

Merrilactone A

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Isolation from *Illicium merrillianum* and Structure Determination :
Y. Fukuyama et al., *Tetrahedron Lett.*, 41, 6111 (2000)

Biological Activities : neurotrophic activity, expected to show therapeutic potential for the treatment of neurodegradation associated with Alzheimer's and Parkinson's diseases

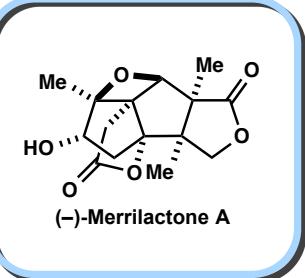
Racemic Total (Formal) Syntheses:

- S. J. Danishefsky et al., *J. Am. Chem. Soc.*, 124, 2080 (2002)
- M. Hirama et al., *J. Am. Chem. Soc.*, 125, 10772 (2003)
- G. Mehta et al., *Angew. Chem. Int. Ed.*, 45, 953 (2006)
- A. J. Frontier et al., *J. Am. Chem. Soc.*, 129, 498 (2007)
- A. J. Frontier et al., *J. Am. Chem. Soc.*, 130, 300 (2008); full paper
- M. F. Greaney et al., *Angew. Chem. Int. Ed.*, 49, 9250 (2010)
- H. Zhai et al., *Angew. Chem. Int. Ed.*, 51, 5897 (2012)
- M. F. Greaney et al., *Org. Lett.*, 14, 3720 (2012); formal

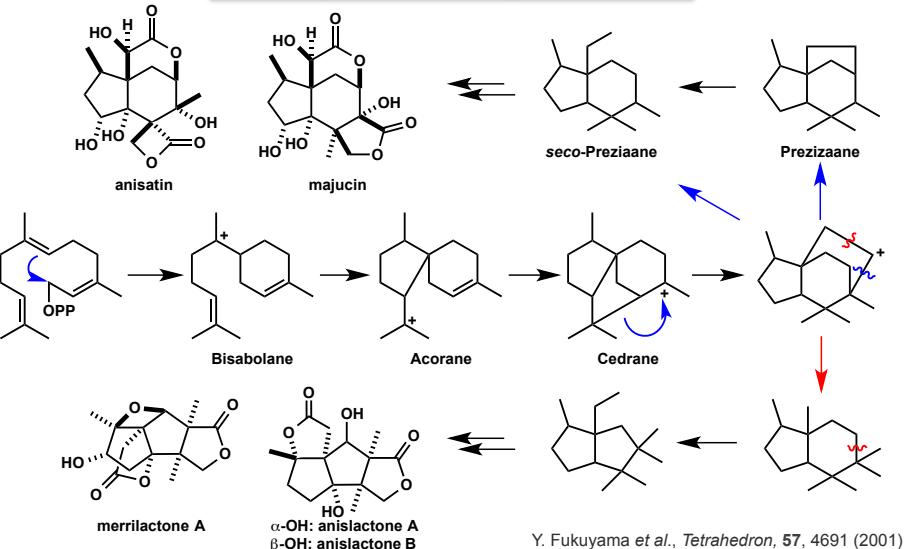
Asymmetric Total (Formal) Syntheses:

- S. J. Danishefsky et al., *Angew. Chem. Int. Ed.*, 44, 1511 (2005); formal
- M. Inoue et al., *Angew. Chem. Int. Ed.*, 45, 4843 (2006)
- M. Inoue et al., *J. Org. Chem.*, 72, 3065 (2007); ent-(+)

Review: M. Inoue et al., *有機合成化学協会誌*, 65, 419 (2007), *Tetrahedron*, 65, 6271 (2009)

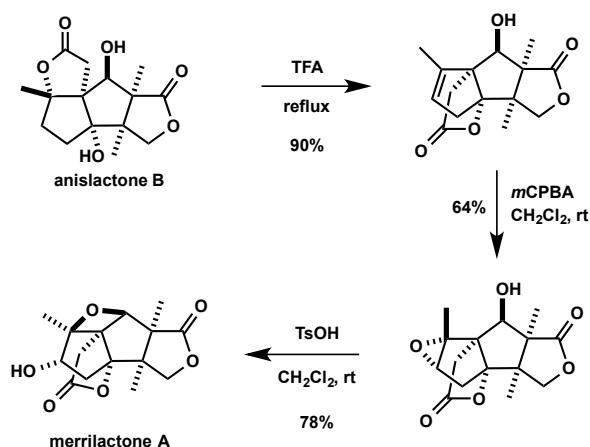


Proposed Biosynthesis



Y. Fukuyama et al., *Tetrahedron*, 57, 4691 (2001)

Fukuyama's Important Findings



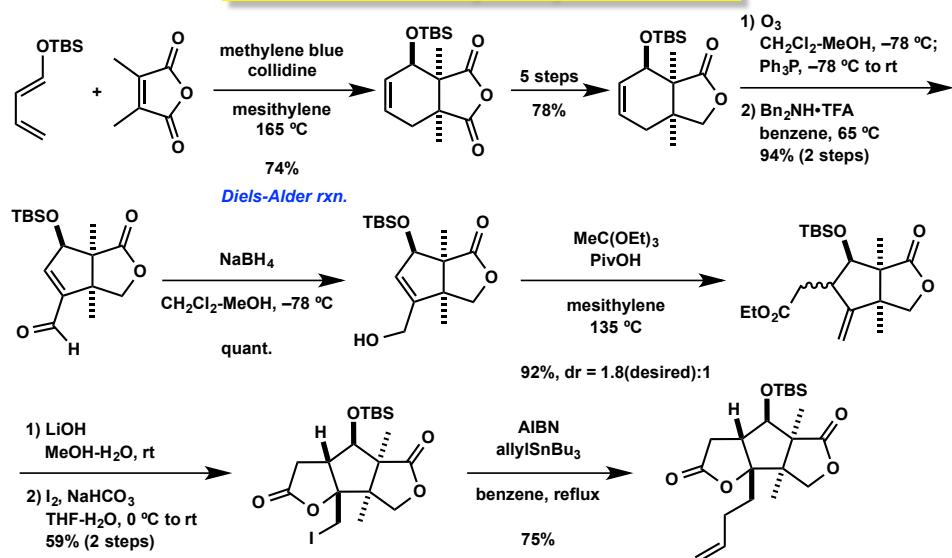
Y. Fukuyama et al., *Tetrahedron*, 57, 4691 (2001)

Synthetic Strategies

- radical cyclization
Danishefski (2002)
Hirama (2003)
Inoue (2006, 2007)
Frontier (2007)
Greaney (2010)
- alkylation of β -dicarbonyl compound
Mehta (2006)
- reductive coupling of dicarbonyl compound
Zhai (2012)
- domino 1,4-addition and aldol reaction
Greaney (2012)
- Today's Topic
Danishefsky's Syntheses: p5~p7 (racemic and asymmetric)
- Hiram and Inoue's Syntheses: p8~p11 (racemic and asymmetric)
- Other Total Syntheses: p12~p15 (racemic)
- Diels-Alder reaction
Danishefski (2002, 2005)
- [2+2]-photocycloaddition
Hirama (2003)
Inoue (2006, 2007)
Mehta (2006)
Greaney (2010)
Greaney (2012)
- Nazarov cyclization;
alkylation of β -dicarbonyl compound
Frontier (2007)
- Johnson-Claisen rearr.;
aldol reaction
Zhai (2012)

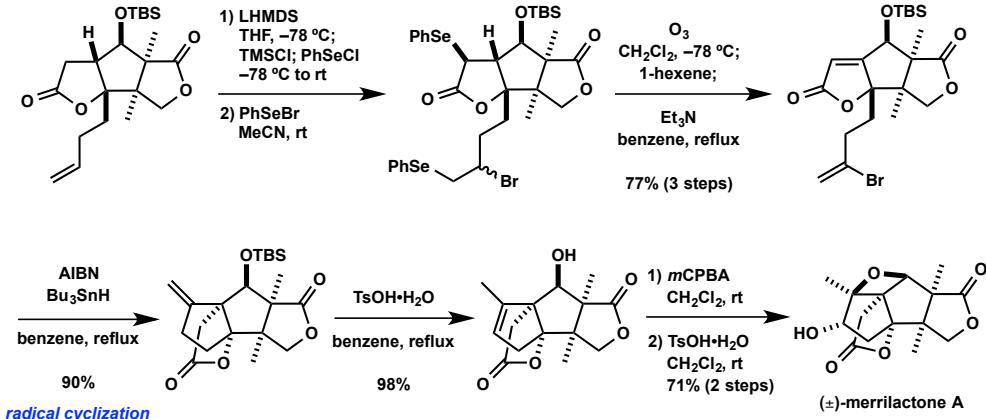
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Danishefsky's Synthesis



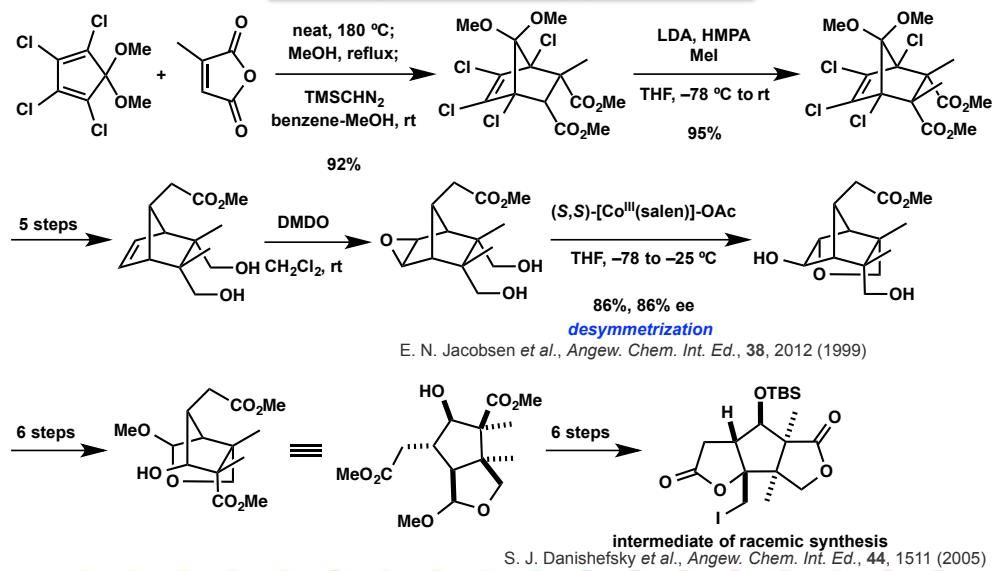
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First Total Synthesis

S. J. Danishefsky et al., *J. Am. Chem. Soc.*, 124, 2081 (2002)

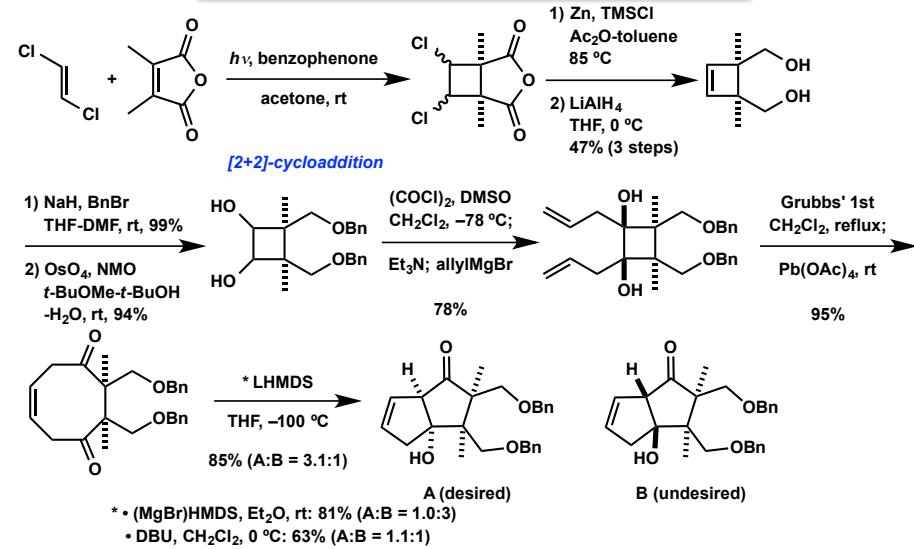
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Asymmetric Approach

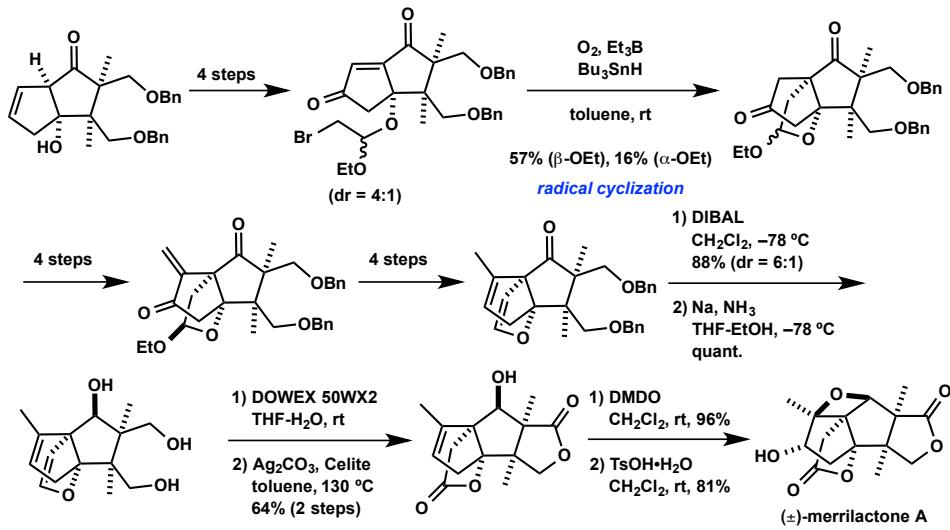


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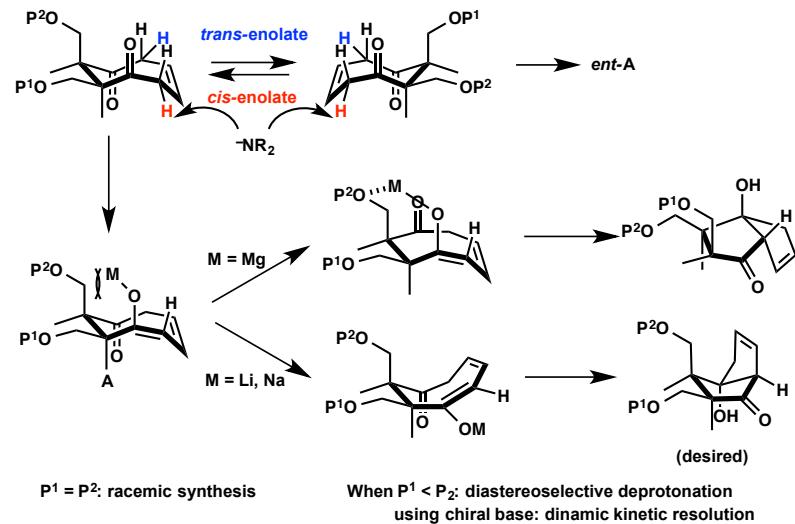
Hirama and Inoue's Synthesis



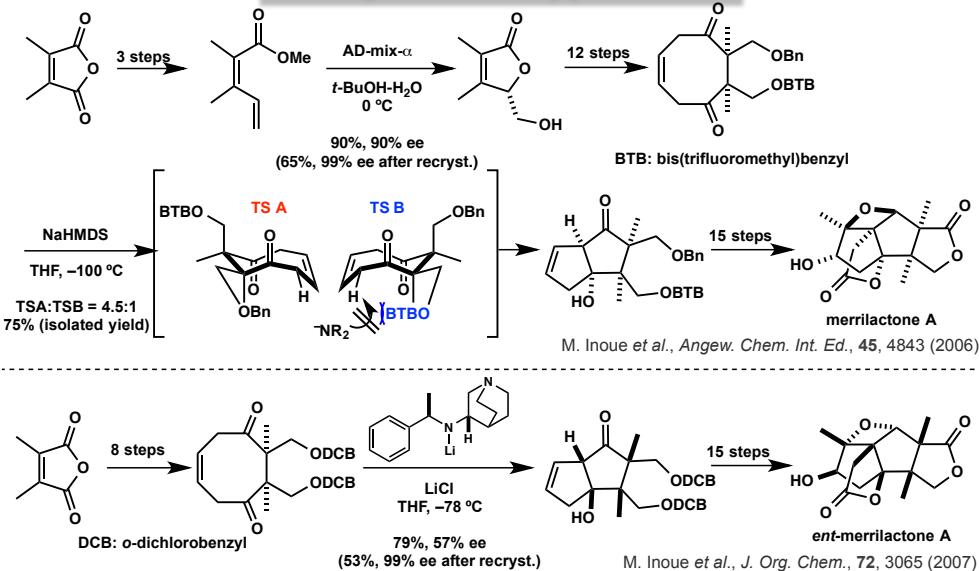
Hirama and Inoue's Synthesis



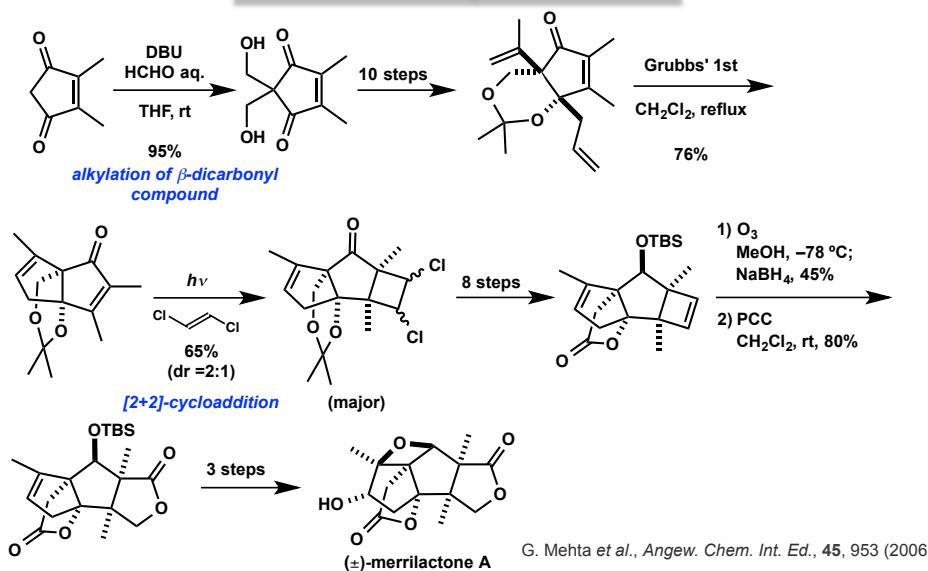
Diastereoselectivity in Transannular Aldol Reaction



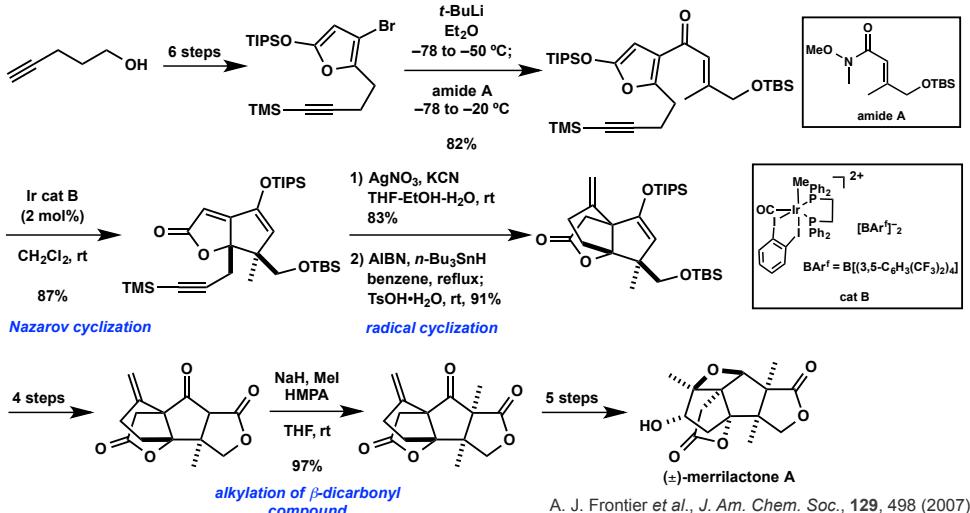
Asymmetric Approach



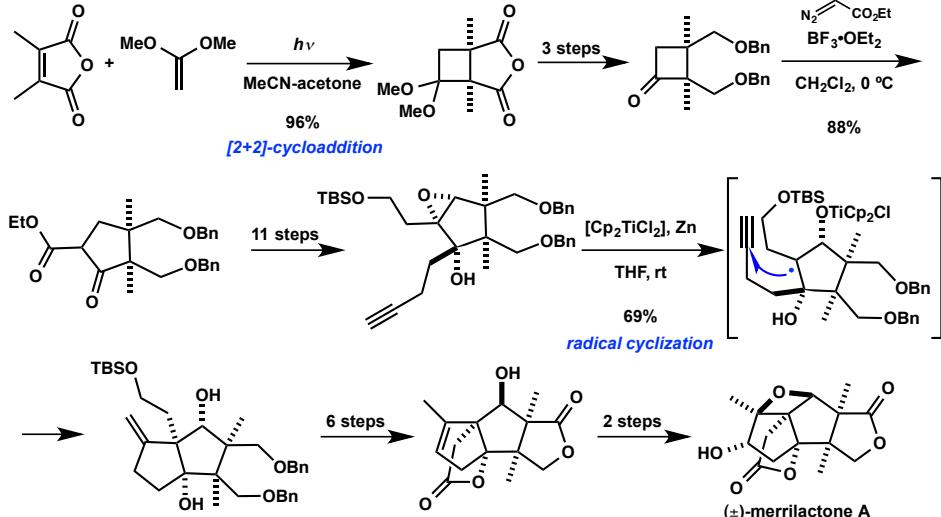
Mehta's Synthesis



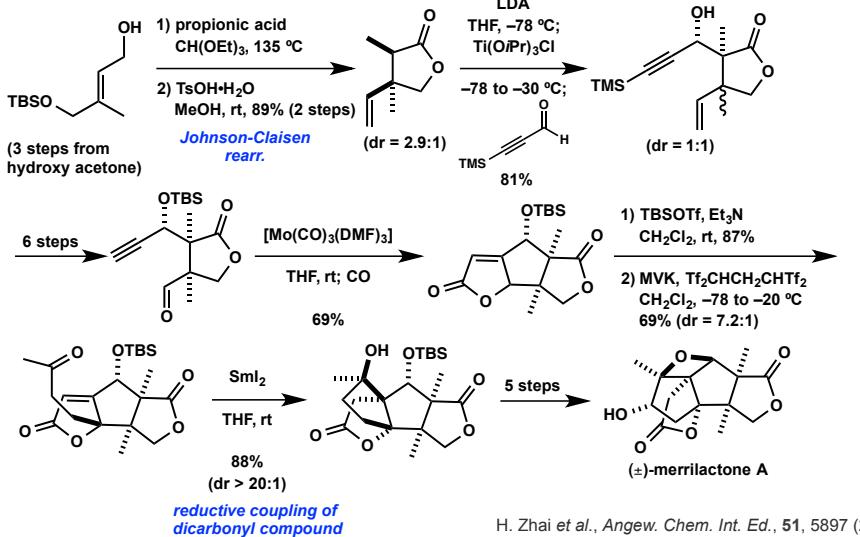
Frontier's Synthesis



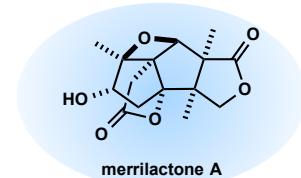
Greaney's Synthesis



Zhai's Synthesis



Summary



Group	Years	Steps	Asymmetric	Features
Danishefski	2002	20		first total synthesis
Hirama	2003	27		transannular Aldol rxn.
Danishefski	2005	29	O	desymmetrization with Jacobsen's cat.
Mehta	2006	31		double alkylation of β -dicarbonyl compound
Inoue	2006	31	O	desymmetrization with pseudo chiral compound
Frontier	2007	20		Nazarov cyclization
Inoue	2007	23	O	desymmetrization with chiral base
Greaney	2010	24		Ti^{III} -mediated radical cyclization
Zhai	2012	18		hetero PKR