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Synthesis of diastereoisomeric pairs of novel analogues of d4T having an isochroman glycon moiety; their enzymatic kinetic resolution, their enantiopure synthesis, molecular modeling and NMR structural study

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Abstract—An efficient route, starting from 2-bromobenzaldehyde, is described to synthesize racemic diastereoisomeric thymine derivatives of isochroman, which are aromatic analogues of Stavudine, an approved anti-HIV drug. The relative configurations were determined by NOE proton NMR experiments in connection with molecular modeling. Following the separation of the latter diastereoisomers, kinetic resolution was achieved via a transesterification reaction catalyzed by lipases. Using this method, moderate ee's were obtained (0.74–0.98). Thus, an alternative strategy starting from D-mannitol was proposed to provide pure enantiomers. The attribution of absolute configurations was made by chemical filiation on the basis of the configurations obtained from D-mannitol. The structural attributions were confirmed by studying the behavior of proton NMR shifts of the corresponding isochroman Mosher's esters.

1. Introduction

Natural nucleosides are of great biological importance in metabolic pathways.[1] For many years, the typical structure of nucleosides was described by scientists as two molecular fragments: D-ribose or D-deoxyribose as the sugar moiety connected by a β-glycosyl linkage to different heterocyclic bases such as thymine, uracil, cytosine, adenine and guanine. This dogma disappeared when different groups reported the isolation of natural nucleosides having D-arabinose or 2′,3′-didehydro-2′,3′-dideoxy-D-glucose instead of the D-ribose part (Fig. 1). In 1950, Bergmann et al. reported the isolation of spongouridine (**1**) and spongothymidine (**2**) from marine Caribbean sponges *Cryptotheca crypta*, which had D-arabinose as the sugar

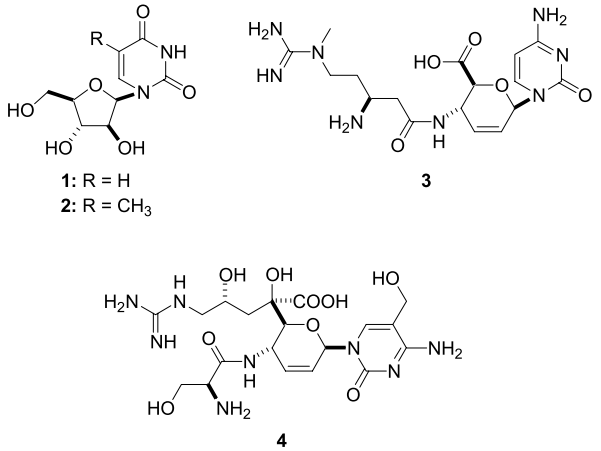

Figure 1. Natural compounds having a nucleoside moiety.

Keywords: d4T Analogue synthesis; Lipase resolution; Enantiopure synthesis; NMR configuration attribution; Molecular modeling.
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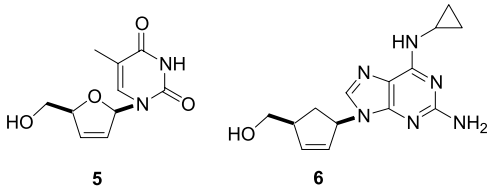


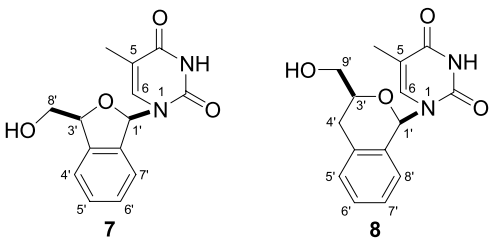
5 6

Figure 2. Stavudine **5** and abacavir **6**.

moiety.[2] In 1958, Y. Yonehara et al. reported the discovery of a metabolite of *Streptomyces griseochromogenes*, Blasticidin S (**3**),[3] which controls rice blast *Pyricularia oryzae*.[4] In 1978, K. Suetomi et al. reported the isolation of antifungal mildiomycin (**4**) from a culture of *Streptoverticillium rimofaciens*.[5]

These discoveries led to a large number of nucleoside analogues that were tested for the treatment of viral diseases.[6] Among the US FDA approved compounds used in the treatment of acquired immunodeficiency syndrome (AIDS), the 2′,3′-didehydro-3′-deoxythymidine d4T (**5**)[7–9] and the carbocyclic 2-amino-6-cyclopropylaminopurine analogue abacavir (**6**)[10,11] showed potent anti-human immunodeficiency virus (HIV) activity (Fig. 2).

However, side effects and drug-resistant variants remained a problem with these antiviral agents.[12–14] Moreover, the introduction of the 2′,3′-double bond in compound **5** resulted in an increased lipophilicity compared to the corresponding natural and saturated 2′,3′-dideoxynucleoside series but decreased the chemical stability in acidic medium. In the course of the search for new antiviral agents with a higher therapeutic index, the obvious emphasis was on the design of drugs with potent activity, high stability, low cytotoxicity, minimal side effects. In our previous studies, we reported the synthesis of pyrimidine nucleoside analogues of d4T based on the 1,3-dihydrobenzo[*c*]furan core **7** (Fig. 3).[15,16] This class of nucleoside with a modified glycon part was attractive because: (i) it retained the phosphorylation site; (ii) the presence of the benzene ring as electron-withdrawing group stabilized the glycosidic bond compared to the olefinic analogue: 2′,3′-didehydro-2′,3′-dideoxynucleoside; (iii) the introduction of the aromatic residue increased the lipophilicity compared to d4T.[17] In an attempt to expand the variety of nucleoside antiviral drugs, a novel range of unsaturated nucleoside analogues of d4T **8** were synthesized to explore their potential as antiviral drugs.



7 8

Figure 3. Isobenzofuran and isochroman derivatives **7** and **8**.

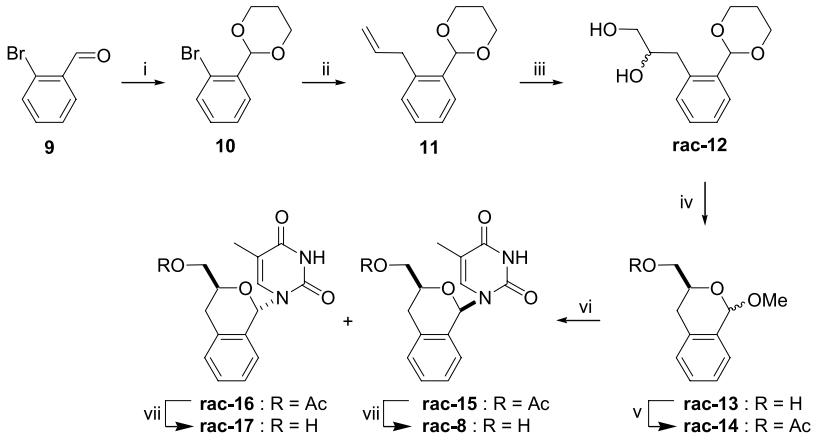
2. Results and discussion

2.1. Synthesis of racemic unsaturated nucleosides and determination of their relative configuration

A retrosynthetic analysis suggested that the starting material for the synthesis of nucleoside analogue **8** was the 2-bromobenzaldehyde (**9**). This compound had the advantage of being stable, inexpensive and easily available.

The aldehyde **9** was converted into the protected compound **10** by acetonide formation in the presence of propan-1,3-diol and catalytic amounts of PTSA in 84% yield (Scheme 1). The aromatic ring of **10** was metalated and allylated to the olefin **11** in 87% yield. Based on the Sharpless mnemonic device,[18–20] asymmetric dihydroxylation (AD) of the terminal olefin **11** using AD-mix α was expected to afford the *S* configuration that was required for the synthesis of the nucleoside analogue **8**. Thus, the alkene **11** was reacted with AD-mix α in a mixture of *tert*-butyl alcohol and water using classical Sharpless dihydroxylation methodology. Unfortunately, this oxidation furnished the diol as a mixture of the expected Sharpless diol having the *S* configuration and the unexpected Sharpless diol having the *R* configuration (ee = 0.2). On the contrary, the catalytic AD system displayed very high enantioselectivity in the preparation of the diol **19** (ee = 0.98) starting from the styrene derivative **18** (Scheme 2).[16] The presence of a methylene group in **11** between the vinyl and the phenyl groups probably decreased the selectivity (ee = 0.98 for **19** vs 0.2 for **12*S***) due to the loss of rigidity.

Considering this low enantiofacial discrimination, the allyl derivative **11** afforded the diol **rac-12** as a racemic mixture, using OsO_4 in the presence of *N*-methylmorpholine-*N*-oxide (NMO) as co-oxidant, in 75% yield. The subsequent removal of the acetal group using HCl 10% in methanol for 2 h resulted in spontaneous cyclization to afford the isochroman derivatives **rac-13** as the major stereoisomers. It was notable that the cyclization between the primary hydroxyl and formyl groups giving 1,3,4,5-tetrahydrobenzo[*c*]oxepine derivative was not observed during this rearrangement. The alcohol **rac-13** was converted into the corresponding acetate **rac-14**, which was used as a glycosyl donor in a Vorbruggen condensation reaction.[21] Thus, treatment of the acetylated derivative **rac-14** with silylated thymine in the presence of $SnCl_4$ afforded a mixture of diastereoisomeric nucleoside analogues **rac-15** and **rac-16** that were readily separated by chromatography. The condensation reaction gave the two isomers **rac-15** and **rac-16** due to the lack of a participating effect by neighboring groups. Classical removal of the acetyl group of **rac-15** and **rac-16** by treatment with saturated methanolic ammonia produced the desired free nucleosides **rac-8** and **rac-17**, respectively, in quantitative yield. The nucleoside analogues **rac-8** and **rac-17** obtained by the method shown in Scheme 1 were of course a pair of enantiomers. Unfortunately, the heterocyclic compounds **rac-8** and **rac-17** gave poor quality crystals thus, precluding the determination of their configurations by X-ray crystallography. Thus, the absolute configurations of the two asymmetric carbons $C_{1'}$ and $C_{3'}$ included in the isochroman core were determined by NMR experiments and



Scheme 1. Reagents and conditions: (i) propan-1,2-diol, PTSA, toluene reflux; (ii) BuLi, THF then CH_2CHCH_2Br; (iii) OsO_4, H_2O, NMO, pyridine, *tert*-BuOH; (iv) HCl, MeOH; (v) Ac_2O, pyridine; (vi) silylated thymine, $C_2H_4Cl_2$, $SnCl_4$; (vii) NH_3, MeOH.

independent chemical correlation. The relative configurations for the nucleoside analogues **rac-8** and **rac-17** were assigned as $1'R$, $3'S$ ($1'S$,$3'R$) and $1'S$,$3'S$ ($1'R$,$3'R$), respectively, on the basis of proton NMR NOE experiments. Thus, in the racemic mixture **rac-8**, irradiation of $H_{1'}$ proton gave enhanced signals for $H_{3'}$ proton. The same was true for $H_{1'}$ proton when $H_{3'}$ proton was irradiated. Conversely, no NOE effect was observed for the same protons of **rac-17** while the irradiation of $H_{3'}$ proton showed an interaction with H_6 proton and vice-versa. The study of the conformational analysis made by means of molecular modeling confirmed these attributions. Thus, for the lowest energy conformer found for **rac-8**, (Fig. 4 and Table 1), the proximity of $H_{3'}$ and $H_{1'}$ explained the NOE interaction observed. Similarly, the lowest energy conformer of **rac-17** (Fig. 4), which presented a closer disposition for $H_{3'}$ and H_6 protons than that of **rac-8**, accounted for the proton dipolar interaction observed for these protons in the former compound.

The comparison of the chemical shifts and coupling constants of $H_{4'}$ protons for the two diastereoisomers was also very interesting. For **rac-8**, the following NMR parameters were measured for $H_{4'a}$ and $H_{4'b}$ protons (subscripts a and b refer, respectively, to the lower cis and to the higher trans $^3J_{3',4'}$ values): $\delta_{H\text{-}4'a}=2.86$ ppm, $J_{3',4'a}=3.2$ Hz and $\delta_{H\text{-}4'b}=2.70$ ppm, $J_{3',4'b}=10.7$ Hz, while for **rac-17**: $\delta_{H\text{-}4'a}=2.72$ ppm, $J_{3',4'a}=2.8$ Hz and $\delta_{H\text{-}4'b}=2.86$ ppm, $J_{3',4'b}=11.5$ Hz. Thus, for the latter, the $H_{4'b}$ proton (high coupling constant) resonated at a lower field than the $H_{4'a}$ proton while in the former the reverse situation was observed. This difference was very probably due to different anisotropic contributions on these proton chemical shifts exerted by $C_{1'}$–$O_{2'}$ and $C_{9'}$–$O_{9'}$ bonds, aromatic and thymine rings. The contribution of the $C_{1'}$–$O_{2'}$ bond could not explain this effect since molecular modeling (Fig. 4 and Table 1) indicated that the positions of $H_{4'a}$ and $H_{4'b}$ protons toward the oxygen atom $O_{2'}$ of the pyran cycle remained the same whichever diastereoisomer was considered.

The effect of the aromatic ring was also unable to explain the chemical shift differences since, for each diastereoisomer, the same orientations of $H_{4'a}$ and $H_{4'b}$ protons toward the plane of the cycle were observed on the molecular

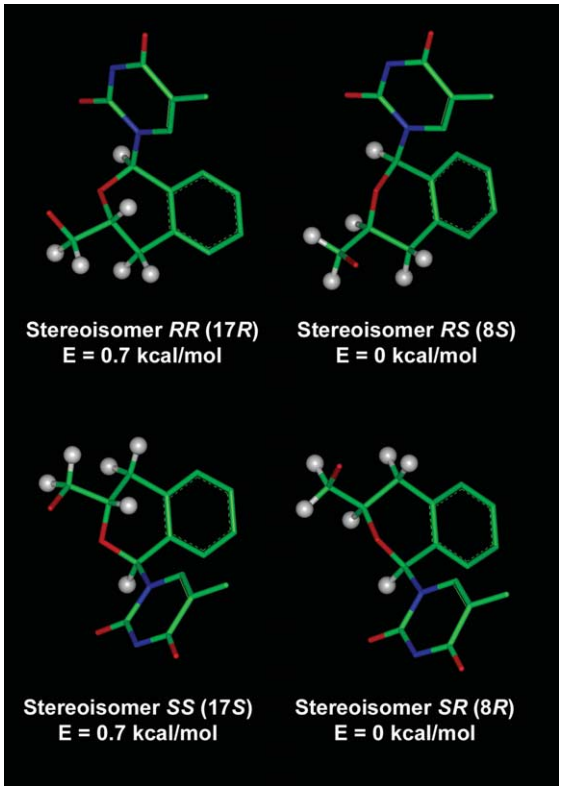
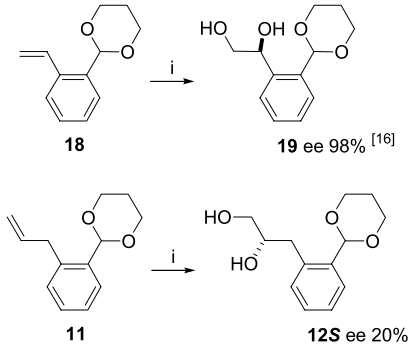


Figure 4. Lowest energy conformers obtained by molecular modeling for **rac-8** and **rac-17**.

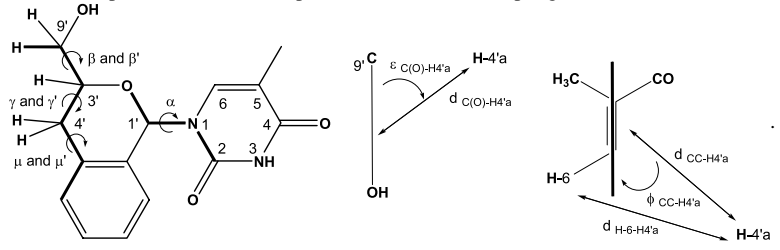


Scheme 2. Reagents and conditions: (i) AD-mix α, *tert*-BuOH, H_2O.

Table 1. Angles (deg) and interatomic distances (Å) for the lowest energy conformer of **rac-8** and **rac-17**

Angles (deg)	**rac-8** 1′*S*,3′*R* (1′*R*,3′*S*)	**rac-17** 1′*S*,3′*S* (1′*R*,3′*R*)	Distances (Å)	**rac-8** 1′*S*,3′*R* (1′*R*,3′*S*)	**rac-17** 1′*S*,3′*S* (1′*R*,3′*R*)
α	92	74	d_{H6-OH}	4.6	5.1
β	−57	+66	$d_{H6-H4'a}$[a]	5.1	4.2
β'	+59	−177	$d_{H6-H4'b}$[a]	3.8	4.9
γ_a[a]	+56	−53	$d_{H6-H3'}$	4.9	2.7
γ_b[a]	+173	−170	$d_{C(O)-H4'a}$[a]	3.1	3.5
μ_a[a]	+37	−37	$d_{C(O)-H4'b}$[a]	2.7	3.4
μ_b[a]	−81	+81	$d_{CC-H4'a}$[a]	6.3	5.4
$\varepsilon_{C(O)-H4'a}$[a]	66	26	$d_{CC-H4'b}$[a]	5.1	5.9
$\varepsilon_{C(O)-H4'b}$[a]	94	15			
$\phi_{CC-H4'a}$[a]	12	30			
$\phi_{CC-H4'b}$[a]	25	19			

[a] The subscripts 'a' and 'b' for 4′ protons refer to their coupling constant with $H_{3'}$; $H_{4'a}$ has the lower *cis J* value while $H_{4'b}$ has the higher *trans J* value



model. Similarly, the influence exerted by the thymine ring looked non-determinant because, in each of the lowest energy conformers of **rac-8** and **rac-17**, the H_6 proton pointed out in the direction of $H_{4'}$ protons (the values for $\phi_{CC-H4'a}$ and $\phi_{CC-H4'b}$ angles were ,respectively, 12 and 25° for **rac-8**, 30 and 19° for **rac-17**). Conversely, the different anisotropic contributions of the $C_{9'}$–$O_{9'}$ bond in the chemical shifts of $H_{4'}$ protons for each diastereoisomer seemed able to explain the effect. Thus, molecular modeling indicated that, for diastereoisomer **rac-8**, the values for angles $\varepsilon_{C(O)-H4'a}$ and $\varepsilon_{C(O)-H4'b}$ were, respectively, 66 and 94°. According to the Mc Connell and Pople relationship[22] giving the anisotropic contribution of an axial symmetry bond (like the $C_{9'}$–$O_{9'}$ bond):

$$\Delta\sigma = \left(\frac{\Delta\chi}{3\,N_0 d_{C(O)-H4'a}}\right)(1-3\cos^2\varepsilon_{C(O)-H4'})$$

where $\Delta\chi$ and N_0 are, respectively, the difference between the susceptibility parallel to the axis and the transverse susceptibility and the Avogadro number, the contribution $\Delta\sigma$ is positive (diamagnetic effect) for $\varepsilon_{C(O)-H4'} > 54°45'$. Thus, both $H_{4'a}$ and $H_{4'b}$ protons of **rac-8** should receive an upfield shielding, a high one for $H_{4'b}$ ($\varepsilon_{C(O)-H4'b} \approx 90°$) and a very low one for $H_{4'a}$ ($\varepsilon_{C(O)-H4'b} \approx 54°45'$). Conversely, both $H_{4'a}$ and $H_{4'b}$ protons of **rac-17**, for which $\varepsilon_{C(O)-H4'a} = 26°$ and $\varepsilon_{C(O)-H4'b} = 15°$, would receive a negative downfield shielding with a more intense effect for $H_{4'b}$ since $\varepsilon_{C(O)-H4'b}$ is lower than $\varepsilon_{C(O)-H4'a}$. These remarks, made on the basis of the most stable conformers obtained from a molecular modeling study, which are in agreement with measured chemical shifts of $H_{4'}$ protons, gave confirmation of the diastereoisomer structural attribution.

2.2. Lipase-catalyzed kinetic resolution of rac-8 and rac-17

The synthesis of enantiomerically pure nucleoside analogues was undertaken. For this purpose, several methods have been described in the literature, for example, enantioselective reaction using Jacobsen epoxidation,[23] enzymatic resolution[24] or formation of diastereoisomeric esters.[25] Considering the practical aspects, the kinetic enzymatic resolution was chosen although enzyme-catalyzed reactions have not been fully exploited in nucleoside chemistry.[26] Thus, compounds **rac-8** and **rac-17** were subjected to enzymatic transesterification using vinyl acetate as an acyl donor and organic solvent in the presence of different lipases. The behavior of six different enzymes (*Candida rugosa* lipase, novozym 435 lipase, pork liver esterase, porcine pancreatic lipase, *Geotricum candida* lipase and *Pseudomas* sp. lipase) was screened. Porcine pancreatic lipase presented the best selectivity and enzymatic activity (Table 2).

Table 2. Lipase screening for the resolution of alcohols **rac-8** and **rac-17** (conditions: 0.2 mg of **rac-8** (or **rac-17**) in 200 μL of vinyl acetate and 3 mg of enzyme powder, +++ means that the conversion reached 50% at the time indicated)

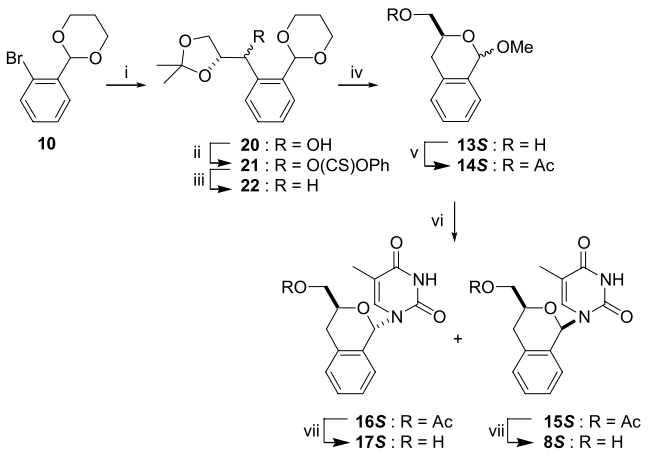
Enzyme	$t=2$ h **rac-17**	**rac-8**	$t=18$ h **rac-17**	**rac-8**	$t=24$ h **rac-17**	**rac-8**	$t=30$ h **rac-17**	**rac-8**	$t=72$ h **rac-17**	**rac-8**
C. rugosa lipase	+	−+	++	+	++	++	++	++	++	+++
Novozym 435 lipase	+++	++	+++	+++	+++	+++				
Pork liver esterase	−	−	−	−	−	−	−	−	−	−
Porcine pancreatic lipase	−	+	+	++	+	++	+	++	++	+++
G. candida lipase	−	−	+	+	+	++	+	++	++	+++
Pseudomas sp. lipase	−	−+	−	+	−	++	−	++	−	+++

Among the enzymes used, novozym 435 lipase gave the highest reaction rates with both **rac-8** and **rac-17**, but did not seem to present a high enantiomeric discrimination factor since the transesterification took place to a great extent beyond 50% conversion. We discarded *Pseudomonas* sp. lipase because it induced very low reaction rates, particularly with **rac-17**. Thus, two enzymes were selected: *C. rugosa* lipase (AY 30 Amano) and porcine pancreatic lipase (PPL). The results, determined by means of chiral HPLC, showed that a better enantiomeric discrimination was obtained when using PPL.

Thus, starting from **rac-8**, the ee's of ester and of remaining substrate were 0.98 (the major being 1′*R*, 3′*S*) and 0.74 (the major being 1′*S*, 3′*R*), respectively, after 33% of conversion (reaction time, 7 h). Starting from **rac-17**, the ee's of ester and residual substrate were 0.74 (the major being 1′*R*, 3′*R*) and 0.78 (the major being 1′*S*, 3′*S*), respectively, after 51% of conversion (reaction time, 48 h), (Fig. 5). The absolute configurations were determined as described later in this paper. Considering these results, enzyme-catalyzed transesterification was not adopted as a method for the separation of the racemic nucleosides **rac-8** and **rac-17**.

2.3. Single enantiomer synthesis using 2,3-*O*-isopropylidene-D-glyceraldehyde

A selective synthetic strategy avoiding the need for resolution procedures was shown to afford the enantiomerically pure target nucleosides **8*S*** and **17*S***. The strategy used for this purpose is shown in Scheme 3. The starting material was enantiomerically pure 2,3-*O*-isopropylidene-D-glyceraldehyde, prepared from the oxidative cleavage of 1,2:5,6-di-*O*-isopropylidene-D-mannitol. The chiral glyceraldehyde derivative was reacted with the metalated aromatic ring of **10** to give the diastereoisomeric mixture of the alcohols **20** (ratio 1:1) in 51% yield. Esterification of the secondary hydroxyl of compound **20** as phenylthionocarbonate esters **21** followed by standard Barton deoxygenation[27] yielded the desired enantiomerically pure compound **22** in 69% yield. The intermediate **22** was then converted to epimeric methoxide **13*S*** as major anomer by treatment with HCl 10% in methanol, followed by acetylation of the primary hydroxyl group to afford acetate **14*S*** in 72% yield. As described in the racemic synthesis, the formation of the thymine derivatives by standard Vorbruggen chemistry[21] resulted in a mixture of anomers **15*S*** and **16*S*** was formed due to the lack of anchimeric assistance. Removal of the acetyl group by treatment with saturated methanolic ammonia produced the desired free nucleosides **8*S*** and **17*S*** in quantitative yield.



Scheme 3. Reagents and conditions: (i) BuLi, THF then 2,3-*O*-isopropylidene-D-glyceraldehyde; (ii) PhO(CS)Cl, DMAP, EtOAc; (iii) Bu_3SnH, AIBN, toluene, 100 °C; (iv) HCl, MeOH; (v) Ac_2O, pyridine; (vi) silylated thymine, $C_2H_4Cl_2$, $SnCl_4$; (vii) NH_3, MeOH.

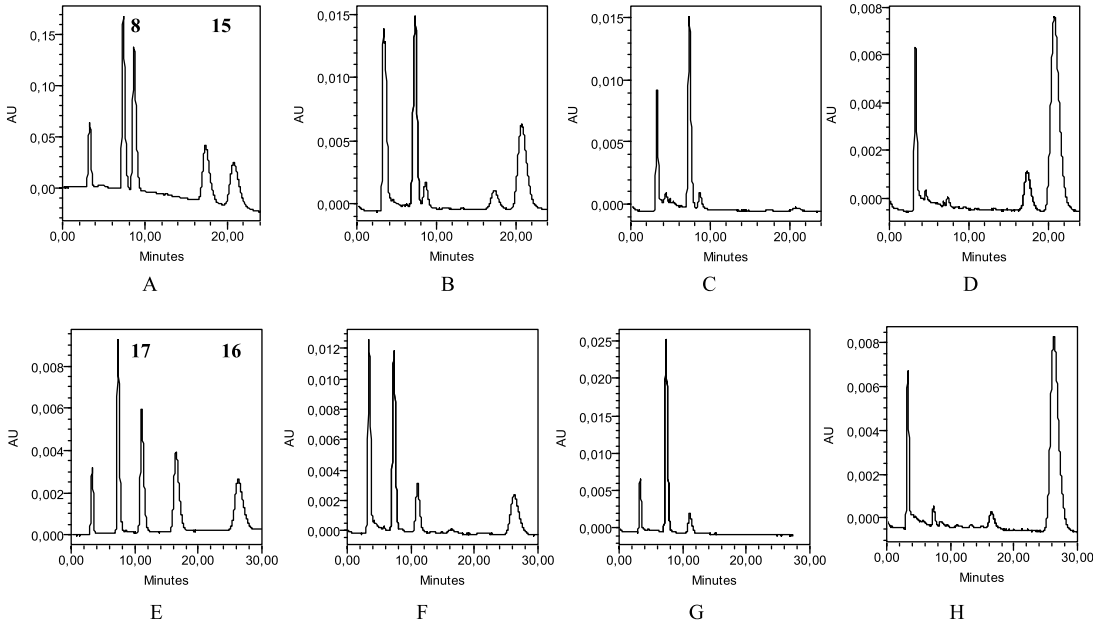


Figure 5. Chiral HPLC chromatograms. A: **rac-15** and **rac-8** (50/50). B: **15** and **8** from the enzymatic reaction without purification. C: **8** from the enzymatic reaction after purification. D: **15** from the enzymatic reaction after purification. E: **rac-16** and **rac-17** (50/50). F: **16** and **17** from the enzymatic reaction without purification. G: **17** from the enzymatic reaction after purification. H: **16** from the enzymatic reaction after purification. Conditions: Chiralcel OJ (250×46 mm), 1 mL/min, 30 °C, EtOH–hexane (30/70), λ=200 nm.

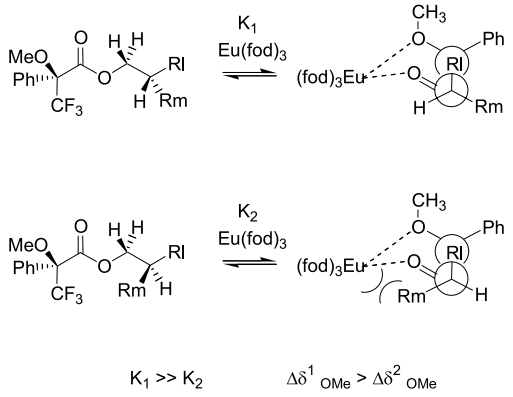
The positive ion ESI mass spectra of nucleosides **8*S*** and **17*S*** indicated a high level of purity (Fig. 6). Indeed, the target molecules **8*S*** and **17*S*** showed abundant cationic monocharged ions: $[M+Na]^+$ *m/z* 311.08 and $[M+K]^+$ *m/z* 327.06. The other ions observed at *m/z* 163.07, 149.03 and 117.07 were attributed to fragments of the sodium adduct by an MS/MS experiment.

Comparison of the proton NMR spectra of **8*S*** and **17*S*** with those of **rac-8** and **rac-17** allowed the respective trans and cis relative configurations to be ascribed. Moreover, due to the 3′-*S* carbon configuration afforded by D-mannitol, the absolute configuration of **8*S*** and **17*S*** were 1′*R*, 3′*S* and 1′*S*, 3′*S*, respectively. As a consequence, it was possible to ascribe by comparison the absolute configurations of the stereoisomers obtained via lipase kinetic resolution.

2.4. Confirmation of the absolute configuration determination of 8*S*, 8*R* and 17*S* and 17*R* isochromans by means of NMR study of their Mosher's esters 23–26

A review about the determination of the absolute configuration of chiral alcohols and amines by means of NMR spectroscopy has recently been published.[28] Thus, the derivatization of the titled enantiomers into diastereoisomeric esters or amides by means of enantiopure acid derivatives (like Mosher's esters, for example) and the study of their chemical shifts induced by an aromatic group of the chiral center of the auxiliary compound was shown to be particularly efficient in the case of secondary alcohols (or amines). The application of this technique to primary alcohols having the chiral center beside the hydroxymethyl group was not so powerful. The reasons were: (i) lower substituent effects due to the greater distance between the perturbing groups of the auxiliary chiral center and the methylene protons; (ii) the presence of supplementary C–C bonds reduces the conformational preference and thus, can make difficult the interpretation of the chemical shift variations usually induced by phenyl substituents. In order to avoid these drawbacks and to enhance the intensity of the perturbing magnetic fields, larger aromatic substituents, like anthryl groups, have been proposed.[29,30] Thus, a number of rules concerning the configuration of aliphatic chiral primary alcohols were drawn from a molecular modeling study that had shown a conservation of the conformational preference in this series.[31] Unfortunately, these rules could not be applied to primary alcohols whose vicinal chiral centres were included in a cycle, which is the case for isochromans **8** and **7**. Meanwhile, it was shown that for Mosher's esters [α-methoxy-α-(trifluoromethyl)phenylacetyl or MTPA esters], the absolute configuration of the vicinal carbon can be deduced from the relative magnitude of the lanthanide-induced chemical shift (LIS) of the methoxy group for each diastereoisomer.[32] In that case, it was assumed that complexation of europium salts with both oxygens of the ester and of methoxy groups induced the existence of the conformers indicated in Scheme 4.

Thus, starting from the isochroman derivatives **8*R***, **8*S***, **17*R*** and **17*S***, the corresponding (*S*)-MTPA esters **23*S***, **23*R***, **24*R*** and **24*S*** (Fig. 7) were prepared using classical methodology



Scheme 4. Application of the lanthanide-induced shifts (LIS) for OCH_3 groups of (*S*)-MTPA esters for the determination of the absolute configuration of alcohols (K_1 and K_2 are the equilibrium constants between the complexed and the free forms of diastereoisomeric Mosher's esters; $\Delta\delta_{OMe}$ = difference between the chemical shift for the methoxy group of the esters with and without the Europium salt).

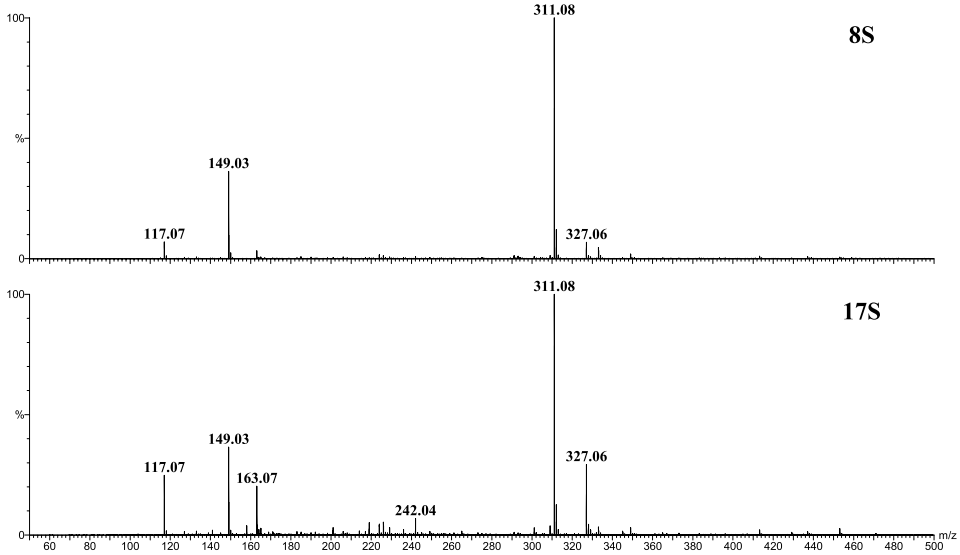


Figure 6. Positive ion ESI mass spectra of compounds **8*S*** (top) and **17*S*** (bottom).

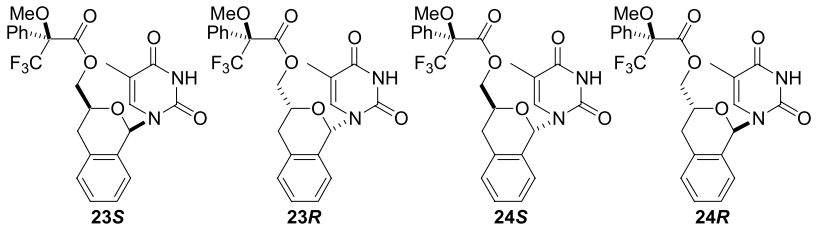


Figure 7. (*S*)-MTPA esters **23*S***, **23*R***, **24*R*** and **24*S***.

and the classical shifts induced by Eu(fod)$_3$ on the methoxy group were studied.

Thus, the lanthanide induced shifts on the methoxy groups of (*S*)-MTPA esters **23** and **24** of the remaining alcohol obtained after lipase resolution (Table 3) gave a clear confirmation of the absolute configurations already determined by the use of 2,3-*O*-isopropylidene-D-glyceraldehyde as an optically pure precursor.

Table 3. Lanthanide-induced shifts on the proton chemical shifts of (*S*)-MTPA esters **23** and **24** and absolute configuration of the major remaining alcohol obtained after lipase resolution

(*S*)-MTPA esters	Remaining	$\Delta\delta_{OCH3}$*	$\Delta\delta_{OCH3}$**	Configuration
23	major	+0.31	+0.52	1′*S*,3′*R*
	minor	+0.24	+0.44	1′*R*,3′*S*
24	major	+0.11	+0.29	1′*S*,3′*S*
	minor	+0.15	+0.36	1′*R*,3′*R*

$\Delta\delta_{OCH3}$ (ppm)=δ_{OCH3} [with Eu(fod)$_3$/$CDCl_3$]−δ_{OCH3} ($CDCl_3$). * And **: molar ratio between MTPA esters and Eu(fod)$_3$ were, respectively, 0.5 and 1.

Previous NMR studies of MTPA esters of primary alcohols showed that there was a correlation between the shape of the signals due to the methylenic protons of the CH_2O group of (*R*)- and (*S*)-MTPA esters and the absolute configuration of the vicinal asymmetric carbon. Thus, in a series of 24-methyl-26-hydroxy steroids, the chemical shift difference between the two OCH_2 protons of (*S*)-MTPA esters was larger when the configuration of C-26 was *S* than when this carbon presented the *R* spatial arrangement.[33] Obviously, this simple rule, established in a series of steroids for which conformational features remained constant throughout the series, could not be applied in our case. Moreover, the low and similar $\Delta\delta_{H9'}$ values measured for each (*S*)-MTPA esters **23*S***, **23*R***, **24*S***, and **24*R*** (ca. 0.04 ppm) (Figs. 8 and 9) have precluded any reliable interpretation.

3. Conclusion

In this work, we have described an efficient route, starting from 2-bromobenzaldehyde, to synthesize racemic diastereoisomeric thymine derivatives of isochroman. The relative configurations were determined by NOE proton NMR experiments in connection with molecular modeling. Following the separation of the latter diastereoisomers, kinetic resolution was achieved via a transesterification reaction catalyzed by lipases. Using this method, moderate ee's were obtained (0.75–0.98). Thus, an alternative strategy starting from D-mannitol was proposed to provide pure enantiomers. The attribution of absolute configurations was made by chemical filiation on the basis of the configurations obtained from D-mannitol. The structural attributions were confirmed by studying the proton NMR LIS of the methoxy group of the corresponding isochroman Mosher's esters **23** and **24**. An attempt to correlate the chemical shifts of $O_{9'}$–$C_{9'}H_2$ protons of the Mosher's esters **23** and **24** with the absolute configuration was unsuccessful because the diastereoisomeric esters exhibited a too small $\Delta\delta_{H9'}$ value. The isochroman derivatives were evaluated for their inhibitory effect on the replication of HIV-1 in human

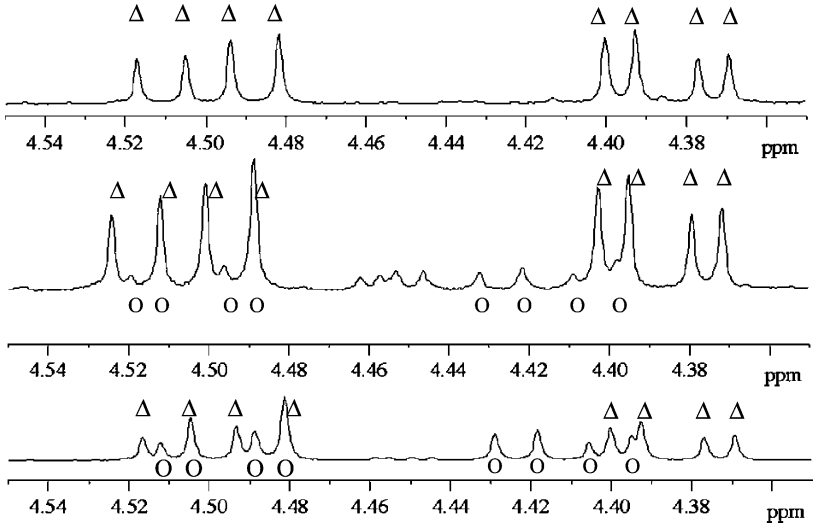


Figure 8. Proton NMR spectra ($CDCl_3$) of $H_{9'}$ protons of Mosher's esters **23*S*** (△) and **23*R*** (○). (a) spectra of pure enantiomers prepared from D-mannitol, (b) spectra of enantiomerically enriched enantiomers obtained via lipase resolution, (c) spectra of racemic mixture.

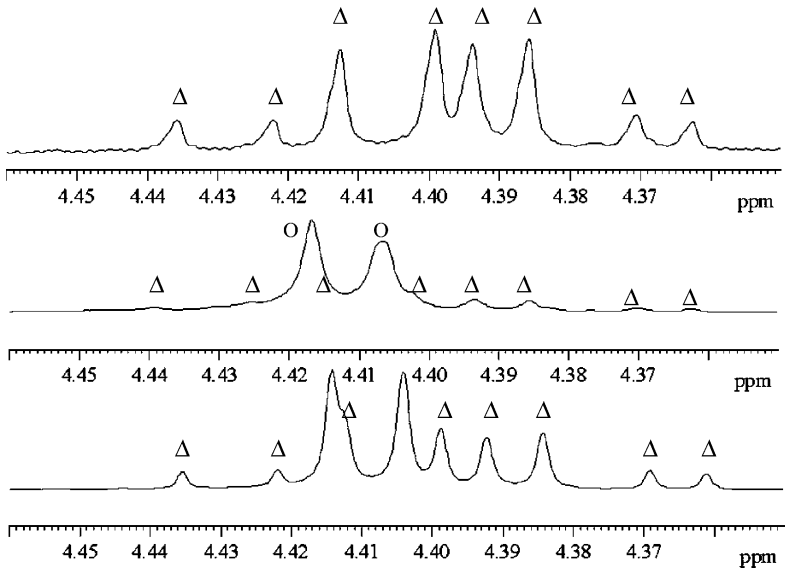


Figure 9. Proton NMR spectra ($CDCl_3$) of $H_{9'}$ protons of Mosher's esters **24*S*** (△) and **24*R*** (○). (a) spectra of pure enantiomers prepared from D-mannitol, (b) spectra of enantiomerically enriched enantiomers obtained via lipase resolution, (c) spectra of racemic mixture.

T4-lymphoblastoid cells, CEM-SS and MT-4. Unfortunately, these compounds were found inactive against HIV-1 replication at concentrations up to 10 μM.

4. Experimental

4.1. General

Melting points were determined on a digital melting-point apparatus (Electrothermal) and were uncorrected. Optical rotations were recorded in $CHCl_3$ or MeOH solutions with a digital polarimeter DIP-370 (JASCO) using a 1 dm cell. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or Me_2SO-d_6 (internal Me_4Si), respectively, at 300.13 MHz (Bruker Avance-300) and at 500 MHz (Bruker AX500). TLC was performed on Silica F254 (Merck) and detection was by UV light at 254 nm or by charring with phosphomolybdic-H_2SO_4 reagent. Column chromatography was carried out on Silica Gel 60 (Merck, 230 mesh). EtOAc, diethyl ether and petroleum ether were distilled before use. Bases and solvents were used as supplied. MeOH–NH_3 was methanol saturated with ammonia gas at rt.

Electron impact analysis (EI) was performed on a Waters-Micromass AUTOSPEC *Ultima* (EBE geometry) high-resolution mass spectrometer (HRMS). Electron energy, emission current and accelerating voltage values were 70 eV, 200 μA and 8 kV, respectively. Accurate mass measurements of molecular and fragment ions were performed using perfluoro kerosene (PFK) as the internal reference. High-resolution electrospray experiments (ESI-HRMS) were performed on a Waters-Micromass Q-TOF *Ultima Global* hybrid quadrupole time-of-flight instrument, equipped with a *Z*-spray ion source. The source and desolvation temperatures were kept at 80 and 150 °C, respectively. Nitrogen was used as drying and nebulizing gas at flow rates of 350 and 50 L/h, respectively. The capillary voltage was 2.5 kV, the cone voltage 100 V and the RF lens1 energy 50 V. For accurate mass measurements, a single internal lock mass correction, using characteristic ions of reference components, was applied. For both EI-HRMS and ESI-HRMS measurements, data acquisition and processing were performed with MassLynx 4.0 software.

Chromatographic analysis was performed on a Waters 600 HPLC system equipped with a Waters 996 photodiode array spectrophotometer. The sample loop was 20 μL (Rheodyne 7125 injector). Chromatographic data were collected and processed on a computer running with Millennium 2010 (Waters). The stainless steel column Chiralcel OJ (cellulose tris-methylbenzoate; 250×4.6 mm i.d.; 10 μm) was purchased from Daicel Chemical Industries. Lyophilized enzymes were kindly donated by Amano Enzyme Inc. (Nagoya, Japan), apart from porcine pancreatic lipase, which was supplied by Sigma (PPL type II). The enantiomeric excesses (ee) of the substrates and of the acetates were determined using chiral high performance liquid chromatography (HPLC, Chiralcel OJ) with the following experimental conditions: sample concentration 0.21 mM; eluent: *n*-hexane/ethanol, 70:30; flow-rate: 1 mL/min; temperature: 30 °C; wavelengths: 200, 226 nm.

Molecular modeling calculations were made on a silicon graphics (SGI) computer. Molecular building and energy calculations were produced by means of InsightII, Biopolymer, Discover and CFF91 (force fields) software from Accelrys (San Diego, CA, USA)

4.2. Synthesis of racemic nucleosides rac-8 and rac-17

4.2.1. 2-(2-Bromophenyl)-1,3-dioxane (10). A stirred mixture of 2-bromobenzaldehyde (10.0 g, 53.9 mmol), propan-1,3-diol (4.9 g, 53.9 mmol), toluene-4-sulfonic acid (0.4 g) and toluene (15 mL) was refluxed for 4 h using a Dean-Stark condenser. Et_3N (2 mL) was added and the reaction mixture cooled and extracted with diethyl ether (8 mL). The extract was worked up and the crude product was purified by flash chromatography (diethyl ether/petroleum ether, 5:95) to yield compound **10** (11.2 g,

84%) as a white solid: mp 54–55 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72 (m, 1H, H aromatic), 7.36 (m, 3H, H aromatic), 5.97 (s, 1H, H-2), 4.29, 4.05 (m, 4H, H-4, H-6), 2.09, 1.47 (m, 2H, H-5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.8 (C), 133.0 (CH), 130.7 (CH), 128.5 (CH), 128.0 (CH), 122.7 (*C*Br), 101.3 (C-2), 68.0 (2C, C-4, C-6), 26.1 (C-5); EI-HRMS: $M^{+\cdot}$ *m/z* 242, found 241.9931, $C_{10}H_{11}O_2Br$ requires 241.9942 and $[M-H^{\cdot}]^+$ *m/z* 241, found 240.9863, $C_{10}H_{10}O_2Br$ requires 240.9864. Anal. Calcd for $C_{10}H_{11}BrO_2$ (241.99 g/mol): C, 49.41; H, 4.56. Found: C, 49.39; H, 4.58.

4.2.2. 2-(2-Allylphenyl)-1,3-dioxane (11). To a solution of bromide **10** (2.0 g, 8.3 mmol) in THF (32 mL) was added *n*-BuLi (10 mL, 1.6 M solution) in THF at −10 °C under argon. After 1 h, a solution of allyl bromide (2.15 mL, 12.3 mmol) was added dropwise to the mixture at the same temperature and the mixture was stirred overnight at rt. The solution was poured into saturated aqueous NH_4Cl solution and extracted with EtOAc (100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 5:95) to yield compound **11** (1.47 g, 87%) as an oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76 (m, 1H, H aromatic), 7.34 (m, 3H, H aromatic), 6.03 (m, CH allyl), 5.73 (s, 1H, H-2), 5.18 (m, CH allyl), 4.29, 4.01 (m, 4H, H-4, H-6), 3.64 (m, 2H, CH_2 allyl), 2.26, 1.41 (m, 2H, H-5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.9 (CH allyl), 137.8 (C), 136.8 (C), 130.1 (CH), 129.3 (CH), 126.6 (CH), 126.5 (CH), 116.1 (CH_2 allyl), 10.3 (C-2), 68.0 (2C, C-4, C-6), 37.1 (CH_2 allyl), 26.1 (C-5); EI-HRMS: $[M-H^{\cdot}]^+$ *m/z* 203, found 203.1072, $C_{13}H_{15}O_2$ requires 203.1072. Anal. Calcd for $C_{13}H_{16}O_2$ (204.12 g/mol): C, 76.44; H, 7.90. Found: C, 76.51; H, 7.86.

4.2.3. 3-(2-(1,3)-Dioxan-2-ylphenyl)-propan-1,2-diol (rac-12). *N*-Methylmorpholine-*N*-oxide (6.9 g, 58.8 mmol), pyridine (0.5 mL), H_2O (0.7 mL) and OsO_4 (32 μL of a 2.5% solution in *tert*-BuOH, 0.1 mmol) were added to a solution of alkene **11** (2.0, 9.80 mmol) in *tert*-BuOH (10 mL). The mixture was stirred at rt overnight then treated with 20% aqueous sodium bisulfite solution (4 mL) and evaporated to dryness. Saturated aqueous NaCl (5 mL) was added and the mixture was extracted twice with EtOAc. The combined extracts were worked up and the crude product was purified by flash chromatography (EtOAc/petroleum ether, 50:50) to yield compound **rac-12** (1.75 g, 75%) as an oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (m, 1H, H aromatic), 6.99 (m, 3H, H aromatic), 5.44 (s, 1H, H-2), 3.94 (m, 5H, H-4, H-6, C*H*OH, 2OH), 3.67 (m, 2H, H-4, H-6), 3.32 (dd, J=11.3, 3.5 Hz, 1H, CH_2OH), 3.22 (dd, J=6.1 Hz, 1H, CH_2OH), 2.68 (d, J=6.6 Hz, CH_2 allyl), 1.87, 1.13 (m, 2H, H-5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.0 (C), 136.8 (C), 131.0 (CH), 129.0 (CH), 126.9 (CH), 126.5 (CH), 100.6 (C-2), 73.4 (CHOH), 67.6 (2C, C-4, C-6), 66.1 (CH_2OH), 30.0 (CH_2 allyl), 25.8 (C-5). Anal. Calcd for $C_{13}H_{18}O_4$ (238.12 g/mol): C, 65.53; H, 7.61. Found: C, 65.60; H, 7.62.

4.2.4. (1*R*,3*S*)- and (1*S*,3*R*)-3-Acetyloxymethyl-1-methoxyisochroman (rac-14). Compound **rac-12** (2.4 g, 10.0 mmol) was dissolved in methanol HCl (1%, 60 mL) and the resulting mixture was stirred for 2 h at rt. Et_3N (4 mL) was added, the mixture was stirred for 30 min at rt and then extracted with EtOAc (100 mL). The extract was worked up and the crude product was co-evaporated successively with toluene (3×10 mL) and pyridine (10 mL). The residue was dissolved in anhydrous pyridine (8.5 mL) and Ac_2O (1.2 mL, 13.0 mmol) was added. The resulting mixture was stirred overnight at rt. MeOH (10 mL) was added and the mixture was evaporated to dryness. The residue was co-evaporated with toluene and purified by flash chromatography (EtOAc/petroleum ether, 30:70) to yield **rac-14** (1.78 g, 75%) as an oil. The major isomer **rac-14** had the (1′*R*,3′*S*) and (1′*S*,3′*R*) configuration; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.07 (m, 3H, H aromatic), 6.91 (m, 1H, H aromatic), 5.36 (s, 1H, H-1), 4.16 (m, 1H, H3), 4.08 (m, 2H, H9a, H-9b), 3.39 (s, 3H, OCH_3), 2.57 (dd, 1H, $J_{4'a,4'b}$= 16.5 Hz, $J_{3',4'b'}$=11.3 Hz, H4′b), 2.39 (dd, 1H, $J_{3',4'a}$= 2.6 Hz, H4′a), 1.94 (s, 3H, $COCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.7 (*C*OCH_3), 134.8, 134.1 (2C, C-10, C-11), 128.8 (CH), 128.5 (CH), 127.8 (CH), 126.6 (CH), 98.5 (C-1′), 66.4 (C-3), 65.4 (C-9), 55.2 (O*C*H_3), 29.9 (C-4), 20.9 (*C*H_3CO). Anal. Calcd for $C_{13}H_{16}O_4$ (236.10 g/mol): C, 66.09; H, 6.83. Found: C, 66.10; H, 6.90.

4.2.5. (1′*R*,3′*S*)- and (1′*S*,3′*R*)-1-(3-Acetyloxymethyl-isochroman-1-yl)thymine (rac-15) and (1′*S*,3′*S*)- and (1′*R*,3′*R*)-1-(3-acetyloxymethyl-isochroman-1-yl(thymine) (rac-16). A mixture of thymine (534 mg, 4.23 mmol), anhydrous HMDS (50 mL) and $(NH_4)_2SO_4$ (10 mg) was refluxed under N_2 until a clear solution was obtained (ca. 12 h). Then the solvent was removed under reduced pressure to give a colorless syrup that was dissolved in anhydrous dichloroethane (10 mL). To the solution of silylated thymine in anhydrous dichloroethane were added acetate **rac-14** (500 mg, 2.12 mmol) in anhydrous dichloroethane and $SnCl_4$ (578 mL, 4.24 mmol) at −10 °C. After stirring the mixture for 3 h at rt, saturated $NaHCO_3$ (50 mL) was added, the mixture was stirred for 30 min and then extracted with CH_2Cl_2. This extract was worked up and the crude product was purified by flash chromatography (EtOAc/petroleum ether, 40:60) to give compound **rac-15** (276 mg, 39%) as a foam as first eluting compound and compound **rac-16** (259 mg, 37%) as a foam as second eluting compound. **rac-15**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.58 (s, 1H, NH), 6.62 (d, J=1.3 Hz, 1H, H-6), 7.30, 7.23, 7.20, 6.97 (4H, H aromatic), 7.00 (s, 1H, H-1′), 4.22 (m, $J_{3',9'b}$=6.1 Hz, $J_{9'a,9'b}$=11.7 Hz, 1H, H-9′b), 4.14 (m, $J_{3',9'a}$=4.1 Hz, 1H, H-9′a), 4.09 (m, $J_{3',4'a}$=5.0 Hz, $J_{3',4'b}$=8.7 Hz, 1H, H-3′), 2.85 (m, $J_{4'a,4'b}$=16.3 Hz, 1H, H-4′a), 2.80 (m, 1H, H-4′b), 2.00 (s, 1H, CH_3CO), 1.73 (d, 1H, CH_3 thymine); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.8 (*C*OCH3), 163.6 (C-4), 151.1 (C-2), 137.0 (C-6), 134.5, 130.8 (2C, C-10′, C-11′), 110.4 (C-5), 79.8 (C-1′), 68.0 (C-3′), 65.6 (C-9′), 29.8 (C-4′), 20.8 (CH_3CO), 12.5 (CH_3 thymine). Anal. Calcd for $C_{17}H_{18}N_2O_5$ (330.12 g/mol): C, 61.81; H, 5.49; N, 8.48. Found: C, 61.79; H, 5.53; N, 8.45. **rac-16**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.85 (s, 1H, NH), 6.68 (d, J=1.3 Hz, 1H, H-6), 7.25, 7.18, 7.14, 6.91 (4H, H aromatic), 7.04 (s, 1H, H-1′), 4.14-4.23 (m, $J_{3',9'b}$=6.7 Hz, $J_{9'a,9'b}$=11.5 Hz, 1H, $J_{3',9'a}$=3.5 Hz, $J_{3',4'a}$=2.4 Hz, $J_{3',4'b}$=11.5 Hz, 3H, H-3′, H-9′a, H-9′b), 2.89 (m, $J_{4'a,4'b}$=16.3 Hz, 1H, H-4′b), 2.70 (m, 1H, H-4′a), 2.05 (s, 1H, CH_3CO), 1.75 (d, 1H, CH_3 thymine); ^{13}C NMR ($CDCl_3$,

75 MHz) δ 170.9 (*C*OCH3), 163.7 (C-4), 151.2 (C-2), 136.7 (C-6), 134.5, 132.0 (2C, C-10′, C-11′), 111.9 (C-5), 81.1 (C-1′), 72.9 (C-3′), 65.9 (C-9′), 29.7 (C-4′), 20.9 (CH_3CO), 12.4 (CH_3 thymine). Anal. Calcd for $C_{17}H_{18}N_2O_5$ (330.12 g/mol): C, 61.81; H, 5.49; N, 8.48. Found: C, 61.81; H, 5.51; N, 8.47.

4.2.6. (1′*R*,3′*S*)- and (1′*S*,3′*R*)-1-(3-Hydroxymethyl-isochroman-1-yl)thymine (rac-8). The protected compound **rac-15** (500 mg, 1.51 mmol) was dissolved in methanolic ammonia (5 mL) and the mixture stirred for 24 h. After evaporation of the solvent the crude product was purified by flash chromatography (MeOH/CH_2Cl_2, 2:98) to yield compound **rac-8** (414 mg, 95%) as a foam, ^{1}H NMR (Me_2SO-d_6, 300 MHz) δ 11.39 (s, 1H, NH), 6.98 (d, *J*=1.1 Hz, 1H, H-6), 7.34, 7.30, 7.25, 7.07 (4H, H aromatic), 6.89 (s, 1H, H-1′), 4.82 (d, *J*=5.8 Hz, 1H, OH), 3.96 (m, 1H, H-3′), 3.52 (dd, $J_{9'a,9'b}$=11.3 Hz, $J_{3',9'a}$=4.8 Hz, 1H, H-9′a), 3.47 (dd, $J_{3',9'b}$=5.4 Hz, 1H, H-9′a), 2.86 (dd, $J_{4'a,4'b}$=16.6 Hz, $J_{3',4'a}$=3.2 Hz, $J_{3',4'b}$=10.7 Hz, 1H, H-4′a), 2.70 (dd, 1H, H-4′b), 1.64 (d, 1H, CH_3 thymine); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.8 (C-4), 151.1 (C-2), 137.6 (C-6), 135.5, 130.2 (2C, C-10′, C-11′), 108.8 (C-5), 78.6 (C-1′), 70.2 (C-3′), 63.5 (C-9′), 29.5 (C-4′), 11.9 (CH_3 thymine). Anal. Calcd for $C_{15}H_{16}N_2O_4$ (288.11 g/mol): C, 62.49; H, 5.59; N, 9.72. Found: C, 62.53; H, 5.65; N, 9.70.

4.2.7. (1′*S*,3′*S*)- and (1′*R*,3′*R*)-1-(3-Hydroxymethyl-isochroman-1-yl)thymine (rac-17). The protected compound **rac-16** (500 mg, 1.51 mmol) was dissolved in methanolic ammonia (5 mL) and the mixture stirred for 24 h. After evaporation of the solvent, the crude product was purified by flash chromatography (MeOH/CH_2Cl_2, 2:98) to give compound **rac-17** (410 mg, 94%) as a foam, ^{1}H NMR (Me_2SO-d_6, 300 MHz) δ 11.45 (s, 1H, NH), 6.96 (d, *J*=1.2 Hz, 1H, H-6), 7.29, 7.24, 7.22, 6.95 (4H, H aromatic), 6.93 (s, 1H, H-1′), 4.87 (d, *J*=5.8 Hz, 1H, OH), 4.03 (m, 1H, H-3′), 3.56 (dd, $J_{3',9'b}$=5.8 Hz, 1H, H-9′a), 3.52 (dd, $J_{9'a,9'b}$=11.6 Hz, $J_{3',9'a}$=4.5 Hz, 1H, H-9′a), 2.86 (dd, 1H, H-4′b), 2.72 (dd, $J_{4'a,4'b}$=16.3 Hz, $J_{3',4'a}$=2.8 Hz, $J_{3',4'b}$=11.57 Hz, 1H, H-4′a), 1.68 (d, 1H, CH_3 thymine); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.7 (C-4), 151.1 (C-2), 136.8 (C-6), 135.7, 132.7 (2C, C-10′, C-11′), 110.3 (C-5), 80.3 (C-1′), 75.5 (C-3′), 63.7 (C-9′), 29.5 (C-4′), 11.9 (CH_3 thymine). Anal. Calcd for $C_{15}H_{16}N_2O_4$ (288.11 g/mol): C, 62.49; H, 5.59; N, 9.72. Found: C, 62.55; H, 5.57; N, 9.75.

4.3. Selective synthesis of nucleosides 8*S* and 17*S*

4.3.1. ((*S*)-2,2-Dimethyl-(1,3)-dioxolan-4-yl)-(2-(1,3)-dioxan-2-ylphenyl)-methanol (20). *n*-Butyl lithium (1.6 M in hexane, 23.8 mL, 38 mmol) was added dropwise to a solution of bromide **10** (4.6 g, 19.0 mmol) in dry THF (50 mL) at −15 °C under argon. After 1 h, a solution of 1,2-*O*-isopropylidene-D-glyceraldehyde[28] (500 mg, 3.84 mmol) in THF (10 mL) was added dropwise at −15 °C under argon. After being stirred overnight at rt, the reaction mixture was treated with aqueous NH_4Cl and extracted with ethylacetate. The extract was worked up and the crude product was purified by flash chromatography (ethylacetate/petroleum ether, 20:80) to yield compound **20** (577 mg, 51%) as an oil; ESI-HRMS: $[M+Na]^+$ *m*/*z* 317, found 317.1361, $C_{16}H_{22}O_5Na$ requires 317.1365. Anal. Calcd for $C_{16}H_{22}O_5$ (294.15 g/mol): C, 65.29; H, 7.53. Found: C, 65.32; H, 7.50. First stereoisomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62 (m, 2H, H aromatic), 7.31 (m, 2H, H aromatic), 5.73 (s, 1H, H-2), 5.22 (dd, *J*=2.0, 5.6 Hz, CHOH), 4.49 (q, *J*=6.1 Hz, CHO), 4.28, 4.00 (m, 4H, H-4, H-6), 4.13 (dd, *J*=6.5, 8.4 Hz, CHO), 3.96 (dd, *J*=6.8 Hz, CHO), 3.24 (d, OH), 2.26, 1.41 (m, 2H, H-5), 1.49 (s, CH_3), 1.39 (s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.6 (C), 136.9 (C), 129.7 (CH), 128.3 (CH), 217.1 (CH), 126.9 (CH), 109.7 (C*iso*), 100.8 (C-2), 78.4 (CH), 69.8 (CHOH), 67.9 (2C, C-4, C-6), 66.0 (CH_2O), 27.0 (CH_3), 26.0 (C-5), 25.7 (CH_3). Second stereoisomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.56 (m, 1H, H aromatic), 7.45 (m, 1H, H aromatic), 7.26 (m, 2H, H aromatic), 5.72 (s, 1H, H-2), 5.10 (dd, *J*=3.0, 7.3 Hz, CHOH), 4.44 (q, *J*=6.7 Hz, CHO), 4.22, 3.95 (m, 4H, H-4, H-6), 3.74 (d, *J*=6.6 Hz, CHO), 3.39 (d, OH), 2.20, 1.41 (m, 2H, H-5), 1.50 (s, CH_3), 1.40 (s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.6 (C), 136.7 (C), 129.7 (CH), 128.5 (CH), 128.0 (CH), 127.5 (CH), 110.2 (C*iso*), 101.2 (C-2), 80.2 (CH), 71.5 (CHOH), 67.8 (2C, C-4, C-6), 66.4 (CH_2O), 27.2 (CH_3), 26.1 (2C, C-5, CH_3).

4.3.2. ((*S*)-2,2-Dimethyl-(1,3)-dioxolan-4-yl)-(2-(1,3)-dioxan-2-ylphenyl)-methane (22). Phenoxythiocarbonyl chloride (282 μg, 2.04 mmol) was added to a solution of alcohol **20** (400 mg, 1.36 mmol) and DMAP (498 mg, 4.08 mmol) in dry AcOEt (20 mL) at rt under argon. The mixture was stirred for 12 h at rt and then diluted with AcOEt (30 mL). The whole was washed with H_2O (3× 20 mL) and the extract was worked up. The residue was co-evaporated twice with toluene then dissolved in toluene (3 mL). Bu_3SnH (3.28 mL, 12.2 mmol) was added to the above solution containing AIBN (44.7 mg, 0.27 mmol) at 100 °C under argon atmosphere. After being heated for 45 min, the solvent was removed in vacuo and the crude product was purified by flash chromatography (ethylacetate/petroleum ether, 10:90) to yield compound **22** (261 mg, 69%) as an oil; $[\alpha]_D^{22}$ +8 (*c* 0.05 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62 (m, 1H, H aromatic), 7.25 (m, 3H, H aromatic), 5.70 (s, 1H, H-2), 4.39 (m, CHO), 4.26, 3.99 (m, 4H, H-4, H-6), 3.96 (dd, *J*=5.9, 8.2 Hz, CHO), 3.70 (dd, *J*=6.9 Hz, CHO), 3.18 (dd, *J*=6.0, 3.9 Hz, CH), 2.95 (dd, *J*=3.2, 13.9 Hz, CH), 2.26, 1.41 (m, 2H, H-5), 1.48 (s, CH_3), 1.37 (s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.3 (C), 135.7.9 (C), 130.7 (CH), 129.3 (CH), 127.2 (CH), 127.1 (CH), 109.3 (C*iso*), 100.6 (C-2), 77.0 (CHO), 69.3 (CH_2O), 67.9 (2C, C-4, C-6), 36.7 (CH_2), 27.5 (CH_3), 26.2 (CH_3), 26.1 (C-5); ESI-HRMS: $[M+Na]^+$ *m*/*z* 301, found 301.1418, $C_{16}H_{22}O_4Na$ requires 301.1416. Anal. Calcd for $C_{16}H_{22}O_4$ (278.15 g/mol): C, 69.04; H, 7.97. Found: C, 69.15; H, 8.02.

4.3.3. (1*R*,3*S*)-Acetyloxymethyl-1-methoxyisochroman (14*S*). Compound **22** (500 mg, 1.80 mmol) was dissolved in methanol HCl (1%, 10 mL) and the resulting mixture was stirred for 2 h at rt. Et_3N (2 mL) was added, the mixture was stirred for 30 min at rt and then extracted with EtOAc (10 mL). The extract was worked up and the crude product was co-evaporated successively with toluene (3×5 mL) and pyridine (5 mL). The residue was dissolved in anhydrous pyridine (3 mL) and Ac_2O (235 μL, 2.5 mmol) was added. The resulting mixture was stirred overnight at rt. MeOH (3 mL) was added and the mixture was evaporated to

dryness. The residue was co-evaporated with toluene and was purified by flash chromatography (EtOAc/petroleum ether, 30:70) to yield the (1*R*,3*S*) isomer **14*S*** as the major isomer; enantiomer **14*S*** had NMR data identical to those for the racemic compound **rac-14**; ESI-HRMS: $[M+Na]^+$ *m/z* 259, found 259.0950, $C_{13}H_{16}O_4Na$ requires 259.0946.

4.3.4. (1′*R*,3′*S*)-1-(3-Acetyloxymethyl-isochroman-1-yl) thymine (15*S*) and (1′*S*,3′*S*)-1-(3-acetyloxymethyl-1-isochroman-1-yl)thymine (16*S*). Compound **14*S*** was converted to the thymine nucleoside analogue by the procedure employed above for the racemate. The mixture of stereoisomers was separated by chromatography as above to give the (1*R*,3*S*) isomer **15*S*** $[\alpha]_D^{22}$ +16 (*c* 0.05 in $CHCl_3$); enantiomer **15*S*** had NMR data identical to those for the racemic compound **rac-15**; ESI-HRMS: $[M+Na]^+$ *m/z* 353, found 353.1118, $C_{17}H_{18}N_2O_5Na$ requires 353.1113 and the (1*S*,3*S*) isomer **16*S*** $[\alpha]_D^{22}$ −4 (*c* 0.05 in $CHCl_3$); ESI-HRMS: $[M+Na]^+$ *m/z* 353, found 353.1098, $C_{17}H_{18}N_2O_5Na$ requires 353.1113.

4.3.5. (1′*R*,3′*S*)-1-(3-Hydroxymethyl-isochroman-1-yl) thymine (8*S*). Compound **15*S*** was converted to the thymine nucleoside analogue by the procedure employed above for the racemate to give the nucleoside **8*S***; enantiomer **8*S*** had NMR data identical to those for the racemic compound **rac-8**; $[\alpha]_D^{22}$ +18 (*c* 0.06 in $CHCl_3$); ESI-HRMS: $[M+Na]^+$ *m/z* 311, found 311.1017, $C_{15}H_{16}N_2O_4Na$ requires 311.1008.

4.3.6. (1′*S*,3′*S*)-1-(3-Hydroxymethyl-isochroman-1-yl) thymine (17*S*). Compound **16*S*** was converted to the thymine nucleoside analogue by the procedure employed above for the racemate to give the nucleoside **17*S***; enantiomer **17*S*** had NMR data identical to those for the racemic compound **rac-17**; $[\alpha]_D^{22}$ +3 (*c* 0.06 in $CHCl_3$); ESI-HRMS: $[M+Na]^+$ *m/z* 311, found 311.0995, $C_{15}H_{16}N_2O_4Na$ requires 311.1008.

4.4. Lipase-catalyzed kinetic resolution of rac-8 and rac-17

4.4.1. Lipase screening for the resolution of isochromans 8 and 17. Ten milligrams of each isochroman of was dissolved in 100 mL of vinyl acetate. Then, 0.2 mL of this solution was incubated at rt in the presence of 3 mg of each lyophilized enzymatic preparation. The course of the transesterification was followed by means of TLC (silica gel plates, eluent petroleum ether/acetone 1:1, R_f 0.35 and 0.73 for 17 and corresponding acetate, 0.29 and 0.69 for 8 and corresponding acetate). Spots were revealed by UV at 254 nm.

4.4.2. Enzymatic resolution of isochroman rac-17. rac-17 31.8 mg (0.11 mmol) in 200 mL of vinyl acetate and 500 mg of freeze-dried PPL lipase were incubated at rt for 48 h with magnetic stirring. Then, the lipase was filtered and vinyl acetate was eliminated under vacuum. NMR analysis of the mixture indicated a conversion of 51%. The reaction products were separated by silica gel flash chromatography (eluent petroleum ether/acetone 1:1), which afforded 16 mg of ester (96% yield, ee=0.74, determined by means of chiral HPLC t_{r1}=16.8 min and t_{r2}=26.8 min) and 14 mg of remaining alcohol (84% yield, ee=0.78, determined by means of chiral HPLC t_{r1}=7.5 min and t_{r2}=11.2 min).

4.4.3. Enzymatic resolution of isochroman rac-8. rac-8 30 mg (0.10 mmol) in 200 mL of vinyl acetate and 300 mg of freeze-dried PPL lipase were incubated at rt for 7 h with magnetic stirring. Then, the lipase was filtered and vinyl acetate was eliminated under vacuum. NMR analysis of the mixture indicated a conversion of 33%. The reaction products were separated by silica gel flash chromatography (eluent petroleum ether/acetone 1:1), which afforded 9 mg of ester (90% yield, ee=0.98, determined by means of chiral HPLC t_{r1}=17.2 min and t_{r2}=20.7 min) and 16 mg of remaining alcohol (80% yield, ee=0.74, determined by means of chiral HPLC t_{r1}=7.5 min and t_{r2}=8.8 min).

4.5. Synthesis of the Mosher's esters 23*S*, 23*R*, 24*S* and 24*R*

4.5.1. General procedure for the preparation of Mosher's esters of isochromans. Purified acetates obtained by lipase transesterification were hydrolyzed in the presence of ammoniac methanol solution. Corresponding alcohols as well as remaining alcohols were derivatized as follows. In an NMR tube, isochroman **8** or **17** (5 mg, 17 μmol) was dissolved in 0.7 mL of pyridine d_5 and 25 μL of a solution of (*R*)-Mosher's chloride (50 mg, 198 mmol in 0.25 mL of CCl_4) was added. The course of the reaction was followed by means of ^1H NMR spectroscopy. When the alcohol had completely disappeared, the solvents were removed under reduced pressure. Then, the residue was dissolved in 20 mL of ether and the solution was washed twice with Na_2CO_3 saturated solution, then twice with water. After elimination of ether, the corresponding (S)-Mosher's esters were obtained with sufficient purity for their further analysis by NMR spectroscopy.

4.5.2. Compound 23*S*. ^1H NMR ($CDCl_3$, 500 MHz) δ 8.22 (s, 1H, NH), 7.25, 7.19, 7.18, 6.97 (9H, H aromatic), 7.00 (s, 1H, H-1′), 6.60 (q, J=1.2 Hz, 1H, H-6), 4.17 (m, 1H, H-3′), 4.41 (dd, $J_{9'a,9'b}$=11.7 Hz, $J_{3',9'a}$=5.1 Hz, 1H, H-9′a), 4.41 (dd, $J_{3',9'b}$=5.1 Hz, 1H, H-9′b), 3.44 (s, 3H, CH_3O), 2.77 (dd, $J_{4'a,4'b}$=16.3 Hz, $J_{3',4'a}$=5.3 Hz, 1H, H-4′a), 2.77 (dd, $J_{3',4'b}$=8.4 Hz, 1H, H-4′b), 1.71 (d, 1H, CH_3 thymine); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4 (COO), 163.4 (C-4), 151.0 (C-2), 136.9 (C-6), 123.2 (CF_3), 110.6 (C-5), 79.7 (C-1′), 67.9 (C-3′), 67.1 (C-9′), 29.8 (C-4′), 12.5 (CH_3 thymine).

4.5.3. Compound 23*R*. ^1H NMR ($CDCl_3$, 500 MHz) δ 8.18 (s, 1H, NH), 7.25, 7.19, 7.18, 6.97 (9H, H aromatic), 6.99 (s, 1H, H-1′), 6.57 (q, J=1.2 Hz, 1H, H-6), 4.12 (m, 1H, H-3′), 4.42 (dd, $J_{9'a,9'b}$=11.7 Hz, $J_{3',9'b}$=6.8 Hz, 1H, H-9′b), 4.38 (dd, $J_{3',9'a}$=4.0 Hz, 1H, H-9′a), 3.45 (s, 3H, CH_3O), 2.77 (dd, $J_{4'a,4'b}$=16.3 Hz, $J_{3',4'a}$=6.8 Hz, 1H, H-4′a), 2.77 (dd, $J_{3',4'b}$=6.8 Hz, 1H, H-4′b), 1.69 (d, 1H, CH_3 thymine); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.5 (COO), 163.4 (C-4), 151.0 (C-2), 136.9 (C-6), 123.3 (CF_3), 110.4 (C-5), 79.7 (C-1′), 67.8 (C-3′), 67.2 (C-9′), 29.8 (C-4′), 12.4 (CH_3 thymine).

4.5.4. Compound 24*S*. ^1H NMR ($CDCl_3$, 500 MHz) δ 8.36 (s, 1H, NH), 7.25, 7.19, 7.12, 6.91 (9H, H aromatic), 7.02 (s, 1H, H-1′), 6.62 (q, J=1.2 Hz, 1H, H-6), 4.25 (m, 1H, H-3′), 4.50 (dd, $J_{9'a,9'b}$=11.7 Hz, $J_{3',9'b}$=6.1 Hz, 1H, H-9′b), 4.38

(dd, $J_{3',9'a}$=3.9 Hz, 1H, H-9′a), 3.48 (s, 3H, CH_3O), 2.67 (dd, $J_{4'a,4'b}$=16.3 Hz, $J_{3',4'a}$=2.8 Hz, 1H, H-4′a), 2.96 (dd, $J_{3',4'b}$=11.6 Hz, 1H, H-4′b), 1.74 (d, 1H, CH_3 thymine); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4 (COO), 163.3 (C-4), 151.0 (C-2), 136.5 (C-6), 123.2 (CF_3), 111.8 (C-5), 81.0 (C-1′), 72.2 (C-3′), 67.0 (C-9′), 29.8 (C-4′), 12.4 (CH_3 thymine).

4.5.5. Compound 24*R*. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.36 (s, 1H, NH), 7.25, 7.19, 7.12, 6.92 (9H, H aromatic), 7.04 (s, 1H, H-1′), 6.61 (q, J=1.2 Hz, 1H, H-6), 4.25 (m, 1H, H-3′), 4.49 (dd, $J_{9'a,9'b}$=11.8 Hz, $J_{3',9'b}$=3.8 Hz, 1H, H-9′b), 4.41 (dd, $J_{3',9'a}$=5.3 Hz, 1H, H-9′a), 3.49 (s, 3H, CH_3O), 2.67 (dd, $J_{4'a,4'b}$=16.3 Hz, $J_{3',4'a}$=2.8 Hz, 1H, H-4′a), 2.93 (dd, $J_{3',4'b}$=11.7 Hz, 1H, H-4′b), 1.69 (d, 1H, CH_3 thymine); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4 (COO), 163.3 (C-4), 149.9 (C-2), 136.5 (C-6), 123.2 (CF_3), 111.8 (C-5), 81.0 (C-1′), 72.1 (C-3′), 67.0 (C-9′), 29.8 (C-4′), 12.3 (CH_3 thymine).

4.6. Molecular modeling

4.6.1. Force fields and energy minimization. The conformational analysis was studied considering molecules without the presence of solvent and with the hypothesis that the energies of the conformations were qualitatively correlated to their existence probability via the Boltzmann relationship. Considering molecular mechanics calculations, only the relative energies of identical configurations were comparable and the lowest energies correspond to the most stable conformations. Since the molecular weights of the molecules studied were relatively low, it was possible to undertake a systematic study of the conformations via a screening of dihedral angles. In connection with this systematic conformational research, the different molecular geometries studied were not obtained from experimental data but were produced from a builder module ('Builder').

4.6.2. Initial molecular building. Enantiomers of isochromans **8** and **17** were first studied. The central bicyclic nucleus presented a low conformational flexibility since the aromatic ring considerably limited the pseudo-rotation of the pyran ring. Thus, this bicyclic system adopted a quasi-planar geometry and the only conformational duality was revealed by the shift of the pyran oxygen atom above or below the plane. The energy barrier between the two resulting conformations was sufficient to divide further energy calculations into two individual classes, unable to interconvert when energy minimizations were applied. In the initial molecular building, two dihedral angles were systematically screened with 10° steps: $C_2N_1C_{1'}O_{2'}$ (α angle already defined in text, see Table 1) and $O_{2'}C_{3'}C_{9'}O_{9'}$.

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