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An Efficient and Highly Diastereoselective Synthesis of GSK1265744, a Potent HIV Integrase Inhibitor

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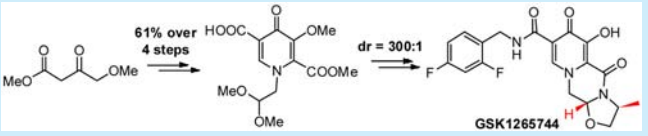
Supporting Information

ABSTRACT: A novel synthesis of GSK1265744, a potent HIV integrase inhibitor, is described. The synthesis is highlighted by an efficient construction of the densely functionalized pyridinone core as well as a highly diastereoselective formation of the acyl oxazolidine moiety. The latter exploits the target molecule's ability to chelate to Mg^{2+}, a key feature in the integrase inhibitor's mechanism of action.



An important step in the replication of human immunodeficiency virus (HIV) in human cells is the integration of the viral DNA into the host cell genome. Inhibition of HIV integrase, the enzyme that mediates this integration process, therefore can halt the further spread of HIV and represents a viable treatment for HIV infection.[1] Recently, GSK1265744 (**1a**, Figure 1) has emerged as a potent HIV integrase inhibitor.

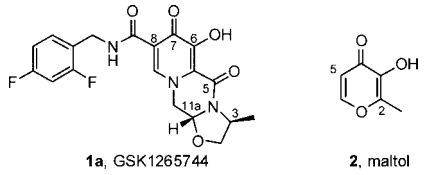


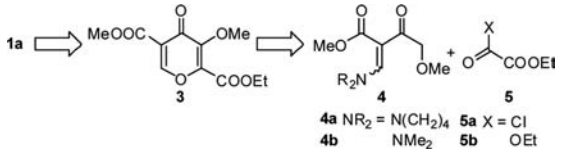
Figure 1. GSK1265744.

It is designed to function as a metal chelator and block the binding of host DNA to metal cofactors in the active catalytic site of the integrase.[2] Herein we report a highly diastereoselective synthesis of this compound which exploits its unique metal-binding affinity for Mg^{2+}.

There are two main challenges in the chemical synthesis of **1a**: the densely functionalized pyridinone core and the stereocontrol of the C-11a center. In the construction of the pyridinone, previous syntheses have taken advantage of the existent ring structure of inexpensive maltol (**2**).[2,3] However, oxidation state manipulation of the C-2 methyl and functionalization of C-5 require tedious sequences involving toxic heavy metal-mediated transformations. Second, the energy difference between the two C-11a epimers is small (*vide infra*) and the diastereoselectivity needs to be carefully managed by kinetic control.

In designing a more efficient and robust synthesis of **1a**, it was initially envisioned that the central pyridinone ring could be derived from pyranone **3**, which in turn would be accessed via a reaction between a *tertiary* vinylogous amide **4** and oxalate **5** (Scheme 1). However, the β-ketoester functionality in **4** and

Scheme 1



3 made this a particularly sensitive reaction.[4] Although vinylogous amide **4** did provide the desired product when treated with oxalyl chloride **5a** or oxalate **5b** in the presence of a base (LHMDS or an alkoxide), the reaction was sensitive to the temperature, base, and N-substituents in **4**, giving yields ranging between <10% and 60%. This is presumably due to the fact that pyranone **3** is an excellent Michael acceptor and thus sensitive to reaction and purification conditions.[5] The sensitivity of **3** placed a great deal of restrictions on downstream manipulations and made it difficult to develop a synthesis that was amenable to large scale. Although this transformation was feasible on laboratory scale, both in our hands and by the independent effort of another group,[6] a more robust procedure was sought.

It was reasoned that the cyclization of a *secondary* vinylogous amide might provide direct access to the target pyridinone and circumvent the more electrophilic, sensitive pyranone. Although the initial acylation could potentially occur on either the nitrogen or the α-carbon, both should lead to the desired pyridinone due to the symmetry of the electrophile. Literature examples of this cyclization have been scarce. To our knowledge, prior to this work, there has been only one report for the direct formation of pyridinones from vinylogous amides.[7]

Treatment of vinylogous amides **6** with dimethyl oxalate and NaOMe in methanol at slightly elevated temperatures furnished

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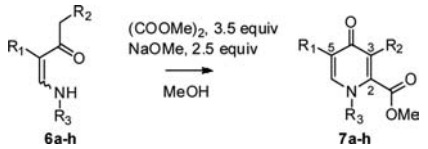
the corresponding pyridinones **7** cleanly (Table 1). The major side reaction was the hydrolysis of the C-2 ester (~5−15%).

Table 1. Direct Formation of Pyridinones from Secondary Vinylogous Amides and Dimethyl Oxalate

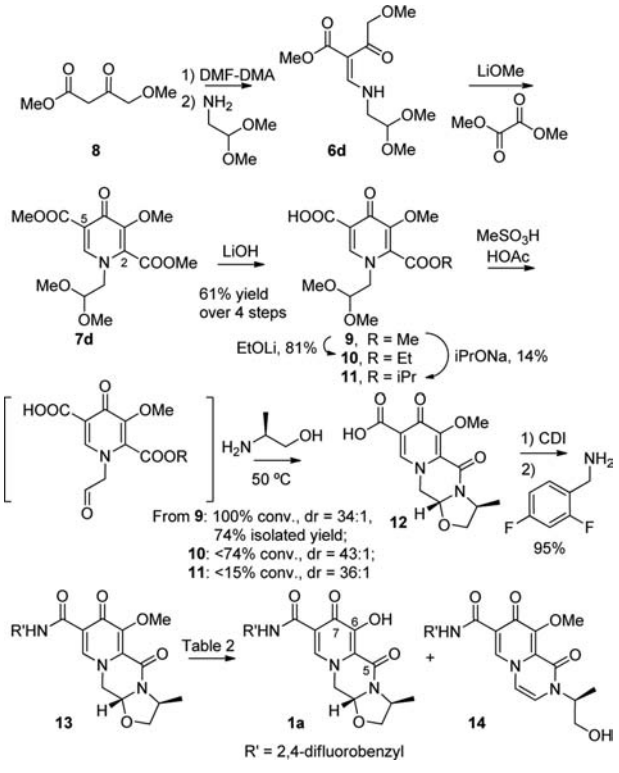


	6, 7	R_1	R_2	R_3	t/°C	yield/%
1	**a**	CO_2Me	H	Bn	30	71
2	**b**	CO_2Me	H	Ph	30−70	69
3	**c**	CO_2Me	H	*i*Pr	30	70
4	**d**	CO_2Me	OMe	$CH_2CH(OMe)_2$	30	73
5	**e**	Me	H	Bn	50	67
6	**f**	Me	Me	Bn	50	60
7	**g**	Ph	H	Bn	50	60
8	**h**	H	H	Bn	50	23

This hydrolysis was more facile with pyridinones bearing a C-5 ester substituent; subsequently the cyclization to form these substrates was carried out at lower temperature (entries 1−4). Both aliphatic and aromatic N-substitutions were tolerated (entries 1−3), although the lower nucleophilicity of the *N*-anilino substrate **6b** required a higher temperature for the ring closure to reach full conversion (entry 2). The reaction also tolerated different substitutions at C-5 (entries 5−7) and C-3 (entries 4 and 6). However, the lack of substitution at C-5 resulted in a lower yield (entry 8).

This cyclization allowed for an efficient construction of the pyridinone core in **1a** (Scheme 2). *β*-Ketoester **8** was converted to vinylogous amide **6d**, which underwent cyclization with dimethyl oxalate in the presence of LiOMe to give pyridinone **7d**. Simple addition of LiOH effected selective hydrolysis of the C-5 ester of **7d**,[8] furnishing advanced intermediate **9** as a white solid in 61% yield in a four-step, one-pot operation. The 2-methyl ester could be further converted to the corresponding Et or *i*Pr esters (**10** and **11**) by transesterification.

Scheme 2



The acetal deprotection of **9** proved challenging. Competitive hydrolysis of the C-2 ester took place under a variety of aqueous conditions, and the resultant C-2 acid failed to undergo the subsequent ring closure reaction. It was found that treatment of acetal **9** with excess HOAc and a catalytic amount of CH_3SO_3H under anhydrous conditions led to a smooth conversion to the corresponding aldehyde. Addition of excess alaninol quenched CH_3SO_3H, and the ring closure proceeded in the presence of HOAc. The desired product **12** was formed in ~30:1 dr in the case of methyl ester **9**, and the diastereomeric purity of the isolated product could be further enriched by crystallization. Increasing the steric bulk at the C-2 ester (**10** and **11**) greatly reduced the reaction rate, but did not lead to a significant improvement in the diastereoselectivity of the ring closure.

After amide **13** was obtained from coupling of **12** with 2,4-difluorobenzylamine, demethylation to give **1a** proved difficult in the presence of the aminal moiety. Widely used boron- and silicon-based demethylation reagents did not discriminate between the two, leading to a large amount of ring-opened product **14**. This indicated that boron or silicon did not coordinate selectively to the methyl ether, and an alternative Lewis acid was needed.

Central to the solution to the demethylation selectivity problem is the metal-chelating ability of **1a**, which forms the basis for its mechanism of action as an integrase inhibitor. It is known that the integrase catalyzes the strand transfer process by binding to two metals through a triad of amino acid carboxylate residues in the active site. The two metals in turn bind to the host DNA and activate a phosphoryl ester for attack by the viral DNA, thus integrating the latter into the host genome. The inhibitor functions by chelating to the metals, occupying the catalytic triad and thus blocking the host DNA from binding.[9] In the case of **1a**, the structural feature that contains the chelating motif would be the C5−C6−C7 region.[2b] *Since Mg^{2+} is believed by most to be the metal cofactor involved in the integration process in vivo and* ***1a*** *is designed as a Mg^{2+} chelator, it is reasoned that Mg^{2+} might selectively bind to the C-6 oxygen of* ***13*** *and therefore facilitate a selective demethylation.*

Indeed, treatment of **13** with a variety of magnesium salts resulted in completely selective C-6 demethylation (Table 2, entries 4−6). The coordination of Mg^{2+} to the C-6 oxygen is so efficient that the demethylation was effected at toom

Table 2. Demethylation of 13[a]

	reagent	conditions	**1a:13:14**
1	BBr_3	−78 °C to rt, 2 h[b]	0:46:54
2	TMSCl/NaBr	50 °C, overnight	0:71:29
3	TMSCl/NaI	50 °C, 5 h	34:58:8
4	MgI_2	rt, 1 h	100:0:0
5	$MgBr_2$	50 °C, 1 h[c]	100:0:0
6	$MgCl_2$	70 °C, 7 h	100:0:0

[a]Reactions in CH_3CN unless otherwise noted. [b]Reaction in CH_2Cl_2. [c]90% isolated yield.

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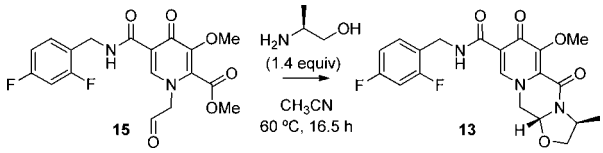
Table 3. Additive Effect on the dr of Ring Closure



	additive (1.5 equiv)	dr	conv/%		additive (1.5 equiv)	dr	conv/%
1	none	10:1	73	5	HOAc	25:1	100
2	$MeSO_3H$	5:1[a]	46	6	*i*PrCOOH	19:1	100
3	TFA	4:1	83	7	*t*BuCOOH	16:1	100
4	$CHCl_2COOH$	4:1	100	8	**$Mg(OTf)_2$**	**300:1**	100

[a]80 °C, 12 h, 7% of **14** also formed.

temperature with iodide as the nucleophile (entry 4), and even by $MgCl_2$, albeit at higher temperature (entry 6). This completes an efficient and practical synthesis of **1a**, which is chromatography-free and performs very well on large scale.[10]

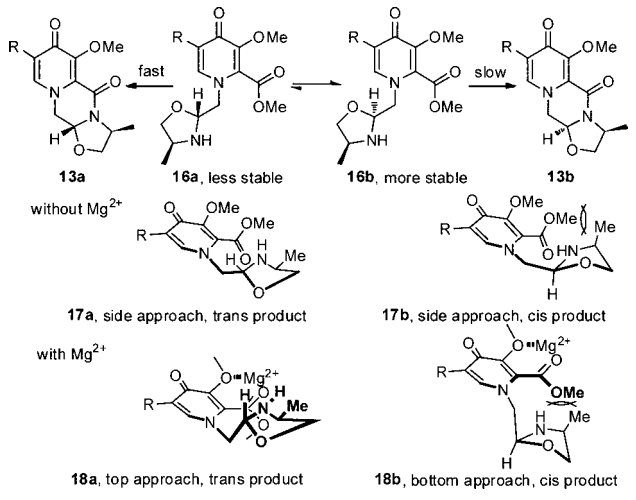
The chelating ability of the target to Mg^{2+} also had a profound impact on the diastereoselectivity of the ring closure. As shown in Table 3, the reaction between **15** and alaninol to form **13** could be mediated by acids, with weak acids ($pK_a \approx$ 4−5, entries 5−7) providing the highest diastereoselectivity (dr ≈ 20:1). The addition of a stoichiometric amount of $Mg(OTf)_2$ led to superior diastereoselectivity (dr = 300:1). The chelation between Mg^{2+} and the substrate appeared critical. The use of $Mg(OAc)_2$ as the additive gave a low dr (~20:1). Coordinating solvents led to complex reaction mixtures with inferior selectivities, as did other metal triflates including Mn^{2+}, Ca^{2+}, and Zn^{2+} (dr from 32:1 to 86:1).[11] It should be further noted that the observed dr resulted from kinetic control: when a mixture of **13** with a dr of 33:1 was treated with CH_3SO_3H in refluxing CH_3CN, the predominant product was **14** (63%). The dr of remaining **13** eroded to 6:1,[12] indicating that the relative thermodynamic stability of the pair did not favor the 11aR isomer (**13a**) by a wide margin.[13,14]

One plausible mechanistic explanation is depicted in Scheme 3: the two oxazolidine intermediates **16a** and **16b** exist in equilibrium via the open-chain imine form.[15] The predominant formation of the desired product **13a** is the result of a Curtin−Hammet situation, where the less stable *trans*-oxazolidine **16a** undergoes a faster ring closure than the more stable **16b** because of the lack of steric interaction between the oxazolidine methyl and the ester in the transition state (**17a** and **18a**).[2b,16] This is consistent with the observed acid effect: the **16a/b** equilibrium is best facilitated by weak acids ($pK_a \approx$ 4−5, entries 5−7 of Table 3) so that the diastereoselectivity reflects the difference in the ring closure activation energy. Stronger acids ($pK_a < 2$, entries 2−4) hinder this interconversion, and thus the selectivity reflects more the relative stability of intermediates **16a**/**16b**, resulting in lower dr.

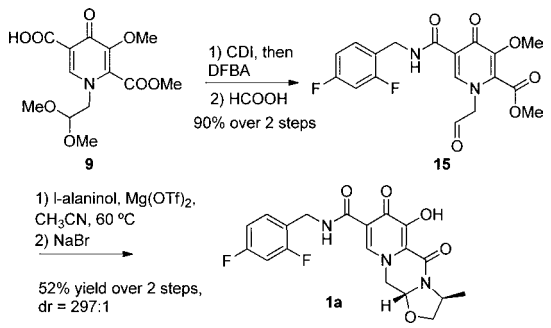
The addition of Mg^{2+} would change the geometry of the transition state and the trajectory of the oxazolidine approach: in the cyclization without Mg^{2+} (**17a**/**b**), the ester is perpendicular to the ring system and the steric repulsion results from the oxazolidine approaching from the side. In the presence of Mg^{2+} (**18a**/**b**), its chelation in the C-5 and C-6 pocket forces the oxazolidine to approach from the top or bottom face.[17] This results in a more rigid and sterically discriminating transition state and a higher diastereoselectivity.

The success of Mg^{2+}-mediated ring closure has led to a highly diastereoselective ring closure−demethylation sequence shown in Scheme 4. Coupling of **9** with 2,4-difluorobenzylamine

Scheme 3



Scheme 4



followed by acetal deprotection in formic acid provided aldehyde **15**, which underwent smooth ring closure with alaninol in the presence of $Mg(OTf)_2$. When the ring closure was complete, simple addition of NaBr in the same pot effected demethylation to produce the desired product with a dr of 297:1, concluding a highly efficient and diastereoselective synthesis of **1a**.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization. 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.

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(5) The product decomposed when the reaction mixture was heated. Sensitivity toward chromatography has also been noted with pyranone-3-carboxylates: See reference 4.

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(8) Although LiOH, NaOH, and KOH all led to somewhat selective cleavage of the C-5 ester, the selectivity was higher when LiOH was used (~10:1 vs 3:1 in the case of NaOH or KOH).

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(10) On kilogram scale the demethylation is better accomplished with LiBr, which is lower in cost and gives an easily stirrable slurry. However, the reaction is much slower (overnight in reflux THF) than that with $MgBr_2$, presumably due to the weaker chelation of Li^+ to **13**.

(11) Involvement of other divalent metals as the metal cofactor in integrase inhibition has also been speculated: (a) Chiu, T. K.; Davies, D. R. *Curr. Top. Med. Chem.* **2004**, *4*, 965. (b) Bacchi, A.; Carcelli, M.; Compari, C.; Fisicaro, E.; Pala, N.; Rispoli, G.; Rogolino, D.; Sanchez, T. W.; Sechi, M.; Sinisi, V.; Neamati, N. *J. Med. Chem.* **2011**, *54*, 8407.

(12) The ring opening and dr erosion only occurred with strong acids (HCl or CH_3SO_3H). No dr erosion was observed with TFA or weaker acids.

(13) The equilibrium dr of 6:1 can be compared to a similar system, where a trans:cis = 86:14 mixture was obtained from acid-catalyzed equilibration: (a) Amat, M.; Bosch, J.; Hidalgo, J.; Cantó, M.; Pérez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074. (b) Amat, M.; Llor, N.; Escolano, C.; Huguet, M.; Pérez, M.; Molins, E.; Bosch, J. *Tetrahedron: Asymmetry* **2003**, *14*, 293.

(14) The energy difference between the two diastereomers of **13** by DFT calculation (B3LYP/lacvp**) is 0.7 kcal/mol favoring the desired trans isomer **13a**.

(15) Lázár, L.; Fülöp, F. *Eur. J. Org. Chem.* **2003**, 3025 and the references cited therein.

(16) The cis isomer **16b** is more stable by 1.0 kcal/mol by DFT calculation (B3LYP/lacvp**).

(17) C-5 esters have shown promising potency in enzyme and antiviral assays, demonstrating an ability to chelate metals: Kawasuji, T.; Johns, B. A.; Yoshida, H.; Taishi, T.; Taoda, Y.; Murai, H.; Kiyama, R.; Fuji, M.; Yoshinaga, T.; Seki, T.; Kobayashi, M.; Sato, A.; Fujiwara, T. *J. Med. Chem.* **2012**, *55*, 8735.

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