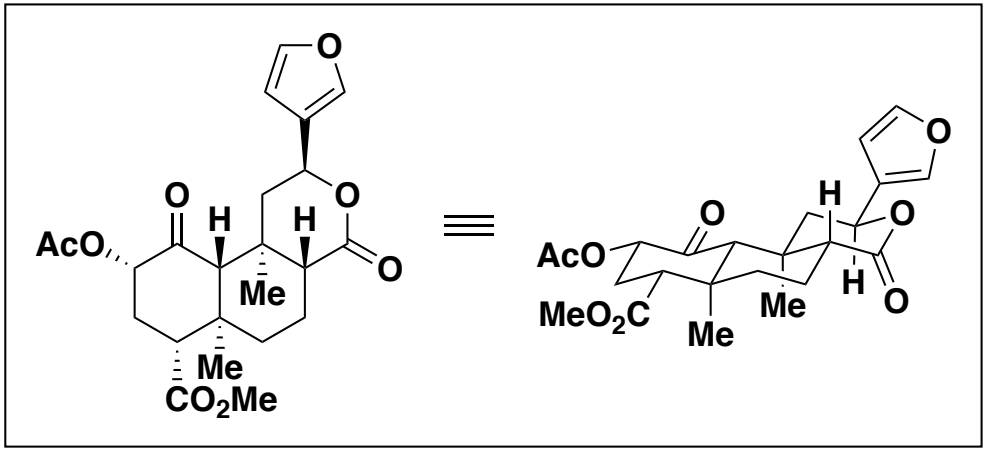
Total synthesis of Salvinorin A

Shenvi, R., Bohn, L. M. and coworkers.
ACS Cent. Sci. **2017**, 3, 1329.

Wipf Research Group - Current Literature

Manwika Charaschanya
August 11, 2018

Salvinorin A

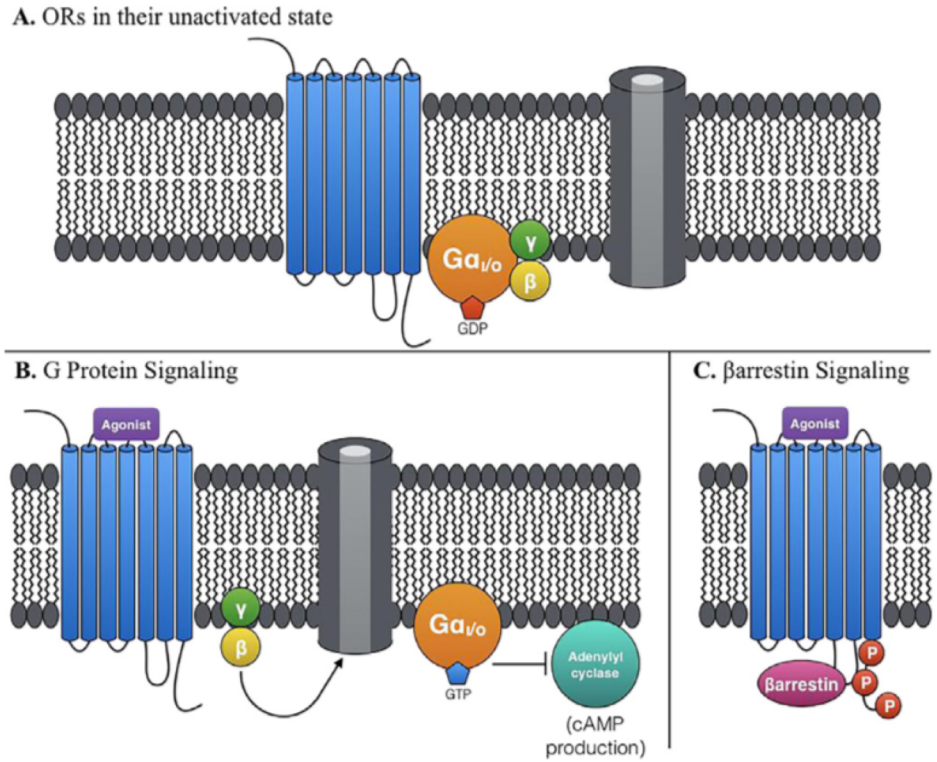


- Plant metabolite of *Salvia divinorum*
- Most potent naturally occurring hallucinogen
- Nonpeptide-like & non-nitrogenous scaffold (vs. opioid motifs)
- Diterpene with 7 chiral centers
- Agonist of *kappa*-opioid receptor (KOR), a subtype of G-protein-coupled receptor (GPCR)
- Selective for KOR over *mu*- and *delta*-opioid receptors (however, low affinity for MOR & shown to be an allosteric modulator of MOR)
- On-going race for biased KOR agonists towards clinical studies

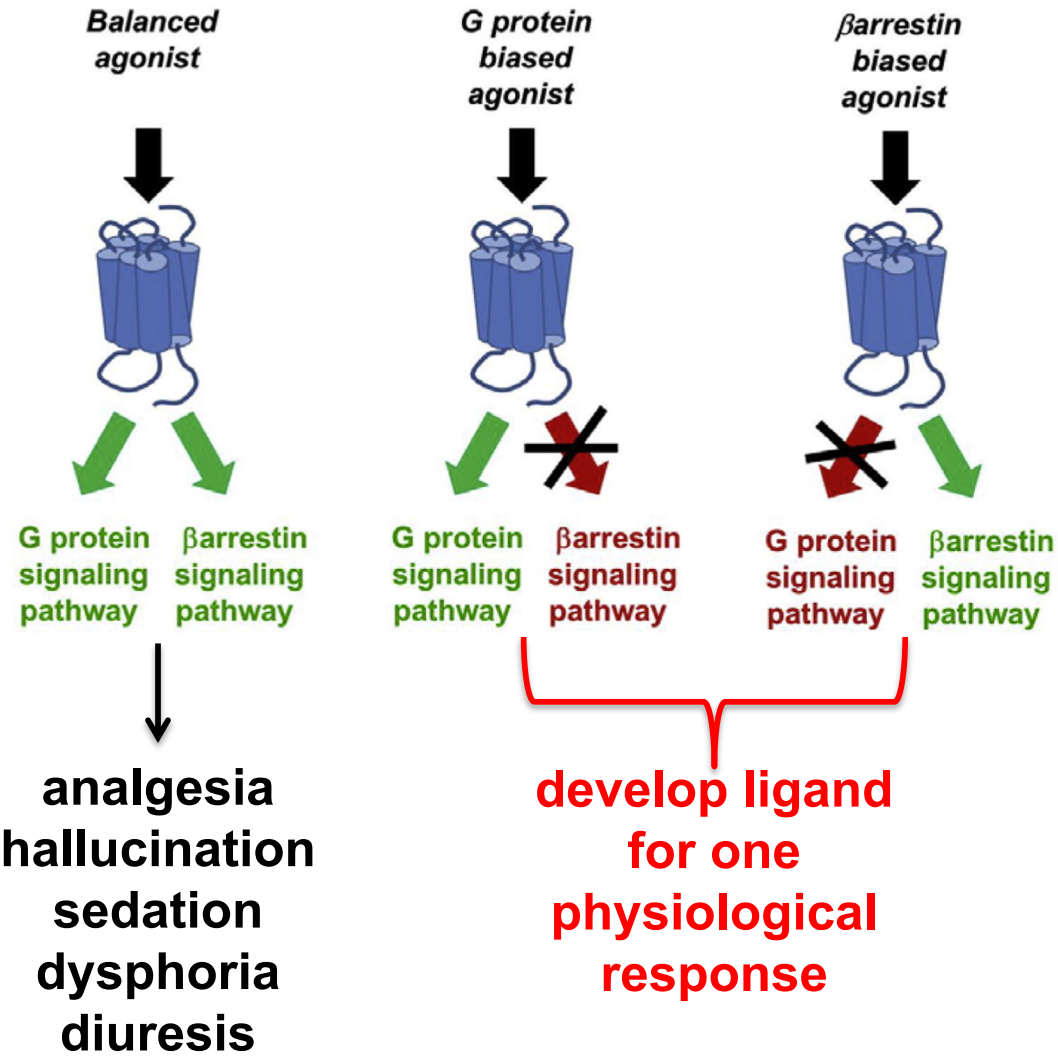
Prisinzano, T. E.; Rothman, R. B. *Chem. Rev*. **2008**, 108, 1732.
Roach, J. J.; Shenvi, R. *Bioorg. & Med. Chem. Lett.* **2018**, 28, 1436.

Kappa opioid receptors

GPCR signaling



'functional selectivity'



Roach, J. J.; Shenvi, R. *Bioorg. Med. Chem. Lett.* **2018**, 28, 1436.
Rankovic, Z.; Brust, T. F.; Bohn, L. M. *Bioorg. Med. Chem. Lett.* **2016**, 26, 241.

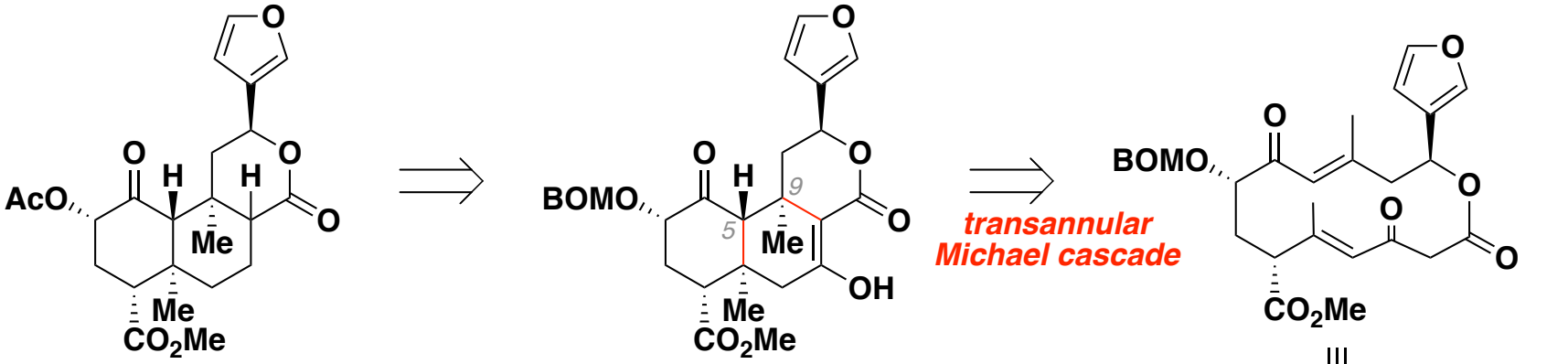
Total syntheses of Sal A

- First total synthesis by Rook (**2006**) was incomplete
- Evan's synthesis of Sal A was reported in 33 steps (**2007**)
- Hagiwara published a series of first- (**2008**) & second-generation syntheses (**2009**)
- Forsyth's synthesis of Sal A was reported in **2016**

Total syntheses of Sal A

- Evan's synthesis of Sal A was reported in 33 steps (**2007**)

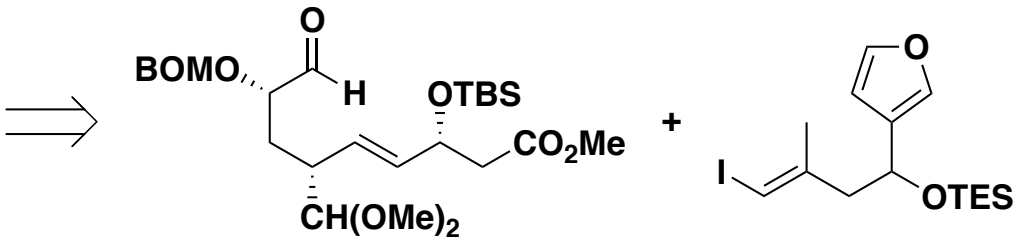
Retrosynthetic analysis:



C8, 2.5:1 (α:β)

- *reduction of α,β-unsaturated lactone using L-selectride yielded C_8-epimer*
- *epimerization with K_2CO_3/methanol*

dr >95:5



- *chelate-controlled addition of Grignard reagent of vinyl iodide to aldehyde followed by macrolactonization*

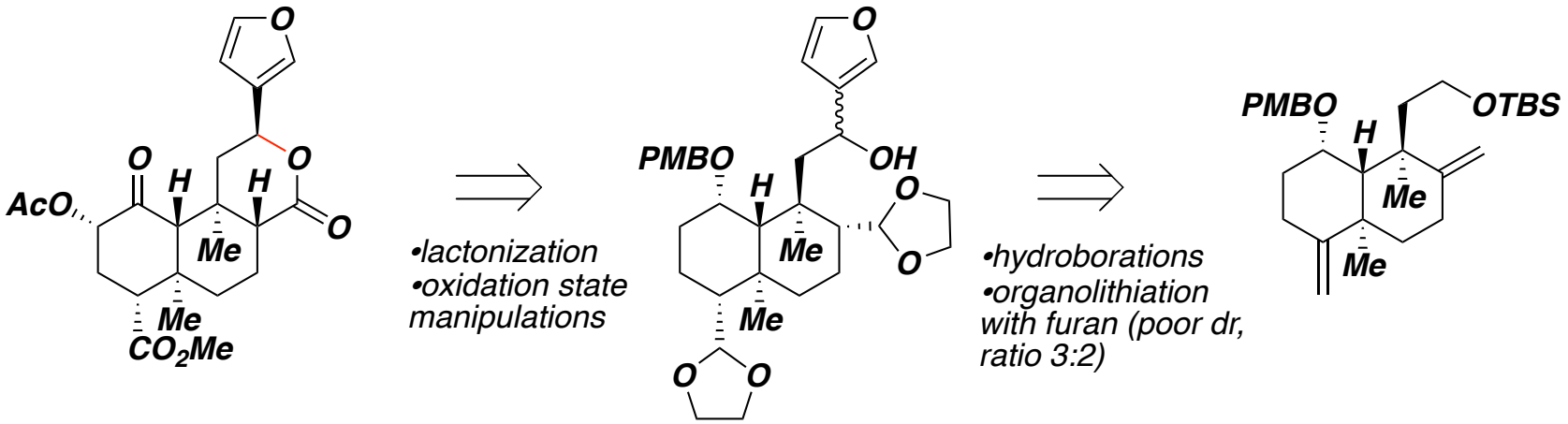
Scheerer. J. R.; Lawrence, J.F.; Wang, G.C.; Evans, D. A. *JACS*. **2007**, 129, 8968

Total syntheses of Sal A

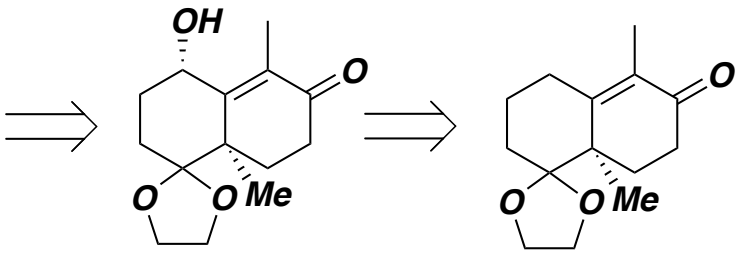
- Hagiwara first- (**2008**) & second-generation syntheses (**2009**)

Retrosynthetic analysis:

(a) First generation



•epimerization of C8 (dr 7:3); analogous to Evan's group



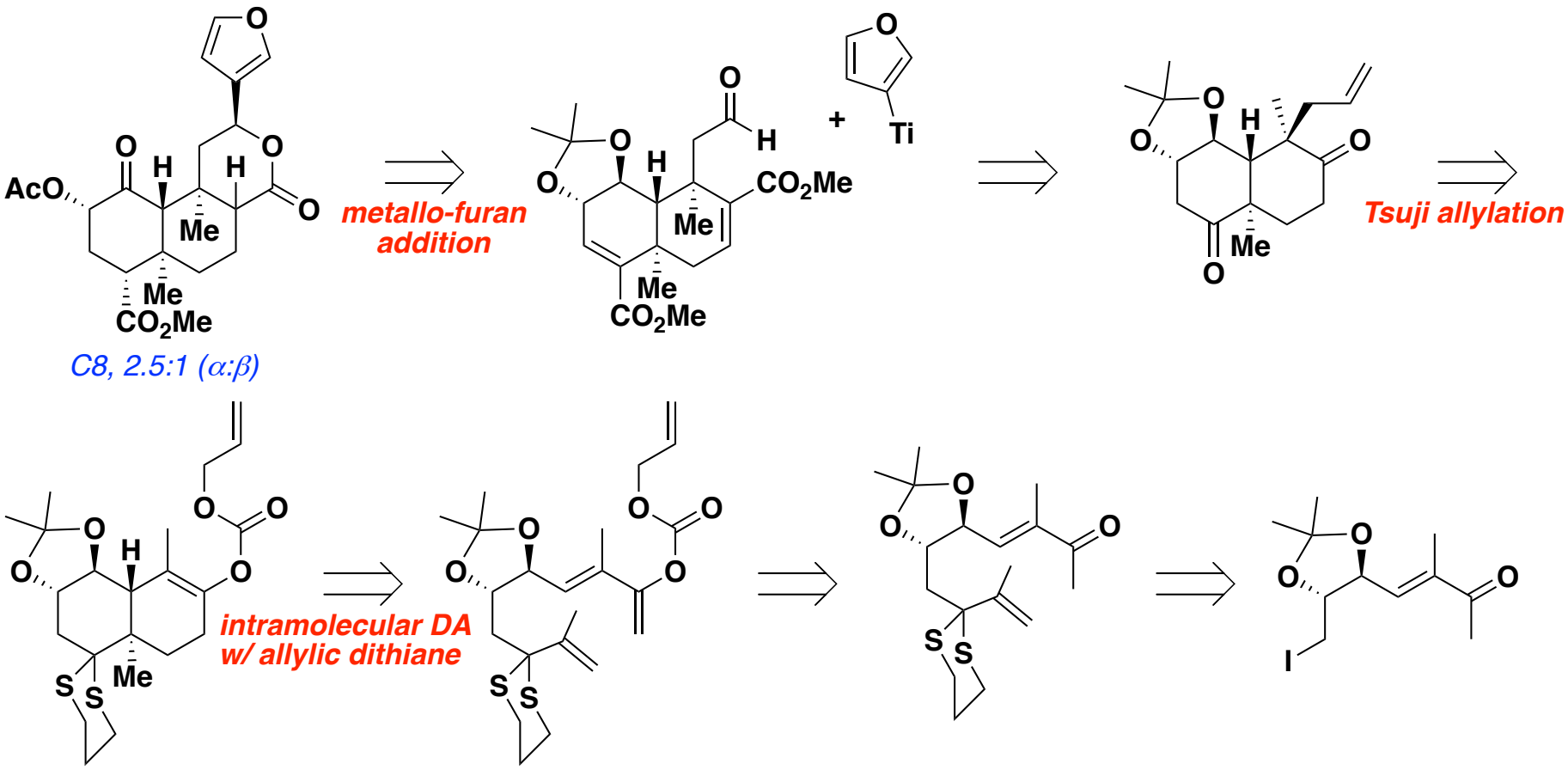
•originates from Wieland-Mischler ketone (known)

(b) Second generation:
- resolved unfavorable selectivity of the 3-lithiofuran addition (use of furyl ketone vs. furyl alcohol)
- established shorter route; 20 steps (0.95% overall yield) to 13 steps (2.8% overall yield)

Hagiwara and coworkers. *Org. Lett.* **2008**, 10, 1365.
Suzuki and coworkers. *Tetrahedron*. **2009**, 65, 4820.

Total syntheses of Sal A

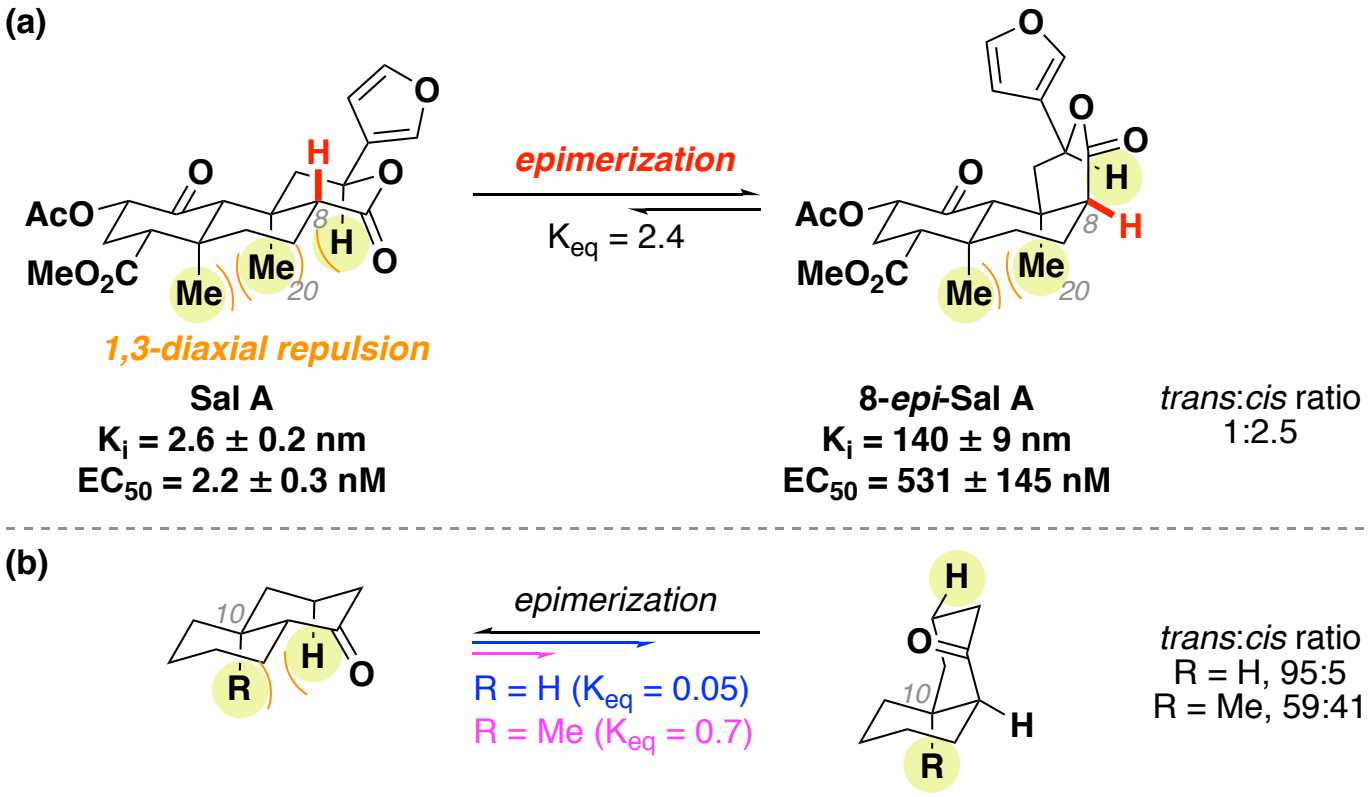
- Synthesis by Forsyth and coworkers (**2016**)



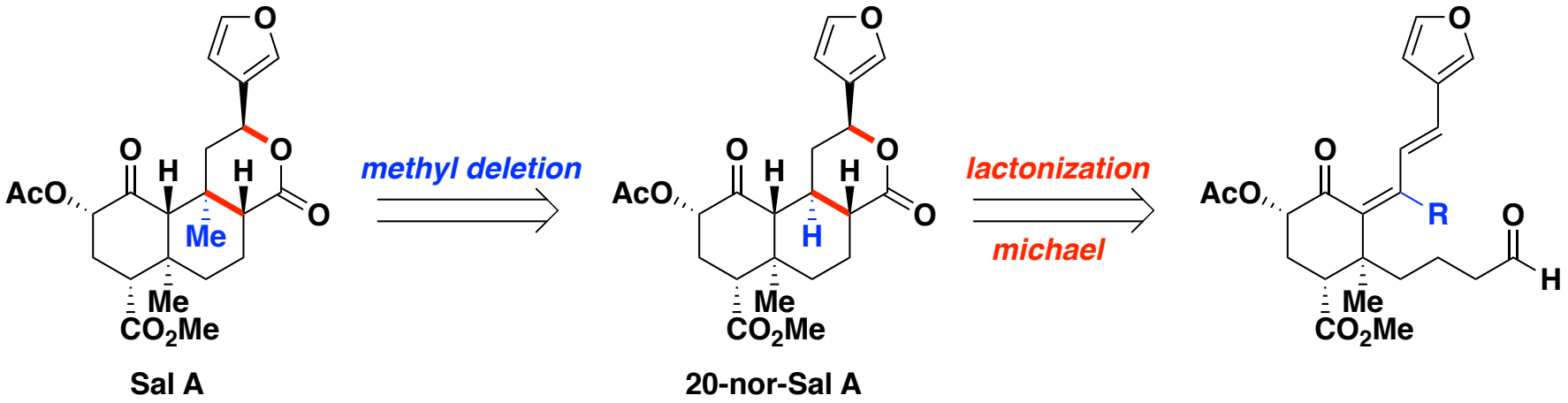
Forsyth and coworkers. *Eur JOC*. **2016**, 129, 8968.

Challenges in the total synthesis of Sal A

- Reactivity & thermodynamic stability of structural features: *trans*-decalin system, 6-membered lactone & furan
- Known configurational liability of C8 carbon – epimerization issue



Dynamic strategic bond analysis yields 10-step synthesis of 20-nor-Sal A



Sal A

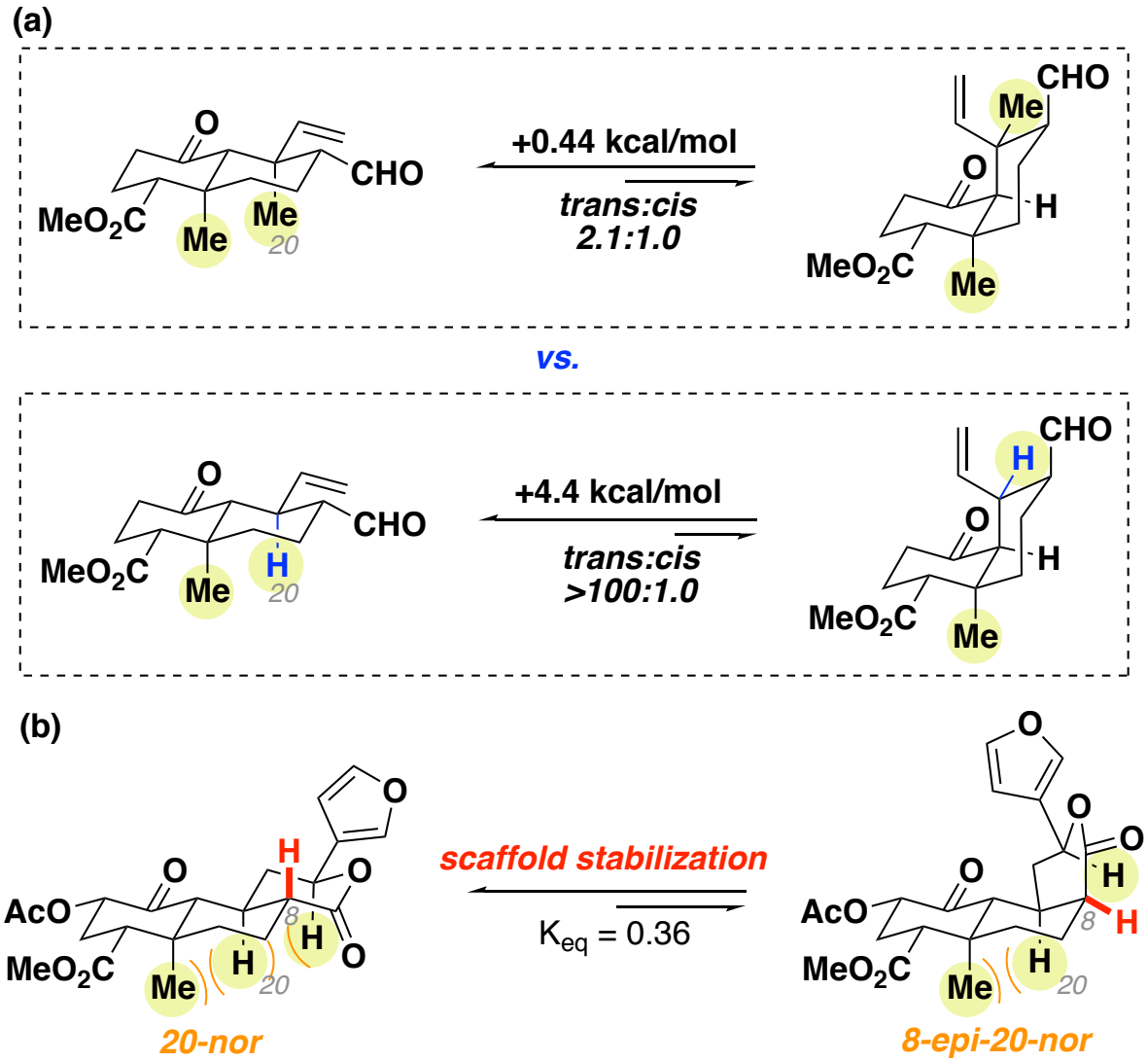
20-nor-Sal A

Retrosynthetic analysis

- Hypothesis-driven
- Directly addresses known problem of configurational liability at C8
- Improve material access for med chem by 10-step synthesis

Dynamic strategic bond analysis yields 10-step synthesis of 20-nor-Sal A

Hypothesis driven:



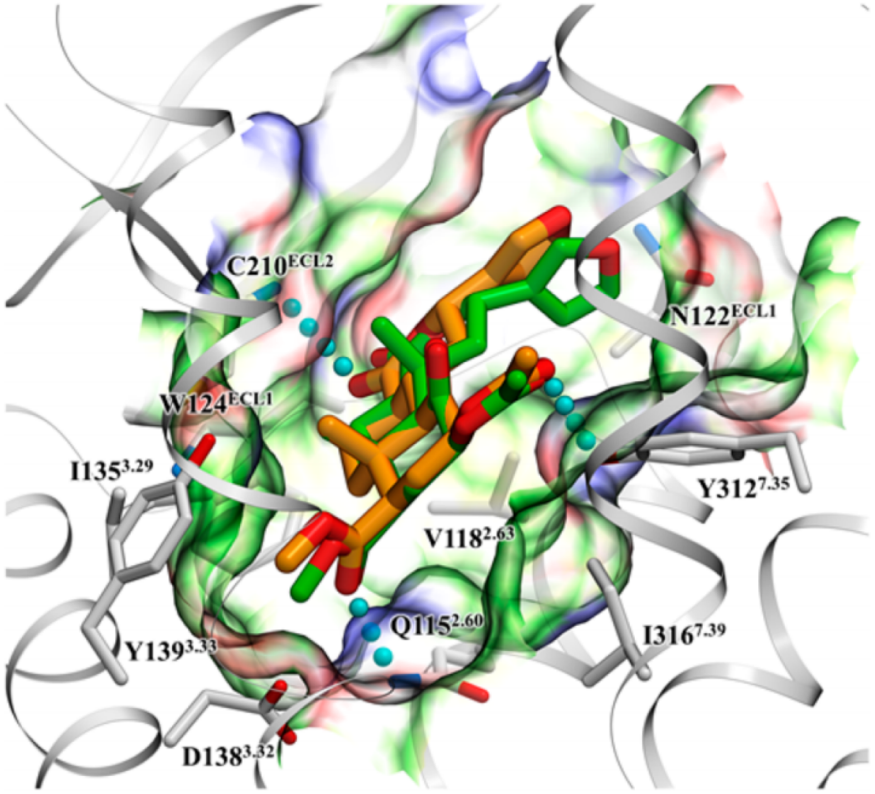
Docking mode of Sal A ligands

- Sal A & 20-nor-Sal A bind in similar poses with comparable binding scores

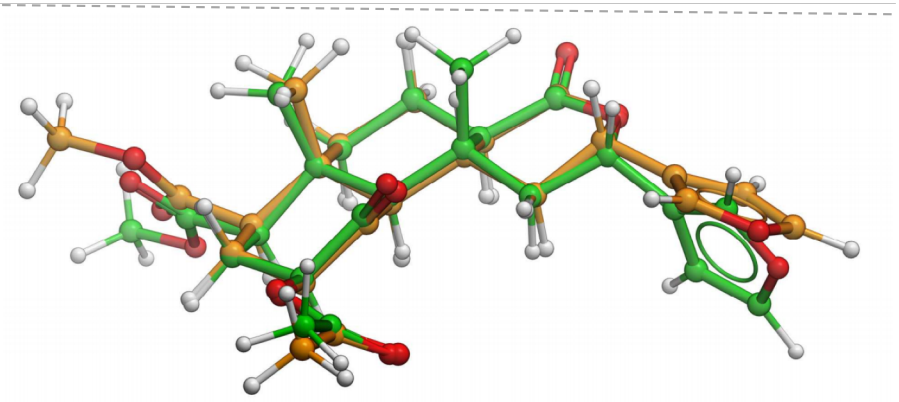
- This binding pose suggested comparable binding affinity for Sal A & 20-nor-Sal A

- 20-methyl group directed toward extracellular region with no interactions with receptor

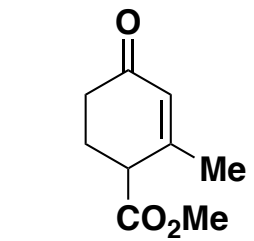
- Superimposition of structures show the geometry of the ring system maintained, however, removal of 20-methyl slightly displaces C-19 methyl and C-12 of lactone ring; resulting in subtle deviation in the position of the furan ring



20-nor-Sal A (orange)
Sal A (green)



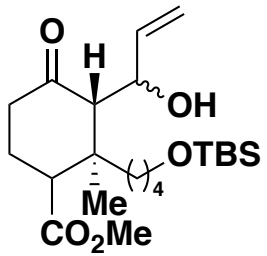
Forward synthesis



Hagemann's ester

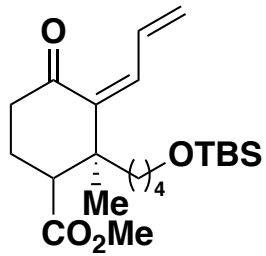
ClMg(C_4H_8)OTBS
CuBr•DMS, THF, HMPA
-70 ºC to 0 ºC

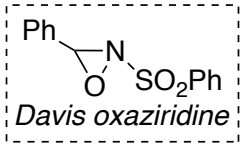
acrolein
$ZnCl_2$, -78 ºC
(61%, 6:1 dr)



MsCl, TEA,
DCM, 0 ºC

DBU, 22 0 ºC
57%, >20:1 Z:E



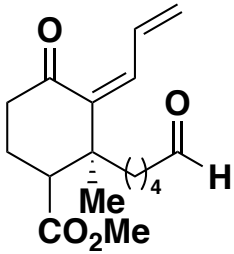


1. LDA, -78 ºC;
Davis oxaziridine
(80%, >10:1 dr)

2. Ac_2O, DMAP,
DBU, 22 to 80 ºC
(84%, 5:1 dr)

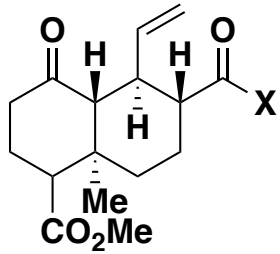
1. 2M HCl, THF 0 ºC

2. $(COCl)_2$, DMSO,
TEA, -78 to 22 ºC
79% overall 2 steps



pyrrolidine, AcOH,
THF/MeOH, 65 ºC;
K_2CO_3, 65 ºC

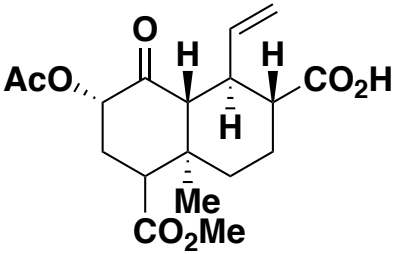
53% (>15:1 dr)



$NaClO_2$, t-BuOH,
NaH_2PO_4, C_5H_{10}

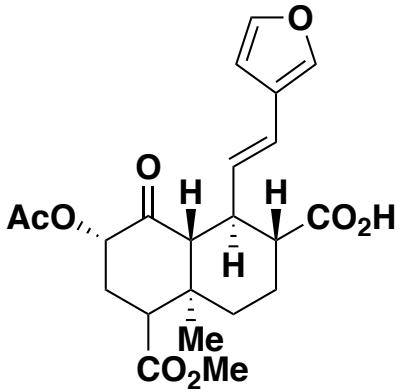
X = H

X = OH



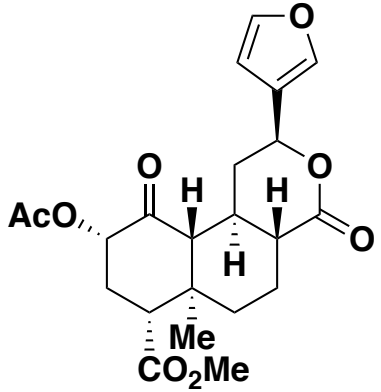
3-bromofuran
$Pd(OAc)_2$ (10 mol%)
XPhos (20 mol%)

K_2CO_3
DMF, 80 ºC
(81%)



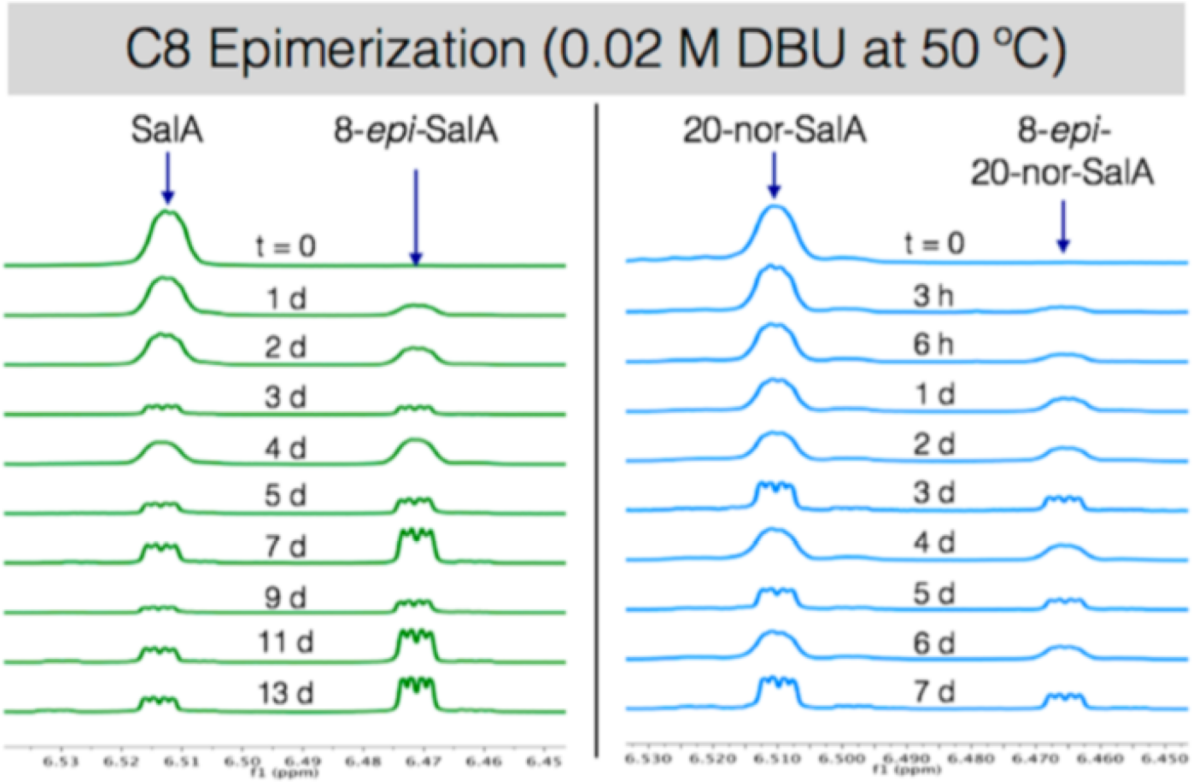
HFIP, 100 ºC 1 h
(77%, 1.5:1 dr)

or
HFIP, 50 ºC, 48 h,
63% conversion, 4:1 dr



C8 Epimerization studies

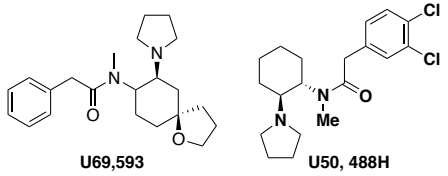
- 20-nor Sal A stabilizes the Sal A scaffold relative to its C8 epimer

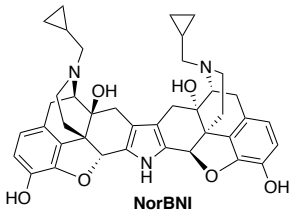


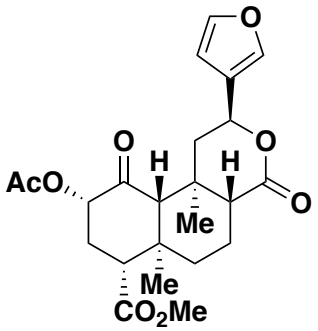
- *Follow-up paper (Bioorg. Med. Chem. 2018, in press): 06C-20-nor Sal A does not epimerize…even though ketone is more acidic than lactone*

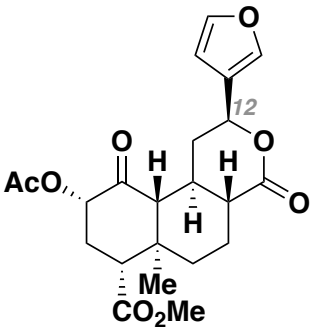
Biological activity

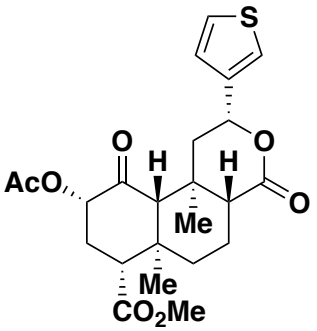
Compound	Binding Affinities (K_i, nM) KOR	MOR	DOR	K_i ratios MOR/KOR	DOR/KOR	Inhibition of cAMP EC_{50}, nM	% E_{MAX}
U69,593	1.07 ± 0.30	5176 ± 345	>10,000	4424	>153,177	5.7 ± 0.9	100
U50,488H	0.39 ± 0.24					7.5 ± 2.4	97 ± 1
NorBNI	0.04 ± 0.01					*(antagonist)*	
SalA	**0.16 ± 0.05**	616 ± 251	3417 ± 882	4741	26,285	**0.9 ± 0.3**	99 ± 1
20-nor-SalA	**1.08 ± 0.36**	7994 ± 2247	>10,000	7402	>10,933	**6.1 ± 1.7**	99 ± 2
12-*epi*-20-nor-**1**	**2.13 ± 1.20**	5113 ± 1547	3628 ± 913	2400	1703	**84 ± 13**	102 ± 1
13	**0.76 ± 0.25**	2841 ± 422	2367 ± 748	3738	3114	**23 ± 5.9**	100 ± 0
14	**0.53 ± 0.20**	4546 ± 516	>10,000	8577	>23,206	**16 ± 5.8**	95 ± 3
12-*epi*-**14**	**0.79 ± 0.22**	5683 ± 1543	5171 ± 633	7194	6546	**15 ± 3.5**	101 ± 1

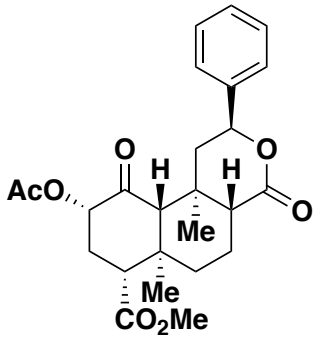






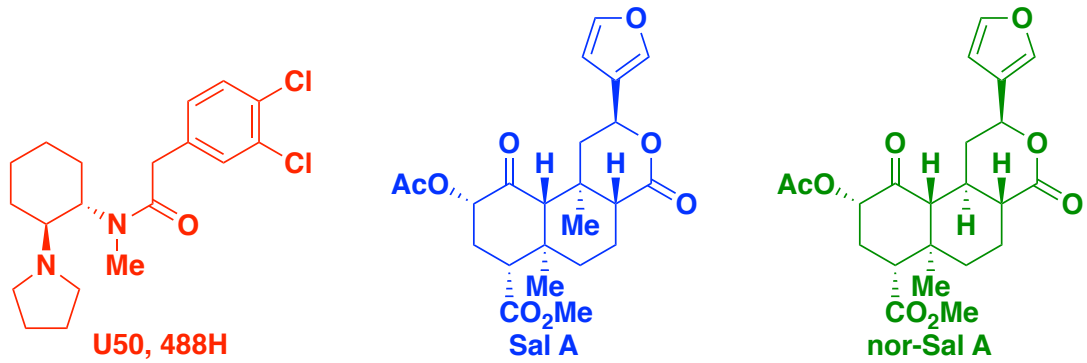


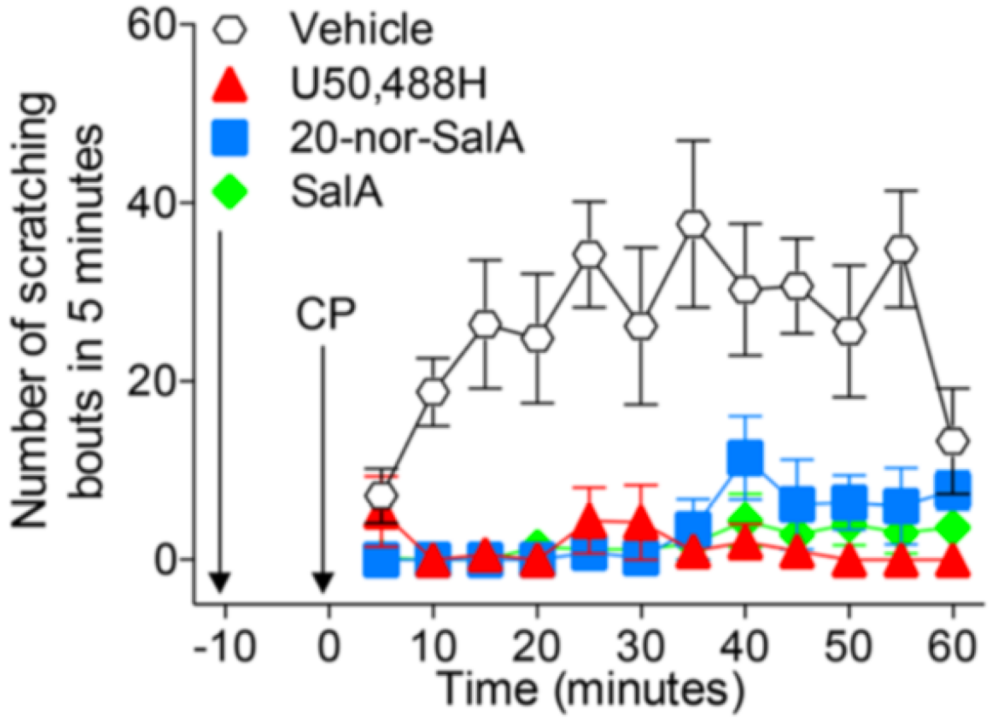




Biological activity

- Kappa agonists suppress chloroquine phosphate-induced pruritus in mice

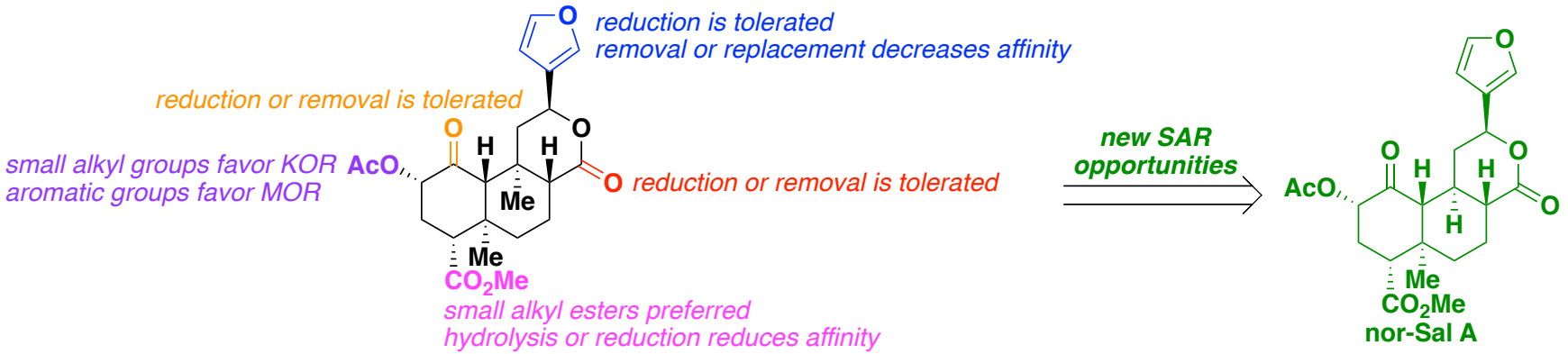




Summary

- Integration of *in silico* docking and retrosynthetic analysis can prompt scaffold redesign --- *dynamic retrosynthetic analysis* ---
  - ✓maintained scaffold complexity w/ synthesis simplification
  - ✓maintained target engagement w/ increased scaffold stability

- New opportunities to identify opioid receptor probes & drugs



SAR summary of sal A analogs (*Chem. Rev. 2008*)

Roach. J.J; Shenvi, R. A. *Bioorg. Med. Chem*. **2018**, 28, 1436.