcantoni, E.; Paoletti, M. *J. Org. Chem.* **2007**, *72*, 6029. (c) Khodaei, M. H.; Khosropour, A. R.; Kookhazadeh, M. *Synlett* **2004**, 1980. (d) Christoffers, J.; Kauf, T.; Werner, T.; Rössle, M. *Eur. J. Org. Chem.* **2006**, 2601.

(12) (a) Haines, A. H.; Lamb, A. J. *Carbohydr. Res.* **2000**, *325*, 323. (b) Jenkinson, S. F.; Booth, K. V.; Gullapalli, P.; Morimoto, K.; Izumari, K.; Fleet, C. W. J.; Watkin, D. J. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2008**, *64*, o1705. (c) Methling, K.; Kopf, J.; Michalik, M.; Reinke, H.; Burger, C.; Oberender, H.; Peseke, K. *J. Carbohydr. Chem.* **2003**, *22*, 537.

(13) We thank one of the referees for suggesting conjugated dihydropyridine intermediate in the mechanistic sequence in Scheme 3.