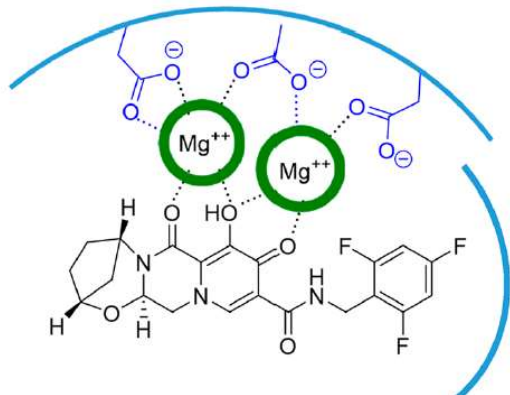


### Amino acid triad



- Approved in the US and the EU in 2018 for the treatment of HIV-1 infections
- Belongs to a class of antiretroviral drugs known as integrase strand transfer inhibitors (INSTIs)
- Inhibits HIV-1 replication by blocking the strand transfer step of viral DNA integration into the host genome
- A substituted benzyl group binds within a hydrophobic pocket near the active site, and a chelating oxygen atom triad coordinates two Mg<sup>2+</sup> ions



Tsiang, M. *Antimicrob. Agents. Chemother.* **2016**, 60, 7086. <http://dx.doi.org/10.1128/AAC.01474-16>  
Hughes, D. *Org. Process Res. Dev.* **2019**, 23, 716. <https://doi.org/10.1021/acs.oprd.9b00031>

For other INSTI drugs, see:

Yi, DOTW: [https://8cf9eb7e-b5ec-48cd-9fdd-580cfdeede43.filesusr.com/ugd/31ec9c\\_db8b9518235b4bdead49a215c895bc39.pdf](https://8cf9eb7e-b5ec-48cd-9fdd-580cfdeede43.filesusr.com/ugd/31ec9c_db8b9518235b4bdead49a215c895bc39.pdf)

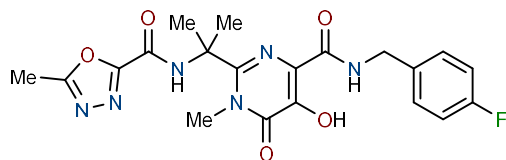
Ungarean, DOTW: [https://8cf9eb7e-b5ec-48cd-9fdd-580cfdeede43.filesusr.com/ugd/31ec9c\\_a80acea99fdd4f00b8c812fd3932df8a.pdf](https://8cf9eb7e-b5ec-48cd-9fdd-580cfdeede43.filesusr.com/ugd/31ec9c_a80acea99fdd4f00b8c812fd3932df8a.pdf)

Ungarean, DOTW: [https://8cf9eb7e-b5ec-48cd-9fdd-580cfdeede43.filesusr.com/ugd/31ec9c\\_a80acea99fdd4f00b8c812fd3932df8a.pdf](https://8cf9eb7e-b5ec-48cd-9fdd-580cfdeede43.filesusr.com/ugd/31ec9c_a80acea99fdd4f00b8c812fd3932df8a.pdf)

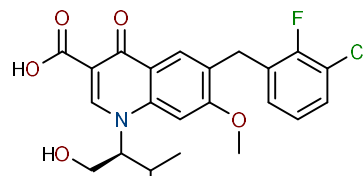
Ungarean, DOTW: [https://8cf9eb7e-b5ec-48cd-9fdd-580cfdeede43.filesusr.com/ugd/31ec9c\\_a80acea99fdd4f00b8c812fd3932df8a.pdf](https://8cf9eb7e-b5ec-48cd-9fdd-580cfdeede43.filesusr.com/ugd/31ec9c_a80acea99fdd4f00b8c812fd3932df8a.pdf)



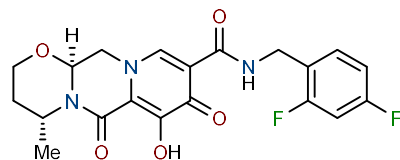
## Previous INSTI drugs



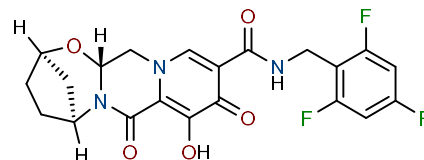
raltegravir (RAL)  
Merck, 2007



elvitegravir (EVG)  
Gilead, 2012



dolutegravir (DTG)  
ViiV, 2013



bictegravir (BIG)  
Gilead, 2018

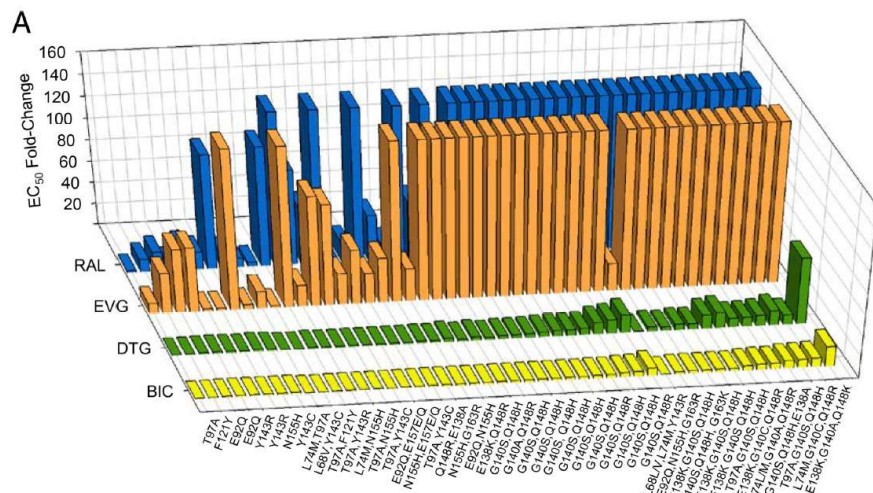
### Raltegravir (RAL), Elvitegravir (EVG)

- The first two drugs approved for antiretroviral therapy
- Dosed twice a day (RAL) or requires coadministration with a pharmacokinetic enhancer (EVG)
- Have an overlapping resistance profile

### Dolutegravir (DTG)

- Unboosted INSTI with a higher barrier to resistance development and improved resistance profile
- Dosed once daily for most patients
- Showed emergence of additional INSTI resistance
- Must be dosed twice a day in patients with INSTI-associated resistance
- Increases the level of human serum creatinine via inhibition of OCT2 in the proximal tubule of the kidney

## High potency with improved resistance profile

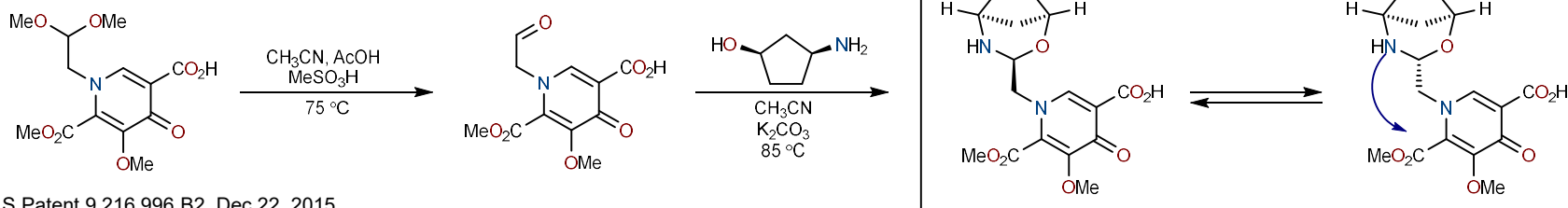


Compounds	IC <sub>50</sub> (nM)	
	Inhibition of strand transfer	Inhibition of 3' processing
BIC	7.5 ± 0.3	241 ± 51
DTG	7.4 ± 0.6	232 ± 33
EVG	8.4 ± 0.7	556 ± 40

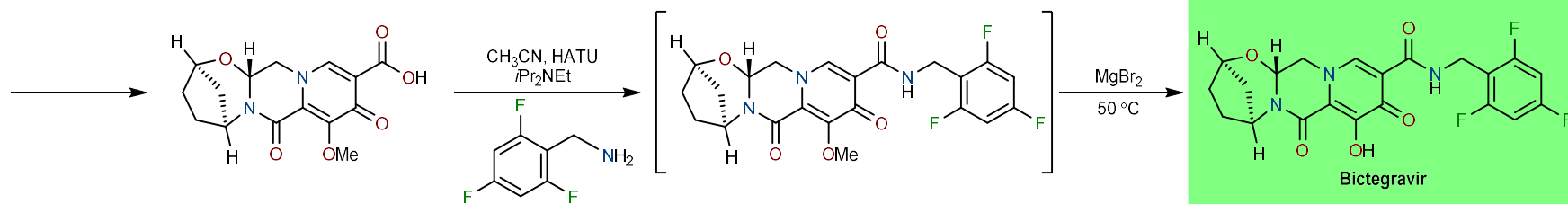
TABLE 2 Inhibition of HIV-1 integration in MT-2 cells by BIC

Compound <sup>a</sup>	Integration failure of 2-LTR circles <sup>b</sup> (fold change)	Assessment of direct effect on integration <sup>b</sup> (fold change)	
		Late reverse transcription products	Alu-LTR integration junctions
DMSO	1.00 ± 0.42	1.00 ± 0.19	1.00 ± 0.41
BIC	5.55 ± 0.34*	0.81 ± 0.09	0.01 ± 0.01*
DTG	2.47 ± 1.26*	0.86 ± 0.08	0.01 ± 0.01*
EFV	0.05 ± 0.04*	0.21 ± 0.07*	0.10 ± 0.05*
DRV	0.57 ± 0.24	0.96 ± 0.11	0.72 ± 0.31

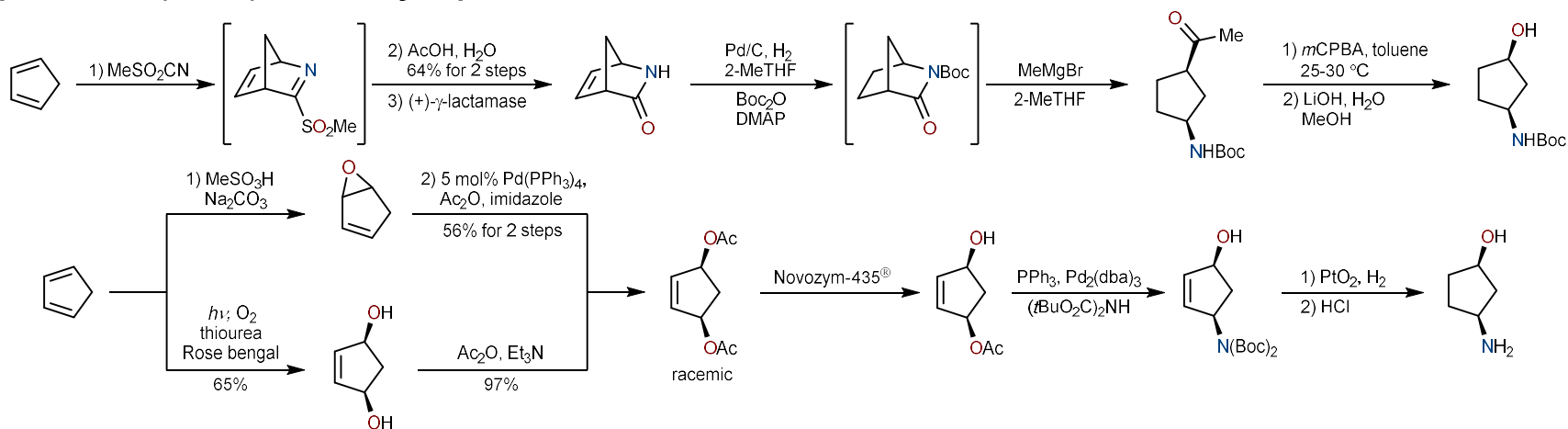
## Initial route



Jin, H. U.S. Patent 9,216,996 B2, Dec 22, 2015.  
Jin, H. U.S. Patent 9,732,092 B2, Aug 15, 2017.



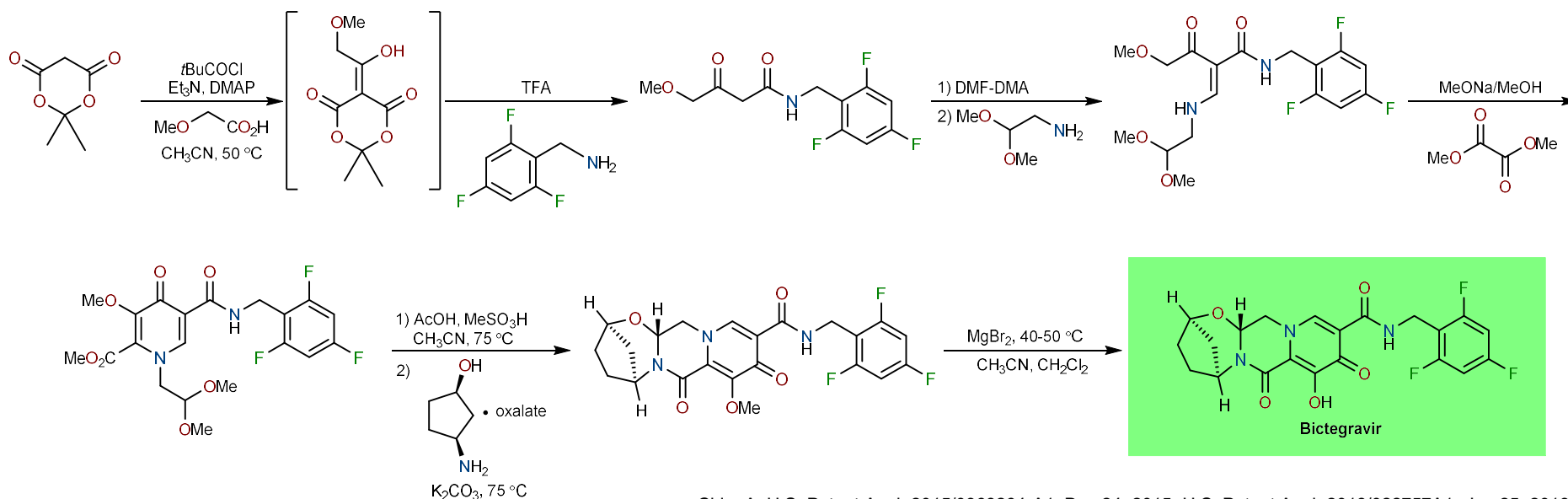
## Preparation of (1*R*,3*S*)-3-aminocyclopentanol



Tietze, L. F. *Synlett* **2007**, 485. <https://doi.org/10.1055/s-2007-967937>  
Putta, S. *Tetrahedron* **2018**, 74, 6673. <https://doi.org/10.1016/j.tet.2018.09.052>

U.S. Patent Appl. 2015/0368264 A1, Dec 24, 2015.  
U.S. Patent Appl. 2018/022757A1, Jan 25, 2018.

## Process route



Chiu, A. U.S. Patent Appl. 2015/0368264 A1, Dec 24, 2015. U.S. Patent Appl. 2018/022757A1, Jan 25, 2018.