Syntheses of Hapalosin A, a MDR reversing Marcocycle

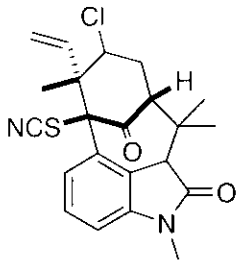
Palomo et al, *J. Org. Chem.* **2004** ASAP

Robert J. Halter

June 5th, 2004

Isolation and Biological Activity

- Isolated in 1994 by researchers at the University of Hawaii and Fox Chase Cancer Center, Philadelphia
- Extracted from an Australian soil fungus, *Hapalosiphon welwitschii*
- The researchers were screening for MDR-reversing agents, this strain produces two such molecules.
- Exists as a mixture (3:1) of *s-cis* and *s-trans* isomers



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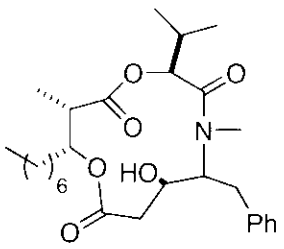


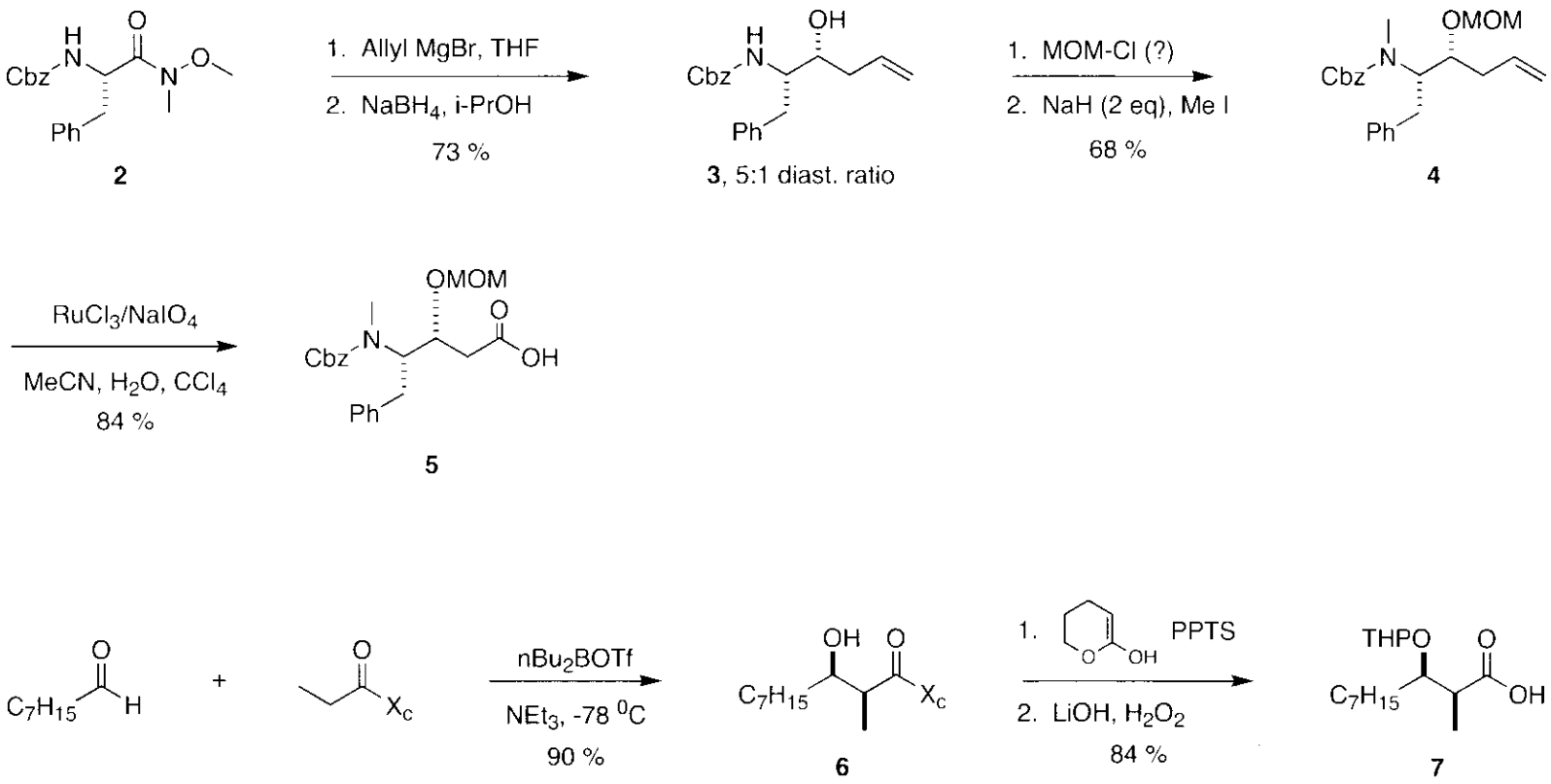
Hapalosin

Stratmann, K., Burgoyne, D. L., Moore, R. E., Patterson, G. M. L. *J. Org. Chem.*, **1994**, *59*, 7219

Multi-Drug Resistance in Cancer Cells

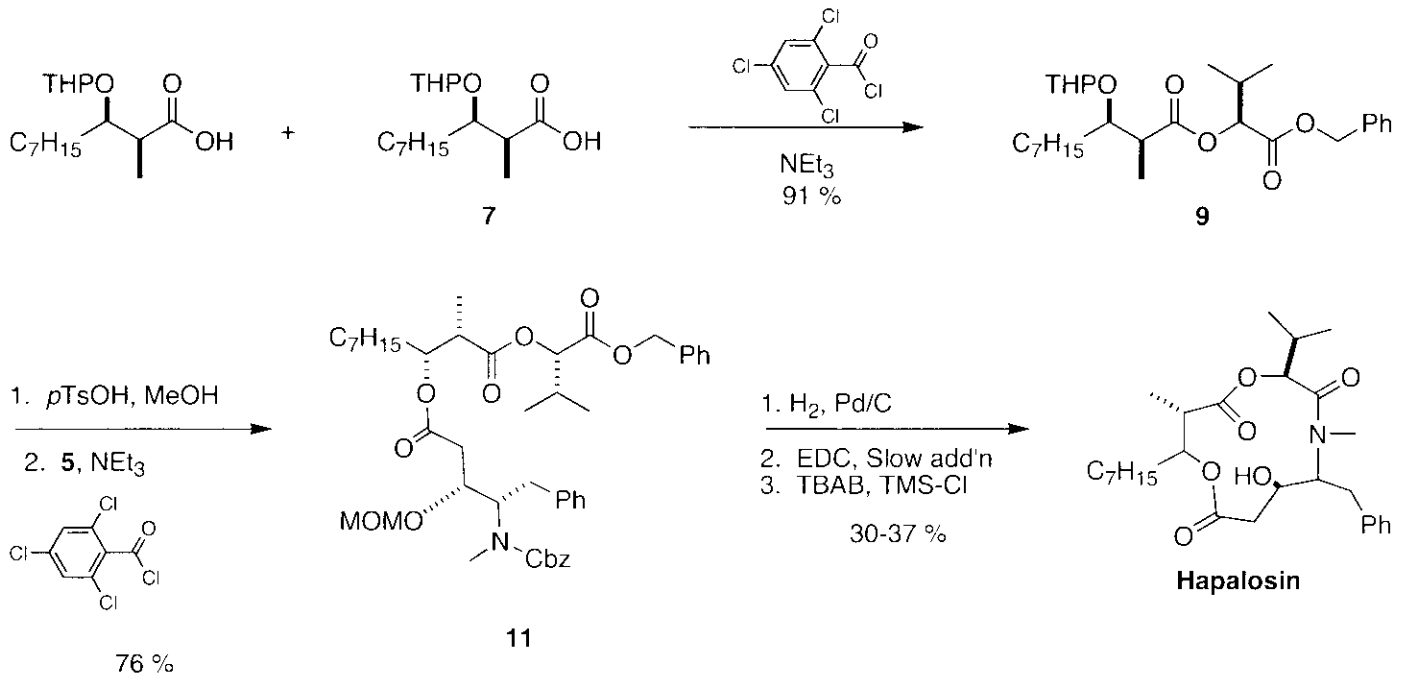
- Over-expression of P-Glycoprotein -- Drugs efficiently removed from the cell
- Two ways to treat
  - New drugs, not transported by P-glycoprotein
  - Use a second drug, that can shut/slow down the P-glycoprotein transport mechanism
- Hapalosin has a fundamentally different structure from other known MDR reversing molecules

First Total Synthesis



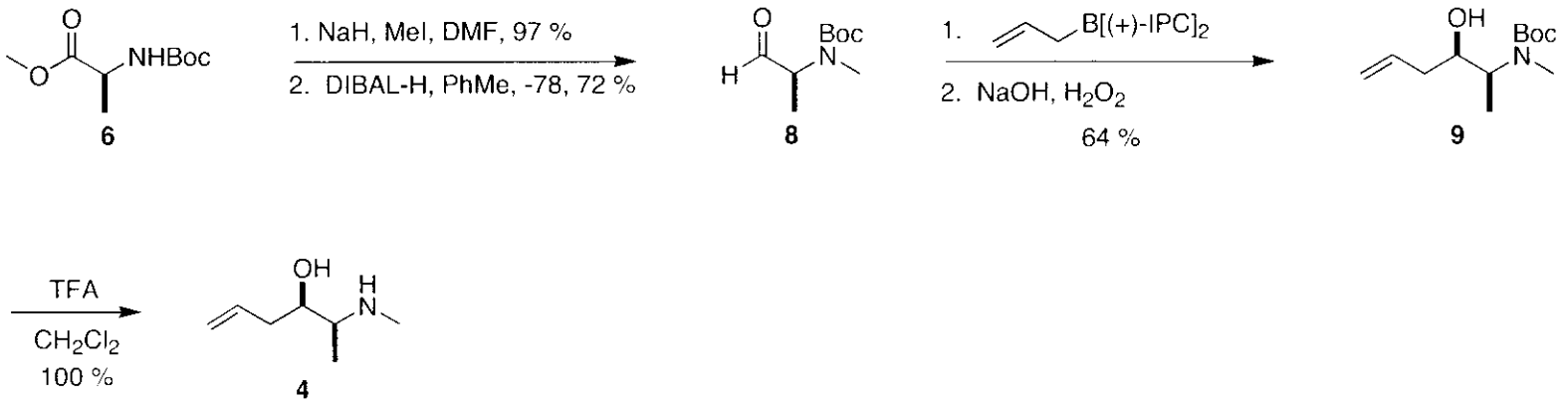
Ghosh, A. K., Wenming, L, Yibo, X., Chen, Z. *Angew. Chem. Int. Ed. Engl.*, **1996**, *33*, 74

First Total Synthesis



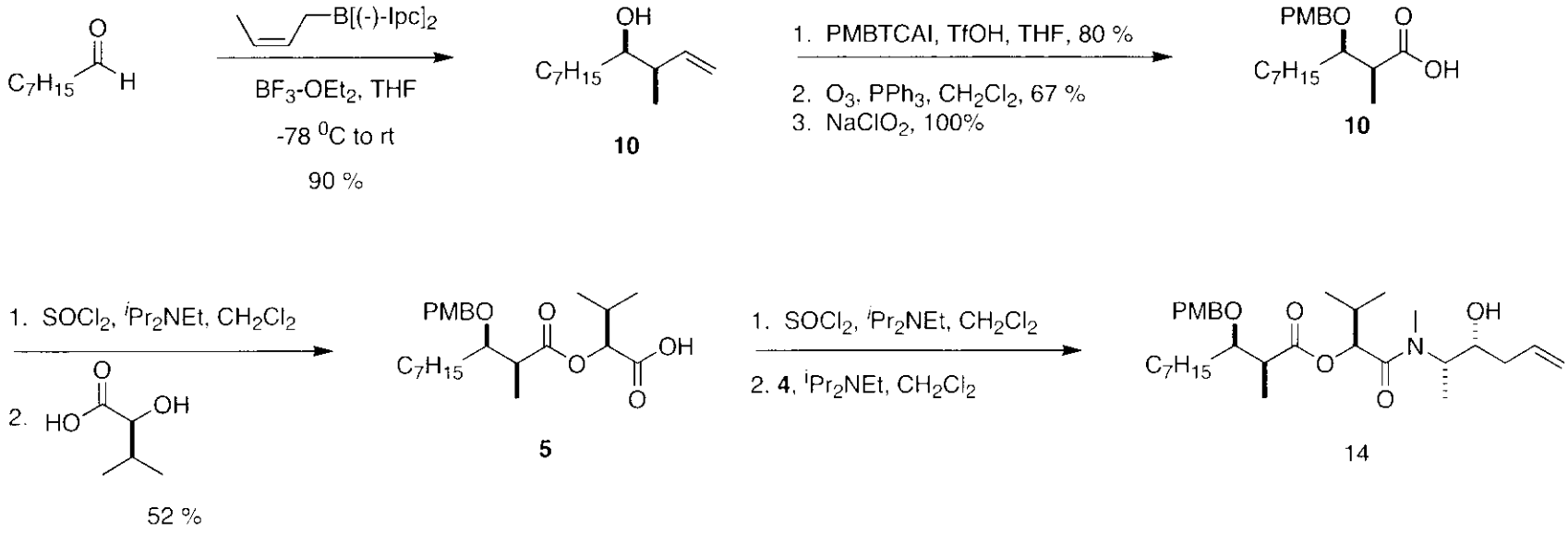
Ghosh, A. K., Wenming, L, Yibo, X., Chen, Z. *Angew. Chem. Int. Ed. Engl.*, **1996**, *33*, 74

Armstrong Synthesis



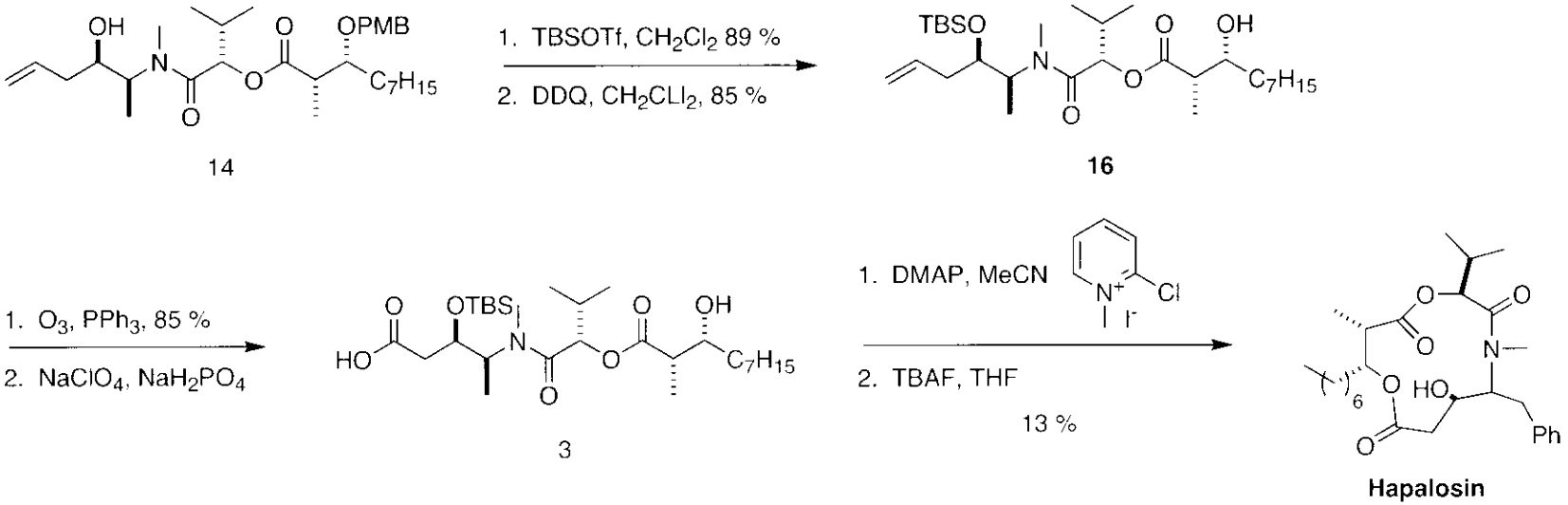
Dinh, T. Q, Du, X., Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6606

Armstrong Synthesis



Dinh, T. Q, Du, X., Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6606

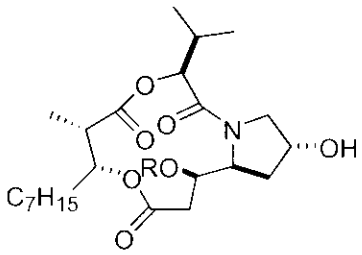
Armstrong Synthesis



- Performed conformational analysis on the product
- Major isomer shown by NOESY to by the *s-cis* amide, supported my molecular modeling calculation
- Also made NH compound, shown to be *s-trans* as only isomer

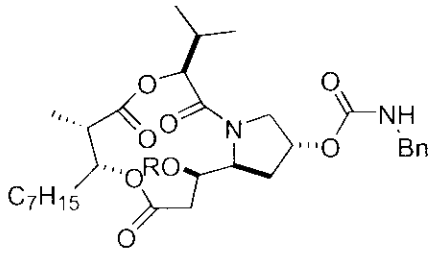
Dinh, T. Q, Du, X., Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6606

Conformational Analysis of Analogs



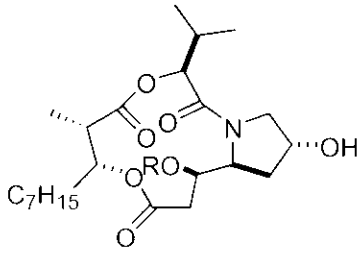
3 R = PMB

1.1:1



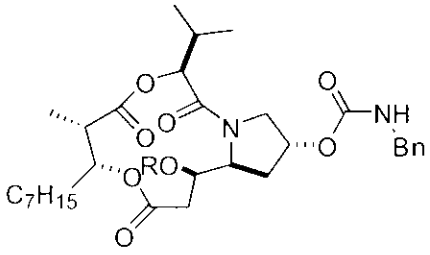
4 R = PMB

1.5:1



5 R = H

6:1



6 R = H

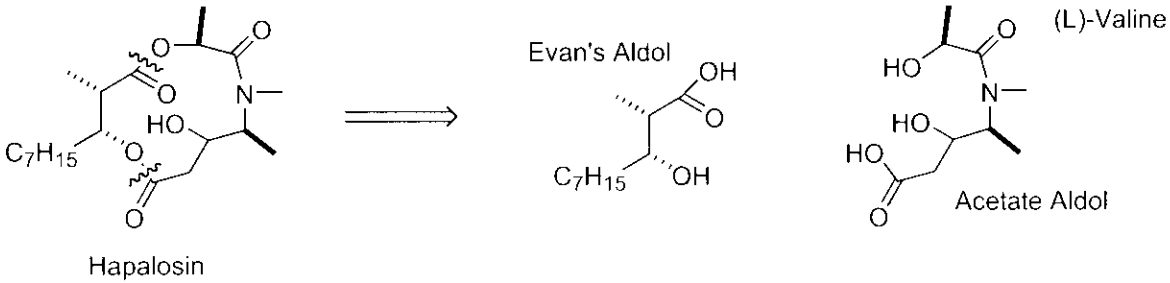
6:1

- No dependence upon lowest energy conformer seen for MDR activity

- Compound 5 is substantially less active. 5 and 6 exhibited simialr conformations via NOE and molecular modeling. Authors suggest an aromatic ring may be important.

Dinh, T. Q, Du, X., Smith, C. D., Armstrong, R. W. *J. Org. Chem.*, **1997**, *62*, 6773.

Palomo Synthesis



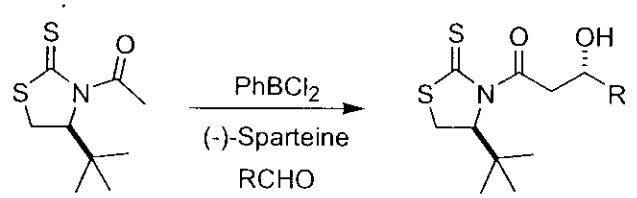
- Multiple syntheses have been done
- Problems identified are the C_6-C_9 section and cyclization
- They propose to have solutions to both problems

Palomo, C., Oiarbide, M, Garcia, J. M., Gonzalez, Al.,, Pazos, R., Odriozola, J. M., Banuelos, P., Tello, M., Linden, A. *J. Org. Chem.* **2004** ASAP

Acetate Aldol

- Much more difficult than propionate aldol
  - Replacement of R group with H decreases diastereotopic selectivity.
- A variety of methods exist for such reactions, many give quite good ee's/dr's.

Asymmetric Acetate Aldol Reactions from Colorado



entry	aldehyde	dr (**5**:**6**)[b]	yield
1	$PhCH_2CH_2CHO$	82:1	84
2	$(CH_3)_2CHCHO$	43:1	90
3	$CH_3(CH_2)_3CHO$	47:1	84
4	$(CH_3)_2CHCH_2CHO$	>100:1	92
5	$BnOCH_2CHO$	24:1	81
6	$TBSOCH_2CH_2CHO$	45:1	85
7	PhCHO	23:1	78
8	*E*-PhCH=CHCHO	9.5:1	65

[a] For a representative procedure, see Supporting Information. [b] Ratios were determined by 500 MHz ^{1}H NMR spectroscopic analysis of the crude reaction mixtures. [c] Yield of the major diastereoisomer after purification.

Zhang, Y., Phillips, A. J., Sammakia, T. *Org. Lett.* **2004**, 23.

Nelson Group Chemistry

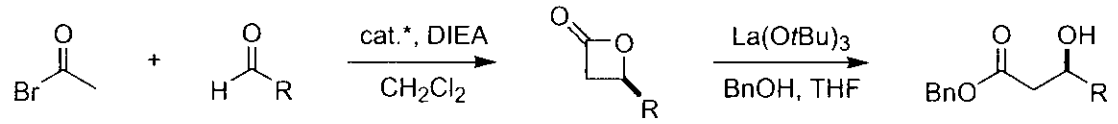


Table 1. Asymmetric Acetyl Bromide–Aldehyde Cyclocondensations[a]

entry	Aldehyde 2 (R)	catalyst [time (h), temp (°C)]	% yield[b]	% ee 3[d] (configuration)
a	$BnOCH_2$—	**5b** (8, -40)	91	92 (*R*)
b	$PhCH_2CH_2$—	**5a** (16, -50)	93	92 (*S*)
	$PhCH_2CH_2$—	**5a** (72, -78)	89	95 (*S*)
c	$CH_2CH(CH_2)_8$—	**5b** (16, -50)	91	91 (*S*)
d	Me_2CHCH_2—	**5a** (24, -50)	80[c]	93 (*S*)
e	$BnOCH_2CH_2$—	**5b** (16, -40)	90	91 (*S*)
f	$TBDPSOCH_2$—	**5b** (16, -40)	74	89 (*R*)
g	$BnOCH_2$—≡—	**5a** (16, -50)	86	93 (*R*)
h	Me_3C—≡—	**5a** (16, -50)	91	85 (*R*)
i	C_6H_{11}—	**5b** (24, -40)	56	54 (*R*)

Nelson, S. G., Peelen, T. J., Wan, Z. *J. Am. Chem. Soc.* **1999** *121*, 9742

Acetate Aldol from Spain

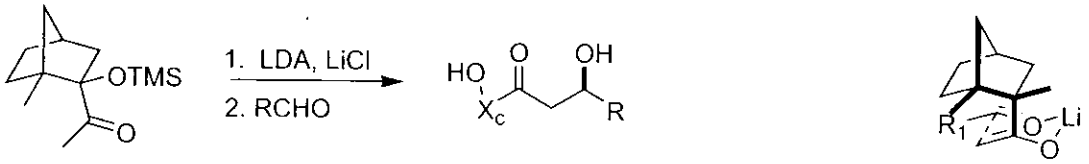


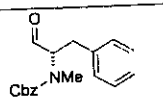
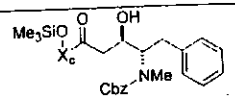
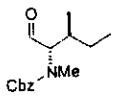
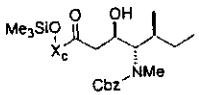
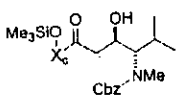
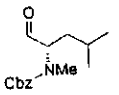
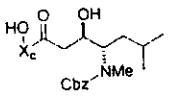
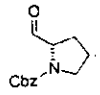
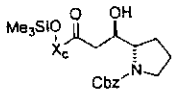
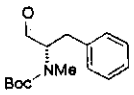
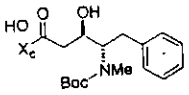
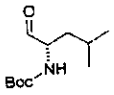
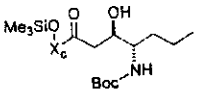
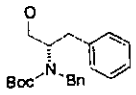
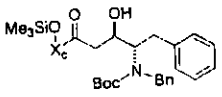
Table 2. Aldol Reaction of the Lithium Enolate of 3 with Representative Aldehydes in the Presence of LiCl[a]

entry	aldehyde	selectivity ratio[b] 5:6	yield 5 (%)[c]
1	C_6H_5CHO	88:12	67
2	4-$CH_3C_6H_4CHO$	93:7	76
3	C_6H_5-CH=CH-CHO	89:11	71
4	CH_3CHO	96:4	70[d]
5	CH_3CH_2CHO	93:7	65
6	$CH_3(CH_2)_3CHO$	94:6	61
7	$CH_3(CH_2)_4CHO$	94:6	60[d]
8	$CH_3(CH_2)_5CHO$	91:9	65
9	$C_6H_5CH_2CH_2CHO$	88:12	75
10	*i*-C_3H_7CHO	95:5	67
11	$(CH_3)_2CHCH_2CHO$	93:7	75
12	$(CH_3)_3CCHO$	>98:2	70

Palomo, C., Oiarbide, M., Azipurua, J. M., Gonzalez, A., Garcia, J. M., Landa, C., Odriozola, I., Linden, A. *J. Org. Chem.* **1999**, *64*, 8193

Acetate Aldol with Amino Aldehydes

TABLE 1. Scope for the Diastereoselective Acetate Aldol Addition with α-Amino Aldehydes

Compound	Aldehyde 4	Product[a] 5	Yield [%][b]
a			78
b			75[c]
c			70
d			55[d]
e			65
f			70[d]
g			62
h			60

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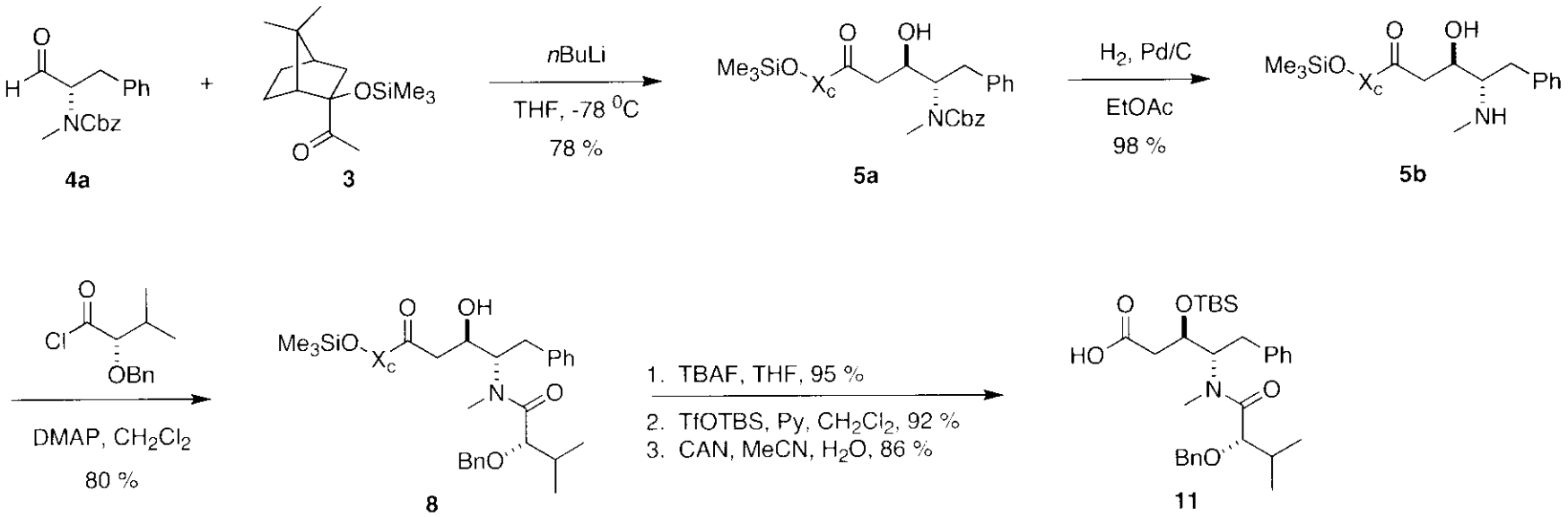
Camphor Auxilary Use in Hapalosin Synthesis

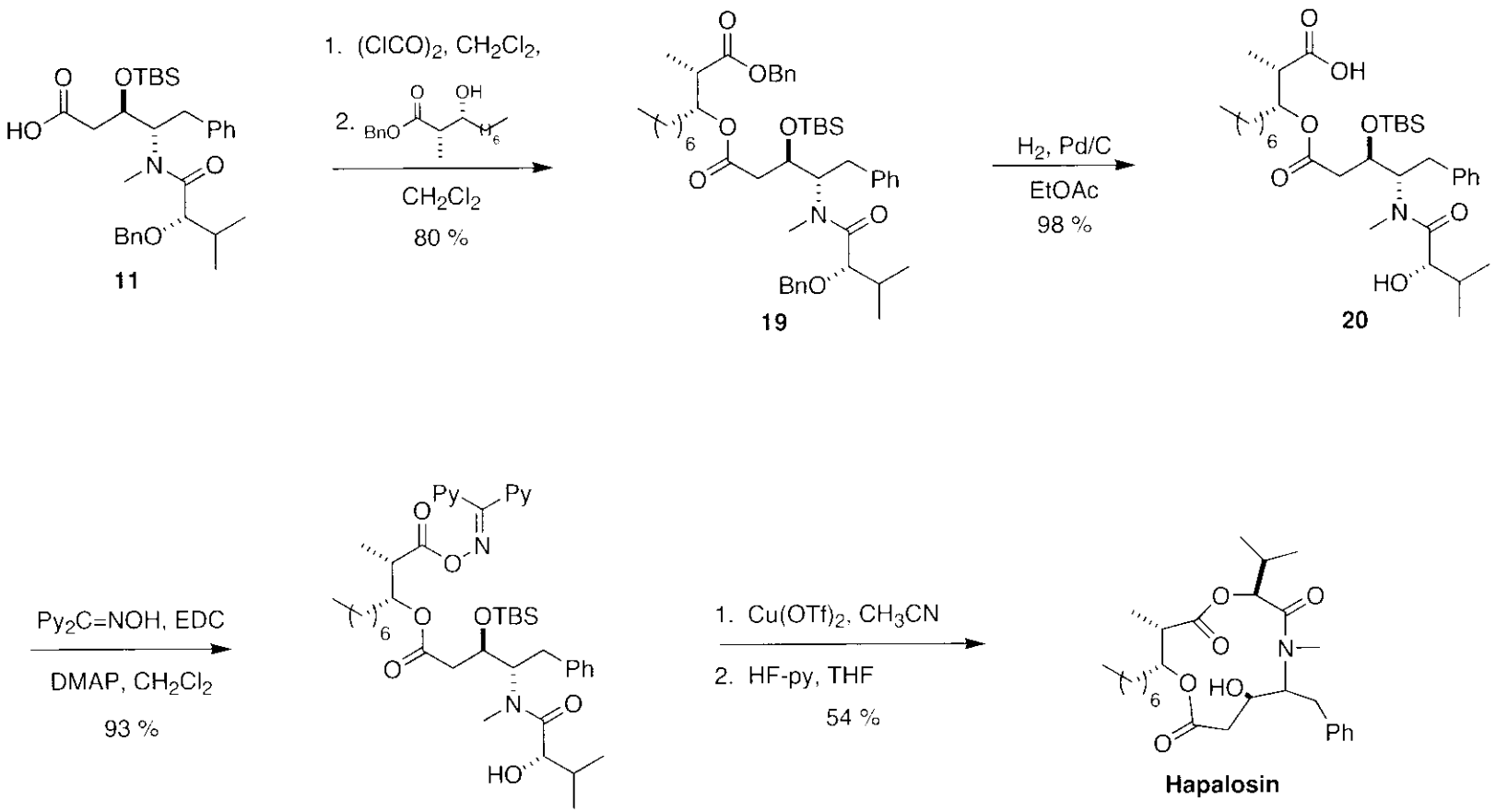


The same fragment has been synthesized in 9 steps (protected) and also in 6 steps.

Reaction appears fast and general

Palomo, C., Oiarbide, M, Garcia, J. M., Gonzalez, Al.,, Pazos, R., Odriozola, J. M., Banuelos, P., Tello, M., Linden, A. *J. Org. Chem.* **2004** ASAP

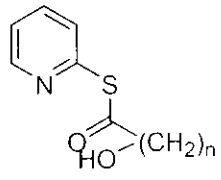
Cyclization

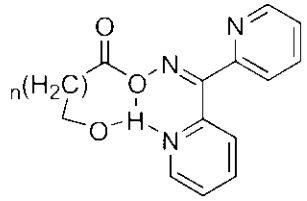


Palomo, C., Oiarbide, M, Garcia, J. M., Gonzalez, Al.,, Pazos, R., Odriozola, J. M., Banuelos, P., Tello, M., Linden, A. *J. Org. Chem.* **2004** ASAP

"Double Activation" Lactonization

- Proposed by Corey in 1974
- Provides impetus for proton transfer to occur
- Good for difficult systems, 12 membered rings are hard to close.





Corey, E. J., Nicolaou, K. C. *J. Am. Chem. Soc.*, **1974**, *96*, 5614.