Organic LETTERS

Letter

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The Synthesis of Tenofovir and Its Analogues via Asymmetric Transfer Hydrogenation

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Supporting Information

ABSTRACT: A series of tenofovir analogues with potential antiviral and immunobiologically active compounds were synthesized through an asymmetric transfer hydrogenation reaction from achiral purine derivatives. Up to 97% *ee* and good to excellent yields were achieved under mild conditions through short reaction steps. The present report suggests an efficient process to acquire tenofovir and its analogues.

Acyclonucleoside and acyclonucleotide analogues which possess a broad spectrum of antiviral activities are currently used in clinics. As a typical example, 9-[2-(*R*)-(phosphonomethoxy)propyl]adenine (*R*-PMPA, tenofovir, Figure 1)[1−5]showed significant anti-HIV/HBV activity. In 2001, tenofovir disoproxil fumarate was approved by the FDA for the treatment of HIV infection. Clinically, this drug can be used by itself or in combination with other drugs. Tenofovir disoproxil fumarate was also approved for therapy of hepatitis B in 2008. The excellent treatment effect has led to significant declines in HIV/HBV-associated morbidity and mortality.[1b,2b,4,6] Surprisingly, some acyclonucleotides owning the same chiral side chain with tenofovir, such as (*R*)-PMPDAP,[7] 6-cypr-(*R*)-PMPDAP,[8] (*R*)-PMPG,[9] and (*R*)-PMPMAP,[2a] have been shown to possess various medicinal activities (Figure 1). Hence, there is considerable interest in the development of effective methods for the synthesis of tenofovir and its analogues.

There were two routes that were mainly employed for the synthesis of optical tenofovir (Scheme 1). One route is based on alkylation of adenine with chiral toslate (**A**) which is synthesized from (*R*)-2-(2-tetrahydropyranyloxy)-1-propanol

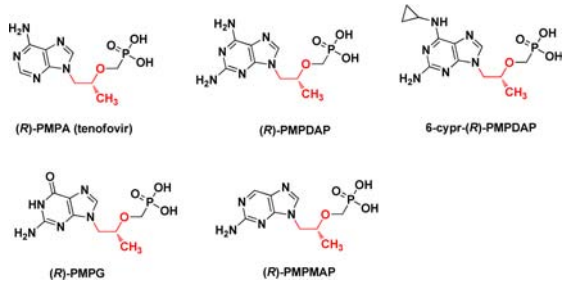
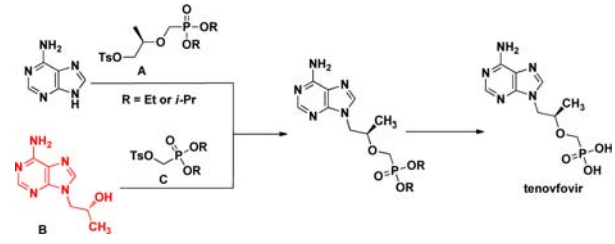


Figure 1. Structures of tenofovir and its analogues possessing medicinal activities.

Scheme 1. Reported Methods for the Synthesis of Tenofovir



through 5 steps.[2a] Another route is based on the condensation of (*R*)-1-(6-amino-9*H*-purin-9-yl)propan-2-ol (**B**) and purchasable toslate (**C**). The latter is used commonly, and four main approaches have been developed for the preparation of **B** (Scheme 2).

As shown in Scheme 2, the reported methods for the synthesis of (*R*)-1-(6-amino-9*H*-purin-9-yl)propan-2-ol (**B**) include the following: (1) In 1967, Schaeffer group first developed a 6 steps route to construct **B**, in which (*R*)-2-hydroxypropanoic acid was used as the chiral starting material (Scheme 2, Route 1);[3] (2) Subsequently, a 5 steps route for the synthesis of **B** was realized, which required NaAl$H_2(OCH_2CH_2OMe)_2$ for the ester reduction and (*R*)-isobutyl 2-hydroxypropanoate as the chiral starting material (Scheme 2, Route 2);[10] (3) The commonly used method in production **B** was started from chiral (*R*)-2-hydroxypropanoate or (*S*)-glycidol in 3 steps, and the hazardous hydrogen and Pd/C were used (Scheme 2, Route 3);[11] (4) In 1996, Jacobsen group prepared product **B** in 5 steps, in which the chiral side chain was synthesized from the asymmetric ring-opening of propylene oxide with (salen)CrN_3 as the catalyst (Scheme 2,

Received: February 24, 2014
Published: March 20, 2014

dx.doi.org/10.1021/ol500583d | *Org. Lett.* 2014, 16, 2014−2017

Scheme 2. Reported Methods of Preparing (*R*)-1-(6-Amino-9*H*-purin-9-yl)propan-2-ol (B) and Our Proposal

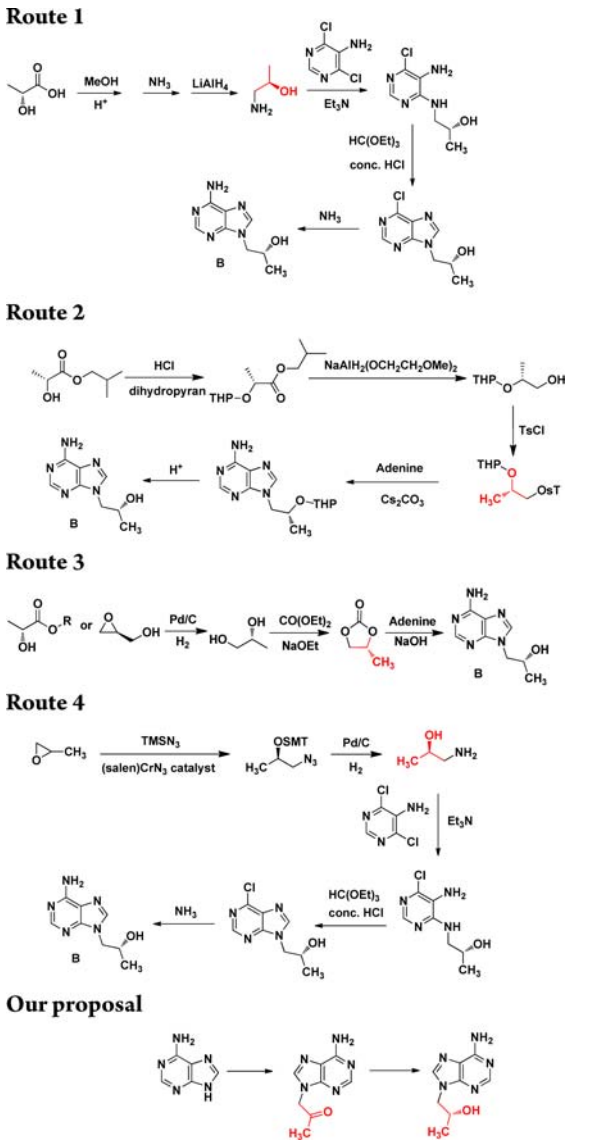
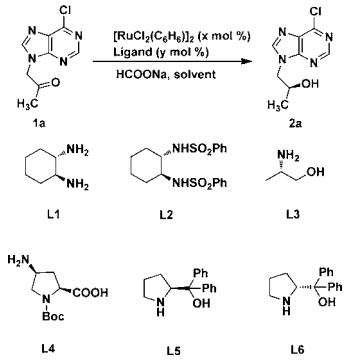


Table 1. Optimization of the Reaction Conditions[a]



entry	*x*	ligand	*y*	solvent	yield (%)[b]	ee (%)[c]
1	5	**L1**	6	H_2O	70	58
2	5	**L2**	6	H_2O	65	8
3	5	**L3**	6	H_2O	80	15
4	5	**L4**	6	H_2O	62	13
5	5	**L5**	6	H_2O	40	75
6	**5**	**L5**	**6**	**CH_3CN**	**97**	**96**
7	5	**L5**	6	*i*-PrOH	78	90
8	5	**L5**	6	EtOH	65	84
9	5	**L5**	6	DMF	50	95
10	5	**L5**	6	THF	35	94
11	5	**L5**	6	DMSO	NR	–
12	1	**L5**	1.2	CH_3CN	23	96
13	3	**L5**	3.6	CH_3CN	60	96
14	4	**L5**	4.8	CH_3CN	81	96
15	5	**L5**	5	CH_3CN	94	95
16	5	**L5**	7.5	CH_3CN	97	96
17	5	**L5**	10	CH_3CN	97	96
18	5	**L5**	12	CH_3CN	90	96[d]
19	4	**L5**	8	CH_3CN	86	96
20	3	**L5**	6	CH_3CN	75	96

[a]Reaction conditions: The metal $[RuCl_2(C_6H_6)]_2$ and the ligands (**L1**–**L5**) were added to the solvent (1.5 mL), and the mixture was stirred for 1 h at ambient temperature (20–30 °C). Then HCOONa (3.0 mmol) was added; after stirring for 10 min, **1a** (0.3 mmol) was added. [b]Yield of isolated product based on **1a**. [c]Determined by chiral HPLC. [d]The reaction time was 52 h, and some byproducts were detected. N.R. = No Reaction.

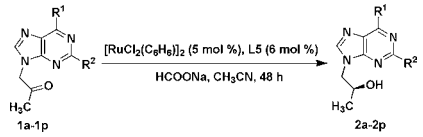
Route 4).[12] Although great efforts have been devoted to the synthesis of product **B** and remarkable progress has been made, there are still some problems unsolved. The current methods all need chiral side chains, and suffer from either multiple-steps procedure, expensive reagents or harsh reaction conditions. Thus, developing a catalytic asymmetric route to construct product **B** with short steps, mild reaction conditions is challenging and desirable.

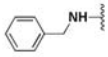
Asymmetric transfer hydrogen processes are attracting increasing interest from people in recent years in view of their operational simplicity and stereoselectivity.[13] The catalytic asymmetric transfer hydrogen of ketones by use of metal complexes is an important process for the synthesis of optically pure alcohols.[14,15] Considering the distinguished advantages of asymmetric transfer hydrogen and our research experiences on the synthesis of purine derivatives,[16] we envisioned that optical **B** could be synthesized by asymmetric transfer hydrogenation of 1-(9*H*-purin-9-yl)propan-2-one (Scheme 2, our proposal). In the present work, we present a method for the synthesis of tenofovir analogues from achiral purine derivatives for the first time.

First, we researched the enantiomeric excess (*ee*) of 1-(6-chloro-9*H*-purin-9-yl)propan-2-ol (**2a**) by asymmetric transfer hydrogenation of 1-(6-chloro-9*H*-purin-9-yl)propan-2-one (**1a**) with $[RuCl_2(C_6H_6)]_2$ and the ligands (**L1**–**L5**) in water at ambient temperature (Table 1). We found that **2a** had a better *ee* with (*S*)-diphenyl(pyrrolidin-2-yl)methanol (**L5**) as the ligand than other ligands (Table 1, entries 1–5). Hence, we began to screen the solvents, and the experimental results showed that the reaction gave the highest yield (97%) and *ee* (96%) in CH_3CN than other solvents (Table 1, entries 5–11). Though the reaction gave a high *ee* in DMF and THF, the yield was low. In addition, surprisingly the reaction cannot proceed in DMSO (Table 1, entry 11). The catalyst loading of $[RuCl_2(C_6H_6)]_2$ had a significant influence on the reaction. As can be seen in Table 1, the yields decreased from 97% to 23% with the catalyst loading of $[RuCl_2(C_6H_6)]_2$ changed from 5 to 1 mol % (Table 1, entries 12–14). The ratio of $[RuCl_2(C_6H_6)]_2$ to ligand also had some effect on the reaction

dx.doi.org/10.1021/ol500583d | *Org. Lett.* 2014, 16, 2014–2017

Table 2. Reaction of Purin-9-yl propan-2-ones with Various Substituents on Purine Rings[a]



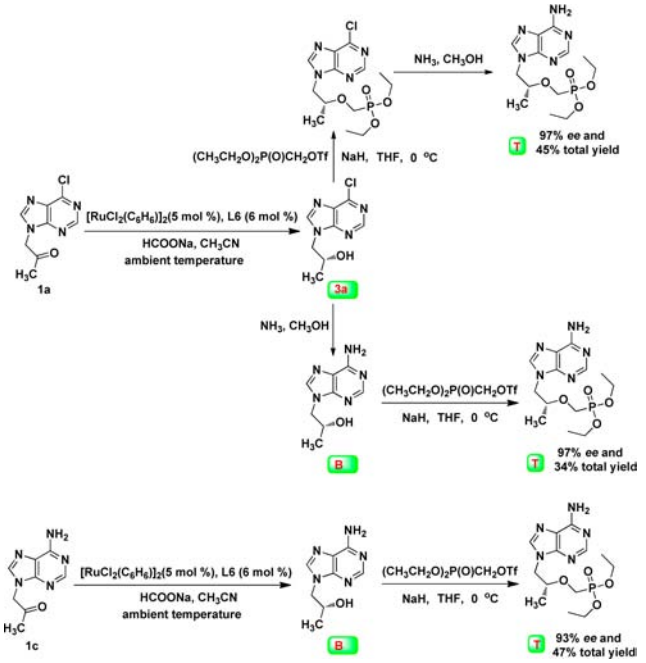
entry	R^1	R^2	product	yield (%)[b]	*ee* (%)[c]
1	Cl	H	**2a**	97	96[e] (*S*)
			3a[d]	96	97[e] (*R*)
2	I	H	**2b**	62	96
3	NH_2	H	**2c**	60	93[e] (*S*)
			B[d]	64	93[e] (*R*)
4	I	Cl	**2d**	50	97
5	Cl	Cl	**2e**	80	94
6	Cl	NH_2	**2f**	58	92
7	$N(Et)_2$	H	**2g**	87	96
8	$N(Et)_2$	Cl	**2h**	97	95
9		H	**2i**	90	94
10		Cl	**2j**	95	95
11		H	**2k**	83	94[e]
12		Cl	**2l**	92	94
13		H	**2m**	54	95[e]
14		H	**2n**	52	94
15		H	**2o**	90	95[e]
16		Cl	**2p**	94	95

[a]Reaction conditions: $[RuCl_2(C_6H_6)]_2$ (5 mol %) and **L5** (6 mol %) were added to CH_3CN (1.5 mL), and the mixture was stirred for 1 h at ambient temperature (20−30 °C). Then HCOONa (3.0 mmol) was added; after stirring for 10 min, purine (0.3 mmol) was added. The reaction was conducted for 48 h at ambient temperature. [b]Yield of isolated product based on **1a−1p**. [c]Determined by chiral HPLC. [d]The ligand was **L6**. [e]The *ee* of the product was determined by its trimethylsilyl ether.

(entries 15−20). Experimental results showed that the reaction can be finished within 48 h. When the reaction was carried out below 20 °C, a low yield resulted with a prolonged reaction time to 56 h. When the reaction temperature rose to above 35 °C, byproducts and a lower *ee* were detected. In addition, we found that 10 equiv of HCOONa were the most suitable in the experiment; reducing the amount of HCOONa resulted in a low conversion rate or long reaction time. From these observations, the best result was achieved with 5 mol % of $[RuCl_2(C_6H_6)]_2$ and 6 mol % of **L5** in the presence of 10 equiv of HCOONa in CH_3CN at ambient temperature (Table 1, entry 6).

To evaluate the general applicability and versatility of the method, a group of different purine derivatives were subjected

Scheme 3. Synthesis of (*R*)-Diethyl (((1-(6-Amino-9*H*-purin-9-yl)propan-2-yl)oxy)methyl)phosphonate (T)



to the optimized reaction conditions and the results are shown in Table 2. As can be seen in Table 2, all of the purine substrates can give high *ee* values (92−97%), but the different substituents of the purine ring have a certain influence on the yields of the products and a very tiny influence on the *ee* of the products. Though some substrates afforded high yields (Table 2, entries 1, 7−12, 15, 16), others only resulted in moderate yields and high *ee*'s. Some alkyl ketones and aryl ketones were also subjected to the optimized reaction conditions. Unfortunately, one of the substrates gave low yields and *ee*'s while the others did not participate in the reaction.[17] The absolute configuration of **2a** and **2c** was determined as *S* by comparison with the reported optical rotations (see Supporting Information for details). In order to obtain **B** and its analogues, we used **L6** in place of **L5** to carry out some of the reaction. To our delight, the desired products **3a** and **B** having an *R* configuration were synthesized with up to 97% *ee*. It is noteworthy that **3a** and **B**[18] could be converted into (*R*)-diethyl (((1-(6-amino-9*H*-purin-9-yl)propan-2-yl)oxy)methyl)phosphonate (Scheme 3, **T**), the final intermediate for tenofovir.[19] Compared with the reported methods[3,10−12] which used chiral side chains principally, our method is more simple and efficient.

For the purpose of examining the synthetic potential of the present approach, gram-scaled **1a** was used for the synthesis of **2a** under the optimal conditions, affording an 85% yield and 96% *ee*.

In conclusion, we have developed a mild, new synthetic method to attain chiral acyclonucleosides from achiral purine derivatives. It is the first report for the synthesis of chiral acyclonucleosides by asymmetric transfer hydrogenation. A wide range of 1-(9*H*-purin-9-yl)propan-2-one compounds are useful substrates. Good to excellent yields (up to 97%) and satisfactory enantioselectivities (up to 97% *ee*) were obtained. The reaction can be amplified to gram scales. Since the target molecules could be further modified conveniently, this method suggests an opportunity for preparing tenofovir and its analogues efficiently.

dx.doi.org/10.1021/ol500583d | *Org. Lett.* 2014, 16, 2014−2017

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and full spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the National Science Foundation of China (No. 21102038), The Program for Changjiang Scholars and Innovative Research Team in University (IRT1061), and The Program for Innovative Research Team in University of Henan Province (2012IRTSTHN006).

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(17) Acetophenone, 1-(4-nitrophenyl)ethanone, and 4-phenylbutan-2-one were subjected to the optimized reaction conditions. Acetophenone and 4-phenylbutan-2-one did not participate in the reaction. 1-(4-Nitrophenyl)ethanone gave 33% isolated yields and 34% *ee*. Prolonging the reaction time or changing the metal/ligand ratio could not increase the yield of 1-(4-nitrophenyl)ethanol.

(18) **1b** could also be converted into **T** through the similar transformation of **1a** using the **L6** ligand.

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