Organic Process Research & Development **2009**, *13*, 450–455

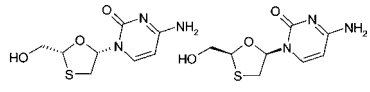
A Novel Method for Large-Scale Synthesis of Lamivudine through Cocrystal Formation of Racemic Lamivudine with (*S*)-(−)-1,1′-Bi(2-naphthol) [(*S*)-(BINOL)]

Bhairab Nath Roy,* Girij Pal Singh, Dhananjai Srivastava, Harishchandra S. Jadhav, Manmeet B. Saini, and Umesh P. Aher
Lupin Research Park, Lupin Ltd., 46A/47A Nande Village, Mulshi Taluka, Pune - 411042, India

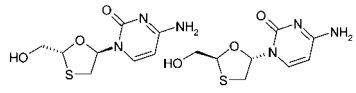
Abstract:
A large-scale synthesis of (−)-[2*R*,5*S*]-4-amino-1- [2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1*H*)-pyrimidin-2-one (lamivudine) through resolution of racemic lamivudine by cocrystal formation with (*S*)- BINOL has been demonstrated. Lamivudine of very high purity with an enantiomeric excess of more than 99.9% was obtained. All four isomers of lamivudine have also been separated and characterized. Interestingly, *cis*-(−)- and *trans*-(−)-enantiomers form cocrystals with (*S*)-BINOL.

1. Introduction

The nucleoside analogue *cis*-(±)-4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1*H*)-pyrimidin-2-one, displays very interesting biological activity. Both the optical isomers, viz. *cis*-(−) and *cis*-(+), inhibit human immunodeficiency virus 1 and 2 in vitro.[1] However, the *cis*-(−)-enantiomer is considerably less cytotoxic than the other optical isomers[2,3] shown below.



cis (-) (2R, 5S) *cis* (+) (2S, 5R)



trans (-) (2R, 5R) *trans* (+) (2S, 5S)

There are several methods reported[1−15] for the synthesis of **A** as a single enantiomer. However, there is no efficient method reported for the synthesis of all the four stereoisomers of lamivudine. We report here a large-scale cost-effective method of lamivudine synthesis having high purity with enantiomeric excess of >99.9% through cocrystal formation with (*S*)-BINOL. The other three pure isomers were also obtained with high enantiomeric excess during the process.

Optical resolution of *cis*-(±)-enantiomer of lamivudine to pure *cis*-(−) optical isomer through diastereomeric salt has been reported to be unsuccessful by commonly used techniques of formation of a diastereomeric salt with acids such as malic acid, mandelic acid, dibenzoyl tartaric acid, 3-bromocamphor-8-sulfonic acid, 10-camphorsulfonic acids, and di-*p*-toluoyltartaric acid. [16]

(*S*)-BINOL is a versatile chiral ligand and extensively used for asymmetric synthesis[17] and reported to form complexes.[18] Resolution of omeprazole, an active pharmaceutical ingredient, via host−guest complex formation is known.[19a,b] Earlier in our laboratory we have demonstrated a resolution of omeprazole[19c] using (*S*)-BINOL through host−guest complex formation[20] from its racemic mixture.

In the present work we have found that (*S*)-BINOL forms a cocrystal with *cis*-(−)-enantiomer resulting in an efficient process for synthesis of lamivudine of very high purity and yield. Interestingly, it has been observed that only *cis*-(−) and *trans*-(−) optical isomers form cocrystal with (*S*)-BINOL leaving behind *cis*-(+) and *trans*-(+) optical isomers in the solution.

The characterization data of all the isomers of lamivudine is summarized (Table 1) and Scheme 1depicts the synthetic sequence for obtaining all the four optical isomers of lamivudine.

2. Results and Discussion

In the present work (Scheme 1), compound **1** was prepared as per reported method.[22] Cis and trans isomers were separated by preparing the salt of (*S*)-(+) mandelic acid. The mandelate salt of *cis*-(±)-**2** was precipitated as solid leaving behind *trans*-(±)-**3**-(*S*)-(+)-mandelate salt in mother liquor. Compound **2** thus obtained was treated with 15% methanolic ammonia at room temperature to get *cis*-(±)-**5**. Compound **5** was heated at 55−60 °C with *S*-(−)-BINOL in methanol to get the cocrystal of (*S*)-BINOL with the *cis*-(−)-enantiomer as a crystalline solid **6** upon slowly cooling to ambient temperature (yield 70−75%). The stoichiometric ratio (*S*)-BINOL with *cis*-(−)-enantiomer was

* Corresponding author. Telephone: +91 2066749403. Fax: +91 2066749560. E-mail: bnroy@lupinpharma.com.

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10.1021/op800228h CCC: $40.75 © 2009 American Chemical Society
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Table 1. **Characterization details of lamivudine and its stereoisomers**

		DSC @ 10 °C/min		TGA				
cmpd	melting point (°C)	peak (°C)	ΔH (J/g)	weight loss %	temp range (°C)	HPLC purity (ee (%)	specific optical rotation (deg) $[\alpha]_D$ at 25 °C (c 0.5%, water)	moisture content (%)
trans-(−)	168.0	174.58	72.31	0.49	20−300	98.85	−120.57	0.22
trans-(+)	172.6	178.49	94.68	0.116	20−300	98.47	+122.41	0.02
cis-(+)	171.4	177.9	144.48	0.00	20−300	98.20	+98.85	0.01
cis-(−)[a]	176.0−177.0	140.34 and 182.05	114.28 and 74.27	1.49	20−300	99.90	−98.32	1.63

[a] Form-1.[21]

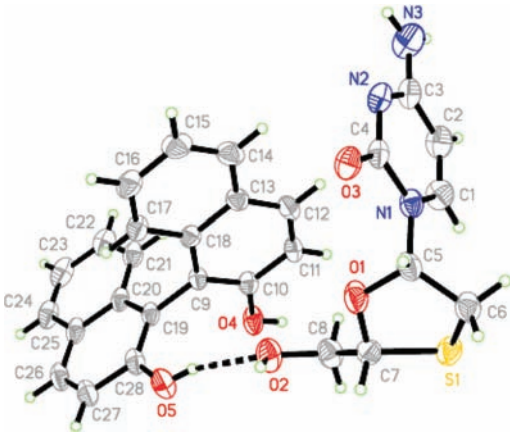

Figure 1. **ORTEP drawing of the (*S*)-BINOL cocrystal (6) showing the cocrystal formation has taken place. Displacement ellipsoids are drawn at the 30% probability level, and H atoms are shown as small spheres of arbitrary radii. Dashed line denotes hydrogen bonds.**

found to be 1:1 in the cocrystal. The solid thus obtained was treated with dilute hydrochloric acid to get lamivudine of very high purity having ee >99.9%.

Interestingly the (+) isomer **B** which did not form the cocrystal with (*S*)-BINOL was isolated from mother liquor **7** by merely washing with ethyl acetate to remove excess of (*S*)-BINOL. The solid thus obtained was recrystallised with water as well as with methanol.

The *trans*-(±)-isomer was isolated from the mother liquor obtained after filtering *cis*-mandalate salt **2**. On treatment of *trans*-(±)-isomer, so obtained, with (*S*)-BINOL in methanol, only *trans*-(−) optical isomer was observed to form a cocrystal with (*S*)-BINOL **8**. The solid thus separated was filtered and dried. The cocrystal thus obtained was treated with dilute hydrochloric acid to get the pure *trans*-(−) optical isomer **C**. The *trans*-(+) optical isomer **D** was isolated from mother liquor **9** as per the procedure adopted for the isolation of optical isomer **B**, which was crystallized either with water or methanol or a suitable mixture thereof.

Moreover, when the mixture of four isomers was treated with (*S*)-BINOL, a mixture of cocrystals of both *cis*-(−)- and *trans*-(−)-isomers was obtained, leaving in the mother liquor *cis*-(+) and *trans*-(+) as a mechanical mixture with (*S*)-BINOL. Although the melting point difference between the two cocrystals **6** (190.1−190.6 °C) and **8** (224.0−227.2 °C) was considerably high, these cocrystals were not isolated in desired purity by fractional crystallization in commonly used solvents like methanol, ethanol, and isopropanol. None of the isomers of compound **A** was found to form cocrystals either with racemic BINOL or with (*R*)-BINOL under identical conditions.

Table 2. **Crystal data and structure refinement**

sr. no.		crystal data
1	empirical formula	$C_8H_{11}N_3O_3S \cdot C_{20}H_{14}O_2$
2	formula weight	515.57
3	temperature	273(2) K
4	wavelength	0.71073
5	crystal system	orthorhombic
6	space group	$P2_12_12_1$
7	unit cell dimensions	$a = 9.0929(9)$ Å; $\alpha = 90°$ $b = 2.3452(12)$ Å; $\beta = 90°$ $c = 22.031(2)$ Å; $\gamma = 90°$
8	volume	2473.0(4) Å^3
9	Z	4
10	calculated density	1.385 Mg/m^3
11	absorption coefficient	0.176 mm^{-1}
12	F (000)	1080
13	crystal size	0.22 mm × 0.17 mm × 0.12 mm
14	θ range for data collection	1.85 to 25.00°
15	limiting indices	$10 \le h \le 10$ $-14 \le k \le 14$ $-26 \le l \le 26$
16	reflections collected/unique	17528/4353 [R(int) = 0.0293]
17	completeness to θ	25.00; 100.0%
18	absorption correction	none
19	refinement method	full-matrix least-squares on F^2
20	data / restraints / parameters	4353 / 0 / 354
21	goodness-of-fit on F^2	1.052
22	final R indices [I > 2σ(I)]	R1 = 0.0292 wR2 = 0.0770
23	R indices (all data)	R1 = 0.0321 wR2 = 0.0798
24	absolute structure parameter	0.02 (6)
25	largest diff. peak and hole	0.188 and −0.129 e·Å^{-3}
26	measurement	Bruker Smart Apex CCD diffractometer
27	software used	SHELXTL-PLUS

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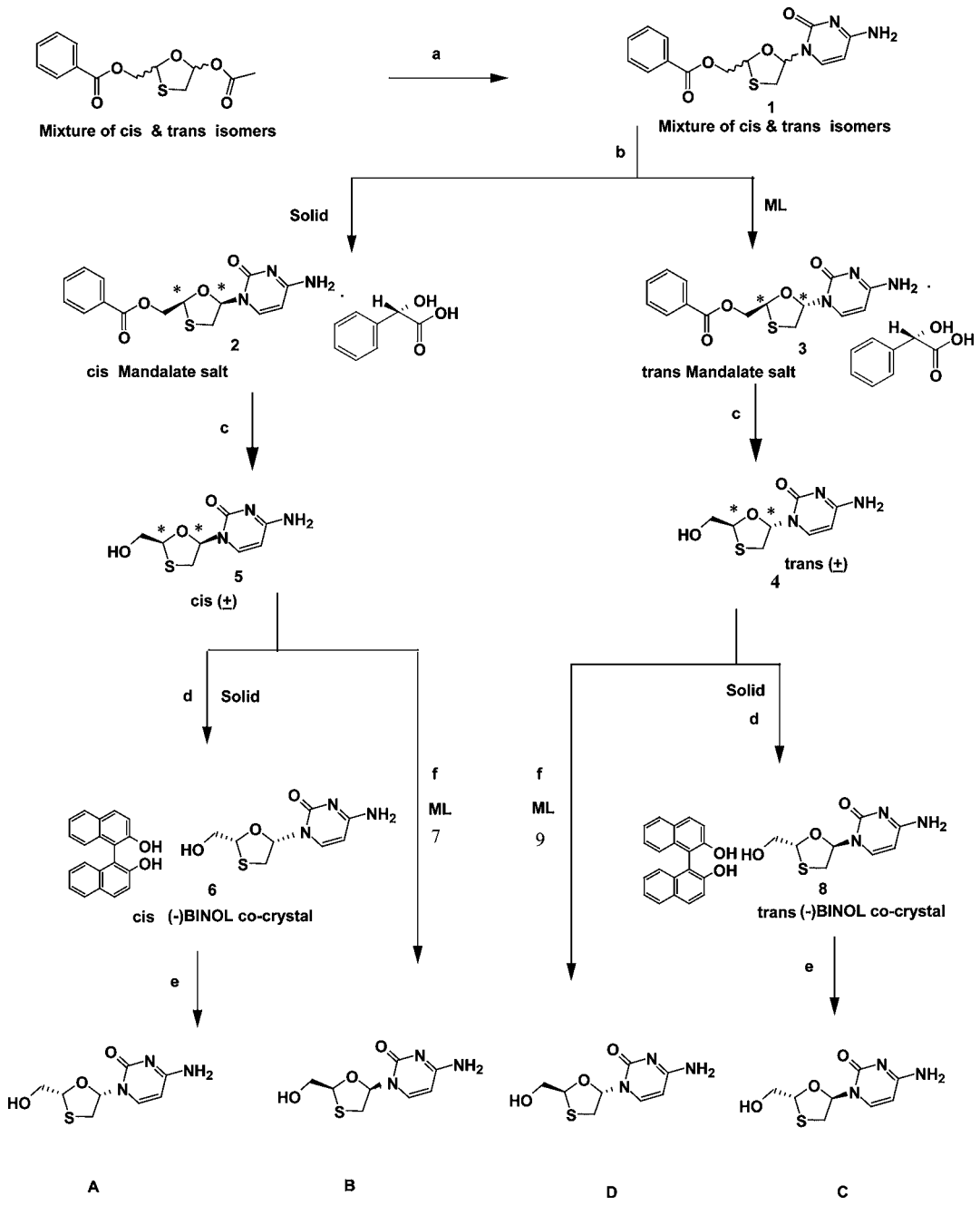
Scheme 1[a]



[a] Reagents and conditions: (a) cytosine, HMDS, TMCS. (b) *S*-(+)-Mandelic acid, ethyl acetate, 70 °C then rt. (c) 25% methanolic ammonia, ethanol. (d) (*S*)-BINOL, methanol, 65°C. (e) Ethyl acetate, water, aq. HCl, NaOH 25°C. (f) Ethyl acetate, water.

2.1. X-ray Diffraction Data of Cocrystal 6. Crystal data of cocrystal **6** are given in Figure 1. Crystal structure was measured on Bruker Smart Apex CCD diffractometer having software SHELXTL-PLUS at temperature 273 (2) K and wavelength 0.71073 Å and θ range for data collection was 1.85−25°. Crystallographic data and hydrogen bonding in compound **6** are given in Table 2 and Table 3, respectively.

3. Conclusion

A highly efficient and large-scale synthesis of lamivudine has been developed. The synthesis involved the

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Table 3. **Hydrogen bonds of compound 6 (BINOL cocrystal)**

D−H···A	*d*(D−H) (Å)	*d*(H···A) (Å)	*d*(D···A) (Å)	∠(DHA) (deg)
O(2)−H(2O)···N(2)[a]	0.89(3)	1.92(3)	2.777(2)	162(3)
O(4−H(4O)···O(3)[b]	0.75(3)	1.91(3)	2.642(2)	169(3)
O(5)−H(5O)···O(2)	0.76(3)	1.99(3)	2.696(2)	156(3)
N(3)−H(3A)···O(1)[c]	0.87(4)	2.28(4)	2.988(3)	139(3)
N(3)− H(3B)···O(4)[d]	0.84(3)	2.32(3)	3.060(3)	147(3)

[a] Symmetry transformations used to generate equivalent atoms: $-x, y + 1/2, -z + 1/2$. [b] $x + 1, y, z$. [c] $-x, y - 1/2, -z + 1/2$. [d] $-x + 1, y - 1/2, -z + 1/2$.

separation of enantiomers by forming the cocrystal with (*S*)-(−)-BINOL. All four isomers were separated. The recovery and recycling of resolving agent (*S*)-BINOL has also been established.

Interestingly, out of four isomers only *cis*-(−)-**A** and *trans*-(−)-**C** formed the cocrystal with (*S*)-BINOL, whereas *cis*-(+)-**B** and *trans*-(+)-**D** isomers did not form the cocrystal. Moreover, it was difficult to separate the mixture of *cis*-(−)- and *trans*-(−)-(*S*)-BINOL cocrystal by fractional crystallization to the extent of obtaining *cis*-(−)-**A** of ee > 99%. Therefore, separation of the *cis*- and *trans*-isomers prior to cocrystal formation with (*S*)-BINOL was necessary through (*S*)-(+)-mandelate salt formation.

4. Experimental Section

All commercially available reagents and solvents were employed without prior purification. Reactions were monitored by thin layer chromatography on silica gel plates (Merck 60_{F254}) and stained by the use of 2,4-dinitrophenylhydrazine.

4.1. Analytical Methods. The enantiomeric excess (ee) was determined by HPLC using a Shimadzu LC 2010 system equipped with a chiral column (Chiracel OJH, 4.6 mm × 250 mm, 5 μm), column oven temperature 15 °C, and UV visible detector. Mobile phase is *n*-hexane (900 mL):ethanol (100 mL):diethyl amine (2 mL):gl. acetic acid (1 mL), with 1.0 mL min^{-1}flow rate, injection volume 20 μL having concentration of 1000 ppm. The retention time for the optical isomer **A** is 24.5 min; NMR spectra were obtained at 200 and 400 MHz Bruker instruments, with $CDCl_3$/DMSO as solvent. Chemical shifts (δ) are given in ppm relative to tetramethylsilane (δ = 0 ppm) or to residual protons in the solvent as internal standard. IR spectra were recorded with a Perkin-Elmer Spectrum (model: Spectrum 100), and absorption bands are given in cm^{-1}. TGA were recorded on Perkin-Elmer model Pyris 1 at the rate of 10 °C/min, and weight loss is given in percentage. DSC was recorded on Perkin-Elmer model Diamond DSC at the rate of 10 °C/min, and endothermic peak is reported in °C and ΔH is reported in J/g. Melting point was recorded on Mettler Toledo apparatus with 1 °C/min heating rate. Moisture content was determined by the Karl Fischer titration method with Metrohm instrument.

4.2. *cis*-(±)-2-Benzoyloxymethyl-5-cytosin-1-yl-1,3-oxathiolane Mandalate 2. Compound **1** (70 kg, 0.14 mol) and *S*-(+)-mandelic acid (40.96 kg; 0.26 mol) was dissolved in ethyl acetate (420 L) at 65−70 °C and stirred for 1−2 h. The reaction mixture was then cooled to ambient temperature. The solid thus precipitated was filtered and washed with methanol (280 L) to afford compound **2** (yield: 23.95 kg, 46.98%).

IR spectra [Nujol Mull] (cm^{-1}): 707, 963, 1060, 1252, 1376, 1459, 1586, 1707, 1719, 2724, 2855, 2923, 2951, 3315, and 3583.

4.3. *cis*-(±)-2-Hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (Racemic Lamivudine) 4. The compound **2** (70 kg; 144.32 mol) was suspended in the 15% methanolic ammonia (1400 L) and stirred for 8−10 h at ambient temperature. After the completion of reaction, excess of solvent was recovered under vacuum. The solid thus obtained was recrystallized with ethanol (280 L) to get **4** (yield: 23.95 kg, 72.46%).

mp 186.3−186.8 °C (lit.[15g] mp 187−188 °C).

IR spectra [KBr] (cm^{-1}) 790, 803, 1057, 1069, 1292, 1402, 1439, 1518, 1605,1660, 3251, 3311, and 3434.

DSC peak 186.4 °C.

^{1}H NMR (DMSO d_6): δ 3.02−3.06 (dd, 1H,J = 4.92,11.68 Hz), 3.34−3.42 (dd, 1H, *J* = 5.24,11.98 Hz), 3.71−3.75 (m, 2H), 5.14 −5.18 (t, 1H,J = 4.55 Hz), 5.30−5.33 (br s, 1H), 5.72−5.74 (d, 1H, *J* = 7.44 Hz), 6.19−6.21 (t, 1H, *J* = 5.15 Hz), 7.19 (br s,1H)−7.24 (br s,1H)-, 7.80−7.82 (d, 1H,7.43 Hz). MS: M^{+1} = 230.

PXRD [2θ] (Cu $K_{\alpha1}$ = 1.54060 Å, $K_{\alpha2}$ = 1.54443 Å, K_β = 1.39225 Å; 40 mA, 45 kV): 15.14, 16.23, 17.15, 18.49, 18.99, 21.53, 22.62, 23.13, 23.80, 24.68, 25.20, 25.46, 29.16, and 34.67.

4.4. *cis*-(−)-2-Hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (*S*)-BINOL Cocrystal 6. The mixture of **4** (30 kg 130 mol) and (*S*)-(−)-BINOL (60 kg, 200 mol) in methanol (360 L) was heated to reflux for 1−2 h. The mixture was then cooled to ambient temperature. The solid thus separated was filtered and washed with methanol (15 L) to get **6** (yield: 22.69 kg, 67.26%).

mp 190.1−190.6 °C. $[\alpha]_D$ at 25 °C = −77° (*c* = 1, MeOH).

IR spectra [Nujol Mull] (cm^{-1}): 722, 753, 827, 961, 1037, 1141, 1202, 1273, 1341, 1376, 1459, 1595, 1645, 2723, 2855, 2924, 3359, and 3583.

^{1}H NMR (DMSO-d_6): δ 2.99−3.08 (dd, 1H, *J* = 2.4,2.4 Hz), 3.36 (dd, 1H), 3.73 (m, 2H), 5.14−5.19 (t, 1H *J* = 4.47 Hz), 5.72−5.76(d, 1H *J* = 7.44 Hz), 6.17−6.23 (t, 1H *J* = 4.936 Hz), 6.90−6.94 (d, 2HJ = 7.80 Hz), 7.12−7.33(m, 8H), 7.82−7.87(m, 6H), 9.24 (bs, 2H).

PXRD [2θ] (Cu $K_{\alpha1}$ = 1.54060 Å, $K_{\alpha2}$ = 1.5444 Å, K_β = 1.39225 Å; 40 mA, 45 kV): 8.02, 10.52, 12.73, 14.33, 14.51, 16.06, 17.06, 17.80, 20.12, 21.94, 22.36, 23.70, 24.06, and 25.05.

4.5. *cis*-(−)-2-Hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (Lamivudine) A. Compound **6** (24.80 kg, 108.29 mol) was suspended in the mixture of water (99.2 L) and ethyl acetate (99.2 L) and pH of the solution was adjusted to

2−3 using dil. hydrochloric acid. The aqueous layer was separated, washed with ethyl acetate, and neutralized to pH 7. Excess of water was evaporated in vacuum. The solid thus obtained, was recrystallized in ethanol−water mixture (7.44 L) to get pure lamivudine form-I (yield: 7.85, 70.02%).

mp 176.0−1770 °C (lit.[21a] mp 126 and 178 °C).

ee = 99.9%. $[\alpha]_D$ at 25 °C = −98.32° (c = 5 water). MS: M + H = 230.

IR spectra [Nujol Mull] (cm^{-1}): 722, 788, 844, 927, 976, 1044, 1106, 1135, 1155, 1193, 1226, 1296, 1676, 14610, 1522, 1600, 1640, 2854, 2923, 3160, and 3330.

^{1}H NMR (DMSO-d_6): δ 2.99−3.07 (dd, 1H, J = 4.86, 11.67 Hz), 3.35−3.38 (dd, 1H, J = 4.86, 11.67 Hz), 3.72−3.74 (m, 2H), 5.14−5.18 (t, 1H J = 4.44 Hz), 5.32−5.38 (t, 1H J = 5.14 Hz), 5.71−5.75 (d, 1H, J = 7.43 Hz), 6.16−6.21 (t, 1H J = 5.11 Hz), 7.22−7.27 (d, 2H J = 8.70 Hz), 7.80−7.83 (d, 1H, J = 7.41 Hz).

PXRD [2θ] (Cu $K_{\alpha1}$ = 1.54060 Å, $K_{\alpha2}$ = 1.54443 Å, K_β = 0.39225 Å; 40 mA, 45 kV): 5.20, 6.66, 8.53, 8.81, 9.65, 9.85, 10.15, 10.41, 11.27, 11.38, 11.63, 12.34, 12.60, 12.93, 13.22, 14.60, 15.01, 15.17, 15.67, 15.81, 16.51, 17.59, 17.98, 18.13, 18.72, 19.10, 19.30, 19.76, 21.79, 23.49, 23.71, 25.44, 25.90, 27.34, 29.46, and 31.00.

4.6. *cis*-(+)-2-Hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane B. Mother liquor of compound **7** was concentrated in vacuum to get solid. The solid thus obtained was washed with ethyl acetate to get crude **B** which, upon recrystallization in water and methanol, afforded compound **B**; mp 171.4 °C.

ee = 98.2%. $[\alpha]_D$ at 25 °C = +98.85° (c = 5 water). MS: M + H = 230.

IR spectra [Nujol Mull] (cm^{-1}): 592.80, 786.23, 918.13, 1059.50, 1286.69, 1496.21, 1651.60, 2836.27, 3075.57, 3203.72, and 3327.26.

^{1}H NMR (DMSO-d_6): δ 2.97−3.06 (dd, 1H, J = 4.93, 11.66 Hz), 3.34−3.43 (dd, 1H, J = 4.93, 11.65 Hz), 3.68−3.77 (m, 2H), 5.12−5.17 (t, 1H J = 4.49 Hz), 5.28−5.33 (t, 1H J = 5.87 Hz), 5.69−5.73 (d, 1H, J = 7.44 Hz), 6.15−6.21 (t, 1H J = 5.16 Hz), 7.21 (d, 2H), 7.78−7.82 (d, 1H, J = 7.42 Hz).

PXRD [2θ] (Cu $K_{\alpha1}$ = 1.54060 Å, $K_{\alpha2}$ = 1.54443 Å, K_β = 1.39225 Å; 40 mA, 45 kV): 10.73, 12.18, 13.42, 17.56, 20.63, 21.45, 24.45, 24.95, 26.52, and 31.47.

4.7. *trans*-(±)-2-Hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane 5. The mother liquor of compound **3** was concentrated in vacuum (35 g; 0.15 mol) and was suspended in 700 mL of methanolic ammonia (25%) and stirred for 8−10 h at ambient temperature. After the completion of reaction, excess of solvent was recovered under vacuum. The solid thus obtained was recrystallized with water (350 mL) to get **5** (yield 14 g, 70.85%); mp 222 °C (lit.[15g] > mp 222 °C). IR spectra [Nujol Mull] (cm^{-1}): 581, 777, 923, 1025, 1292, 1481, 1660, 2915, 3122, 3316, and 3428.

^{1}H NMR (DMSO d_6): δ 3.03−3.10 (dd, 1H, J = 2.74, 11.91 Hz), 3.39 −3.49 (m, 1H,), 3.50 3.71(m, 2H), 5.15−5.21 (t, 1H J = 5.88,), 5.45−5.51(t, 1H J = 5.20 Hz), 5.67−5.71 (d, 1H J = 7.41 Hz), 6.30−6.34 (dd, 1H, J = 2.68, 5.24 Hz), 7.15 (brs, 1 H) 7.19 (brs, 1 H) and 7.55−7.5 9 (d, 1H J = 7.39 Hz).

PXRD [2θ] (Cu $K_{\alpha1}$ = 1.54060 Å, $K_{\alpha2}$ = 1.54443 Å, K_β = 1.39225 Å; 40 mA, 45 kV): 11.68, 16.30, 19.11, 23.28, 29.44, 29.54, and 35.32.

4.8. *trans*-(−)- 2-Hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (*S*)-BINOL Cocrystal (8). The mixture of **5** (25 g; 0.109 mol) and (*S*)-(−)BINOL (50.0 g; 0.17 mol) in methanol (300 mL) was heated to reflux. The mixture was then cooled to ambient temperature. The solid thus separated was filtered and washed with methanol to get **8** (yield: 20.0 g, 71.11%).

mp 224−227.2 °C.

IR spectra [Nujol Mull] (cm^{-1}): 558, 756, 961, 1047, 1285, 1494, 1644, 2942, 3051, 3365, and 3479.

^{1}H NMR (DMSO-d_6): δ 3.05−3.12 (dd, 1H J = 2.73, 11.89 Hz,), 3.34−3.58 (m, 4H), 5.15−5.21(t, 1H J = 5.92 Hz), 5.47−5.52(t, 1H J = 5.04 Hz), 5.69−5.73(d, 1H J = 7.42 Hz), 6.32−6.36 (m, 1H), 6.90−6.94 (d, 2H J = 7.82 Hz), 7.12−7.33 (m, 8H), 7.57−7.61 (d, 1H J = 7.42 Hz), 7.82−7.87(m, 3H), 9.20 (bs, 2H).

PXRD [2θ] (Cu $K_{\alpha1}$ = 1.54060 Å, $K_{\alpha2}$ = 1.54443 Å, K_β = 1.39225 Å; 40 mA, 45 kV): 7.96, 12.87, 14.79, 18.14, 20.10, 22.60, 25.26, 29.77, 31.65, 37.39, and 38.34.

4.9. *trans*-(−)-2-Hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane C. Compound **8** (10 g, 0.019 mol) was suspended in a mixture of water (40 mL) and ethyl acetate (40 mL), and the pH of the solution was adjusted to 2−3 using 25% aqueous hydrochloric acid. The aqueous layer was separated, washed with ethyl acetate, and neutralized to pH 7. Excess of water was evaporated in vacuum. The solid thus obtained was recrystallized in an ethanol/water mixture (3:1, 40 mL) to get pure **C** (yield: 3.5 g, 80.4%).

mp 168.0 °C. ee = 98.85%. MS: M + H = 230. Moisture content: 0.22%. $[\alpha]_D$ 25 °C = −120.57° (c, 0.5% water).

IR spectra [KBr] (cm^{-1}): 713, 782, 962. 1069, 1100, 1192, 1287, 1398, 1491, 1633, 1674, 3085, and 3399.

^{1}H NMR (DMSO-d_6): δ 3.04−3.10 (dd, 1H, J = 3.45, 11.92 Hz), 3.34−3.43 (dd, 1H,, J = 3.52, 11.95 Hz), 3.43−3.49 (m, 2H), 5.19 (t, 1H), 5.47−5.52 (t, 1H J = 4.99 Hz), 5.68−5.72 (d, 1H, J = 7.40 Hz), 6.32 (t, 1H), 7.16−7.20 (d, 2H J = 9.26 Hz), 7.56−7.60 (d, 1H, J = 7.36 Hz).

XRPD [2θ] (Cu $K_{\alpha1}$ = 1.54060 Å, $K_{\alpha2}$ = 1.54443 Å, K_β = 1.39225 Å; 40 mA, 45 kV): 9.98, 14.39, 17.22, 18.31, 20.00, 20.99, 21.76, 25.45, 26.18, 27.01, 27.96, 30.28, 32.32, 33.34, 35.66, 36.67, and 39.76.

4.10. *trans*-(+)-2-Hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane D. Mother liquor of compound **9** was concentrated in vacuum to get solid. The solid thus obtained was washed with ethyl acetate to get crude **D** which, upon recrystallization in water as well as in methanol, afforded compound **D**.

mp 172.6 °C. ee = 98.07%. $[\alpha]_D$ at 25 °C = +124.41° (c 0.5%, water). MS: M + H = 230.

IR spectra [Nujol Mull] (cm^{-1}): 608, 785, 925, 1057, 1192, 1282, 1401, 1486, 1646, 2924, 3191, and 3333.

IR spectra [KBr] (cm^{-1}): 713, 782, 961. 1068, 1099, 1191, 1287, 1397, 1490, 1630, 1675, 3074, and 3396.

^{1}H NMR (DMSO-d_6): δ 3.03−3.10 (dd, 1H, J = 2.74, 11.89 Hz), 3.33−3.49 (dd, 1H, J = 2.72, 11.87 Hz), 3.50−3.71 (m,

2H), 5.15−5.21(t, 1H J = 5.91 Hz), 5.28−5.31 (t, 1H), 5.46−5.71 (d, 1H, J = 7.40 Hz), 6.18−6.34 (t, 1H), 7.15−7.19 (d, 2H, J = 8.02 Hz), 7.55−7.59 (d, 1H, J = 7.42 Hz).

XRPD [2θ] (Cu $K_{\alpha 1}$ = 1.54060 Å, $K_{\alpha 2}$ = 0.54443 Å, K_{β} = 1.39225 Å; 40 mA, 45 kV): 10.02, 14.41, 17.24, 18.33, 20.04, 20.96, 21.81, 25.45, 26.23, 27.08, 28.00, 30.32, 32.36, 33.36, 35.72, 36.71, and 39.77.

Acknowledgment

We sincerely thank Prof. Gautam R. Desiraju, University of Hyderabad, for valuable discussion, Dr. K. Ravikumar, IICT Hyderabad for providing single-crystal XRD data, Dr. P. R. Upadhyay of Analytical Development, Lupin Research Park, Pune, India, for providing valuable analytical support and Dr. Vishvas D. Patil of Intellectual Property Cell, Lupin Research Park, Pune, India, for the entire literature search.

Supporting Information Available

Crystal structure data for cocrystal of (*S*)-Binol with optical isomer A (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review September 16, 2008.

OP800228H