

Antineoplastic agents.

Total synthesis of Dolastatin 16

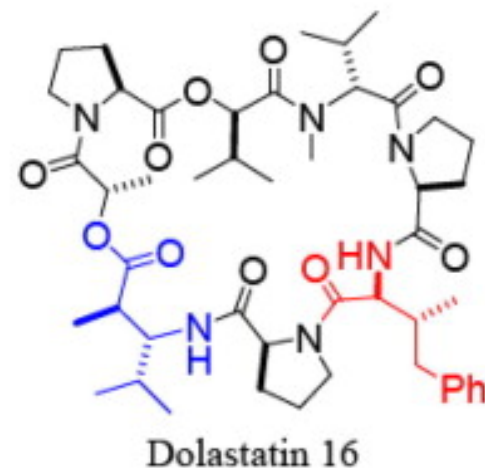
Literature presentation 12.03.2015

Ievgeniia Kovalova

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Introduction

Education:

Ph.D., Wayne State University, 1956



George Robert Pettit

Research Interests:

- chemistry of natural products (peptides, nucleotides, and steroids)
- cancer chemotherapy (anticancer agents from arthropods, marine animals and plants)
- total synthesis of natural products.

Robert Pettit's group is organized to provide the specialized training necessary to undertake problems concerned with the discovery of anticancer substances for the treatment of cancer. Among various activities, they are pursuing a unique program concerned with isolation, structural identification and synthesis of naturally occurring anticancer agents from marine animals, plants, and arthropods.

Nature Sources of Dolastatin 16

Sea hare *Dolabella auricularia*¹
and Madagascan cyanobacterium *Lyngbya majuscula*²



Dolastatin 16 from sea hare *Dolabella auricularia* is an inhibitor of cancer cell growth. ($GI_{50} = 10^{-3} - 10^{-4} \mu\text{g/ml}$)

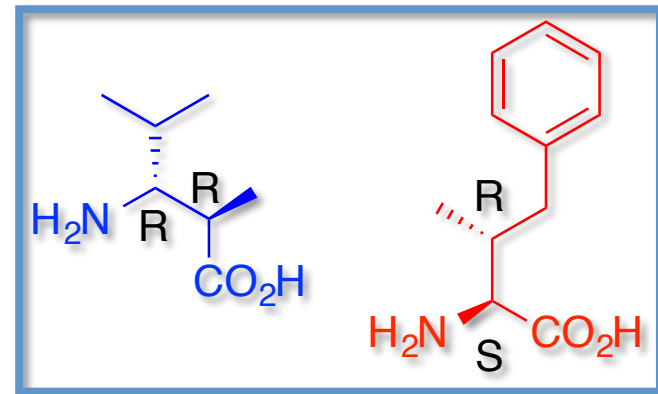
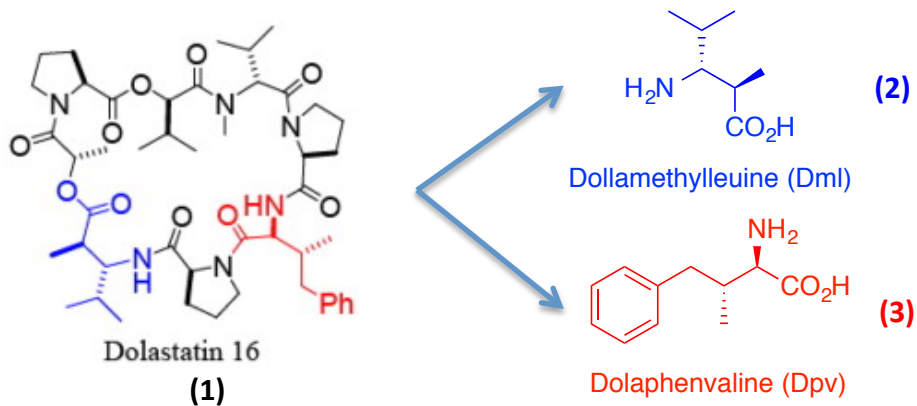
Dolastatin 16 also has antifouling activity ($EC_{50} = 0.003 \mu\text{g/ml}$) against the larvae of the barnacle *Balanus amphitrite*, as well as low toxicity ($LC_{50} = 20 \mu\text{g/ml}$)



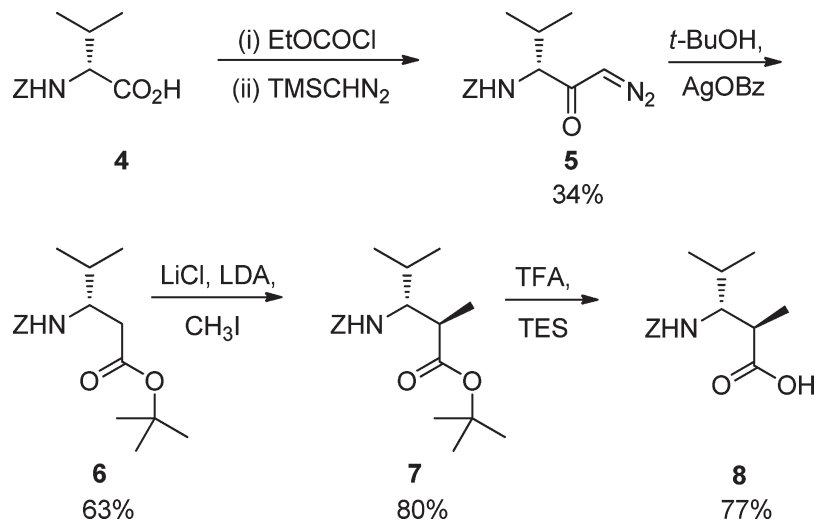
Dolastatin 16 was originally isolated (in $3.1 \times 10^{-7}\%$ yield) as an amorphous powder. Very slow (over three years) crystal formation from acetonitrile and water provided X-ray quality crystals.



1. Pettit, G. R.; Xu, J.-P.; Hogan, F.; Williams, M. D.; Doubeck, D. L.; Schmidt, J. M.; Cerny, R. L.; Boyd, M. R. J. Nat. Prod. 1997, 60, 752–754.
2. Nogle, L.M.; Gerwick, W.H. J. Nat. Prod. 2002, 65, 21-24



Synthesis of the Dolamethylleuine (Dml) as its Z-protected synthon³



Overall yield of **8** = 13%

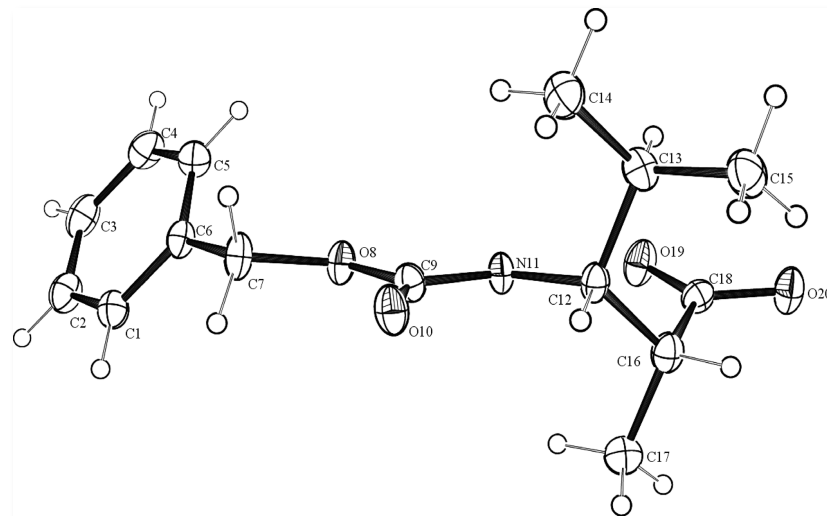
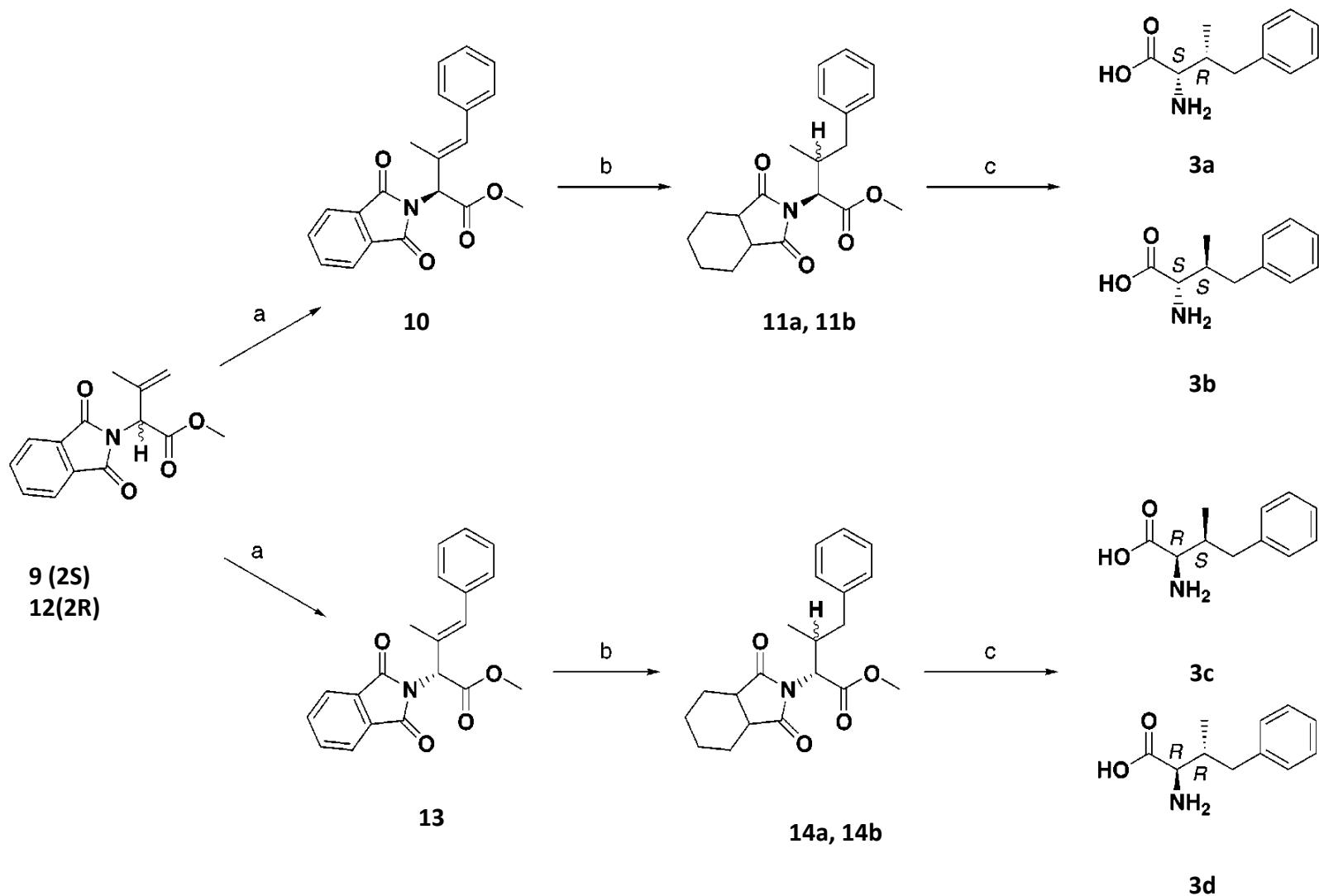


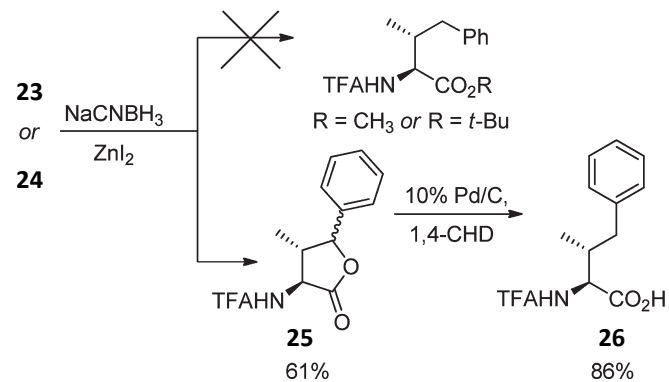
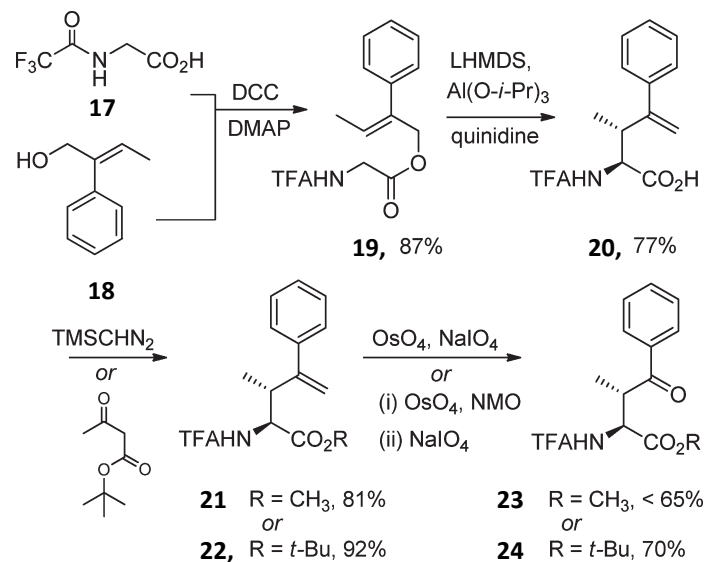
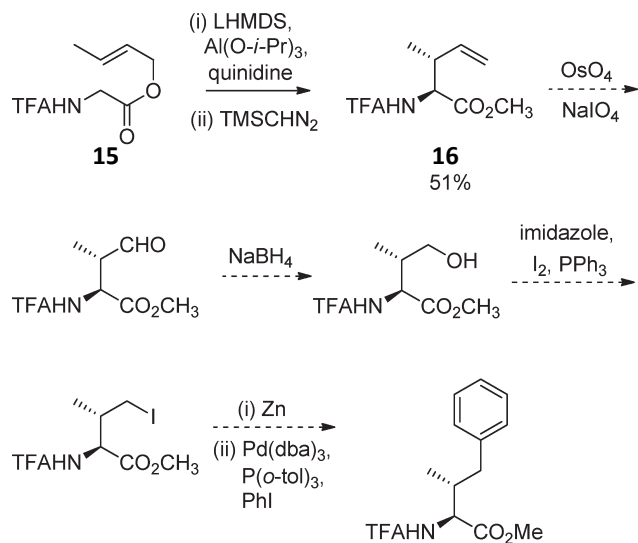
Figure 1. X-ray structure of *N*-Z-dolamethylleuine (**8**). Atoms are displayed as 30% probability thermal ellipsoids.

Synthesis of the Dolaphenvaline (Dpv)⁴

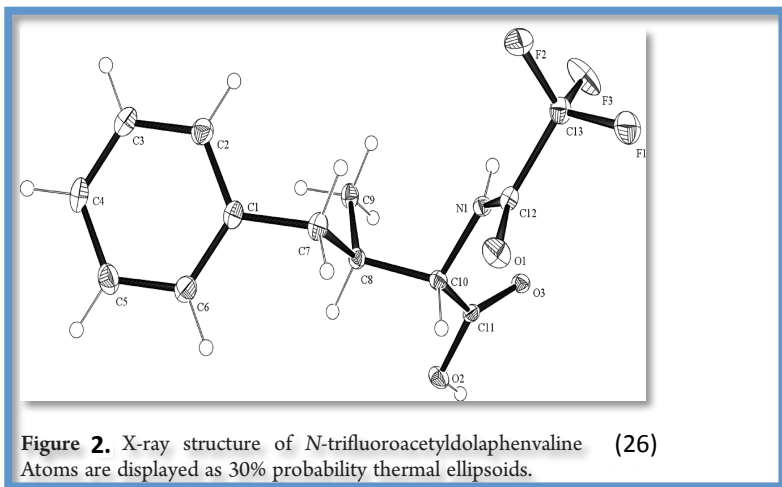


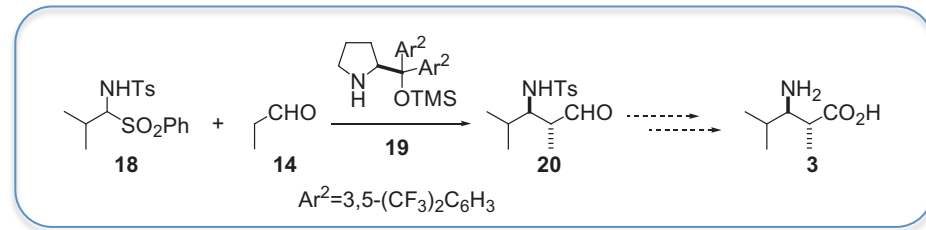
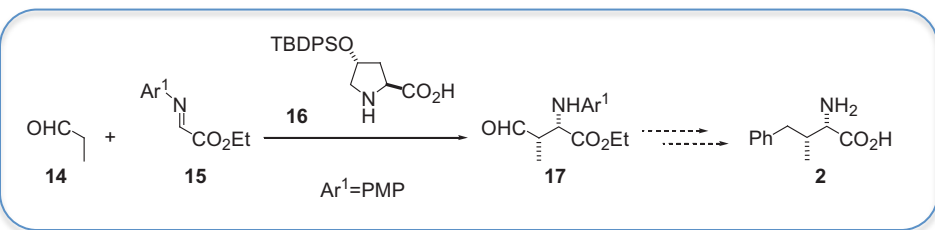
^a (a) Idobenzene, AgNO₃, Pd(OAc)₂, MeCN; (b) H₂, PtO₂, EtOH; (c) 6 M HCl–AcOH (2:1), 120 °C.

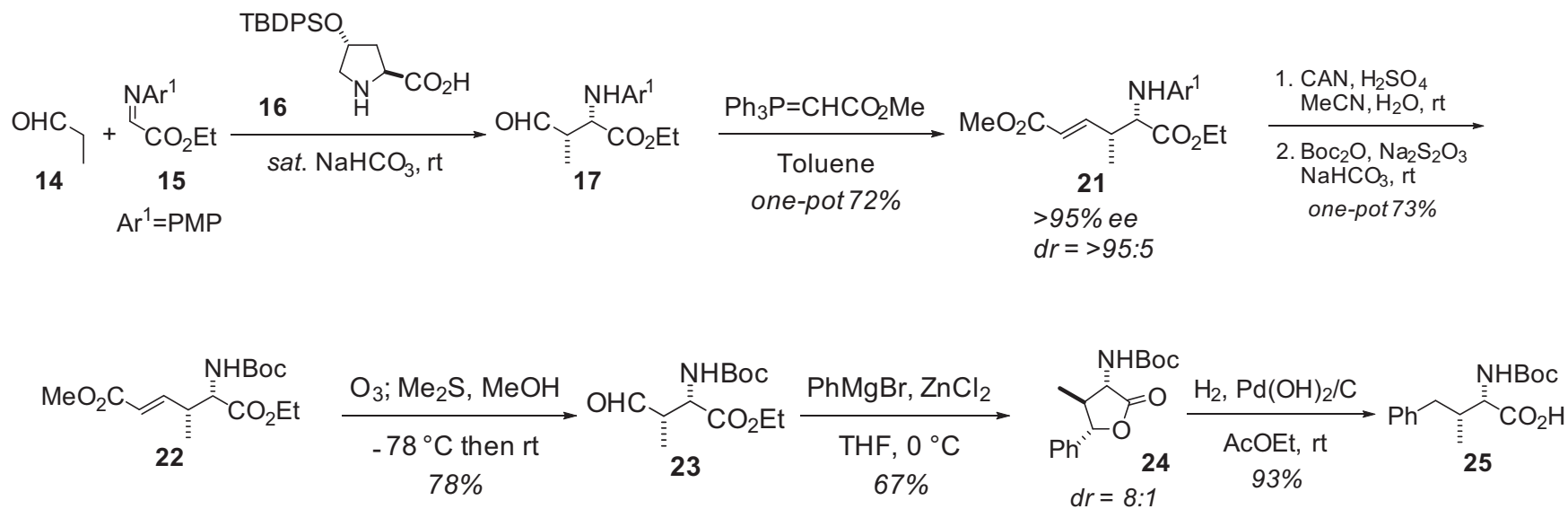
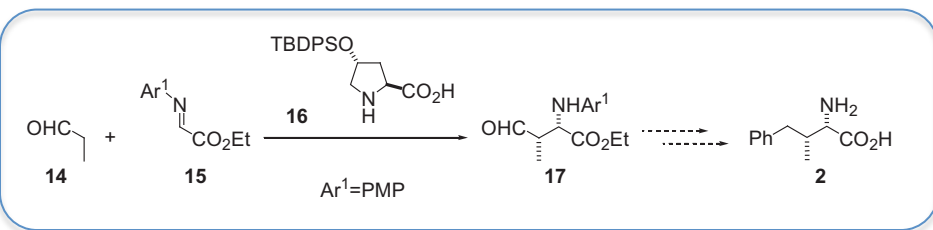
Synthesis of the Dolaphenvaline (Dpv)³

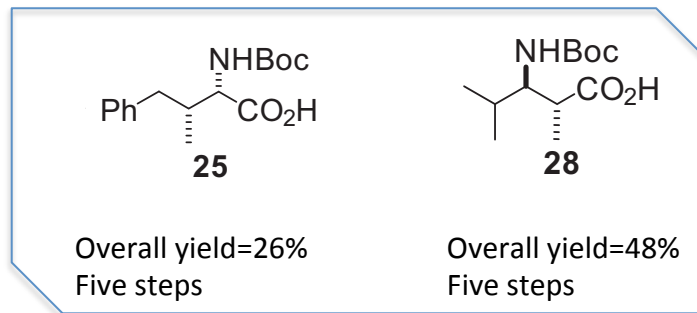
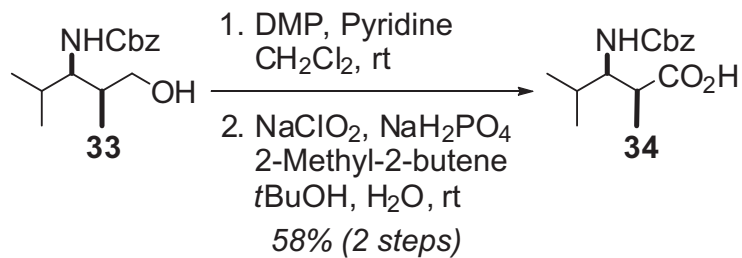
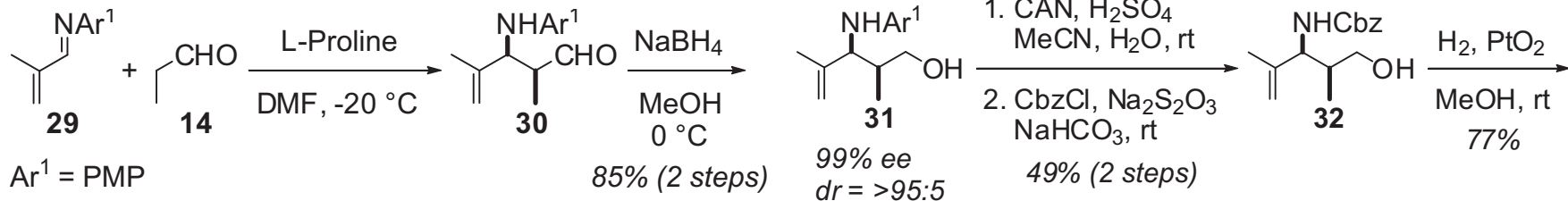
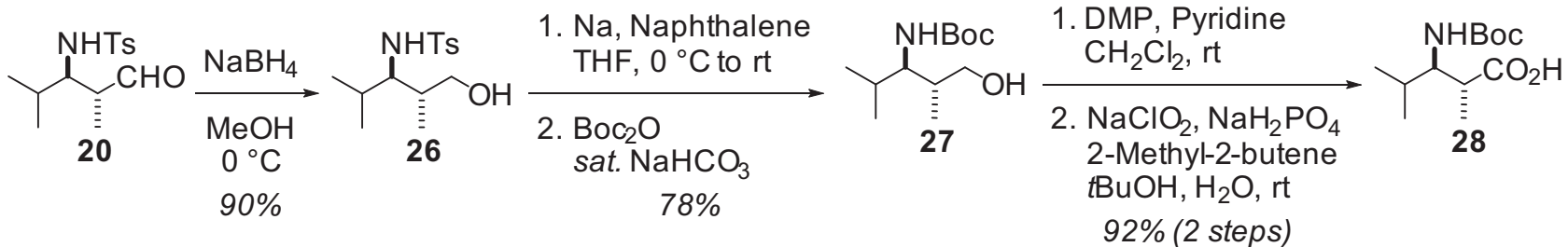
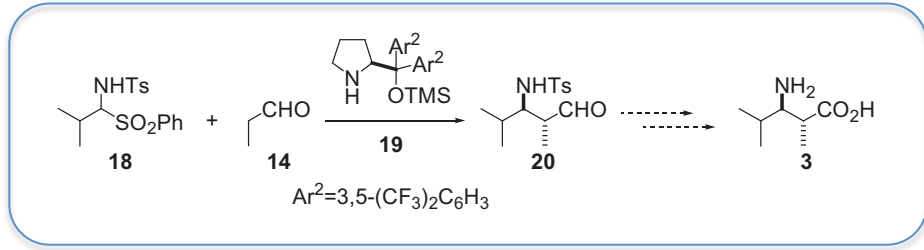


Overall yield=22.6%

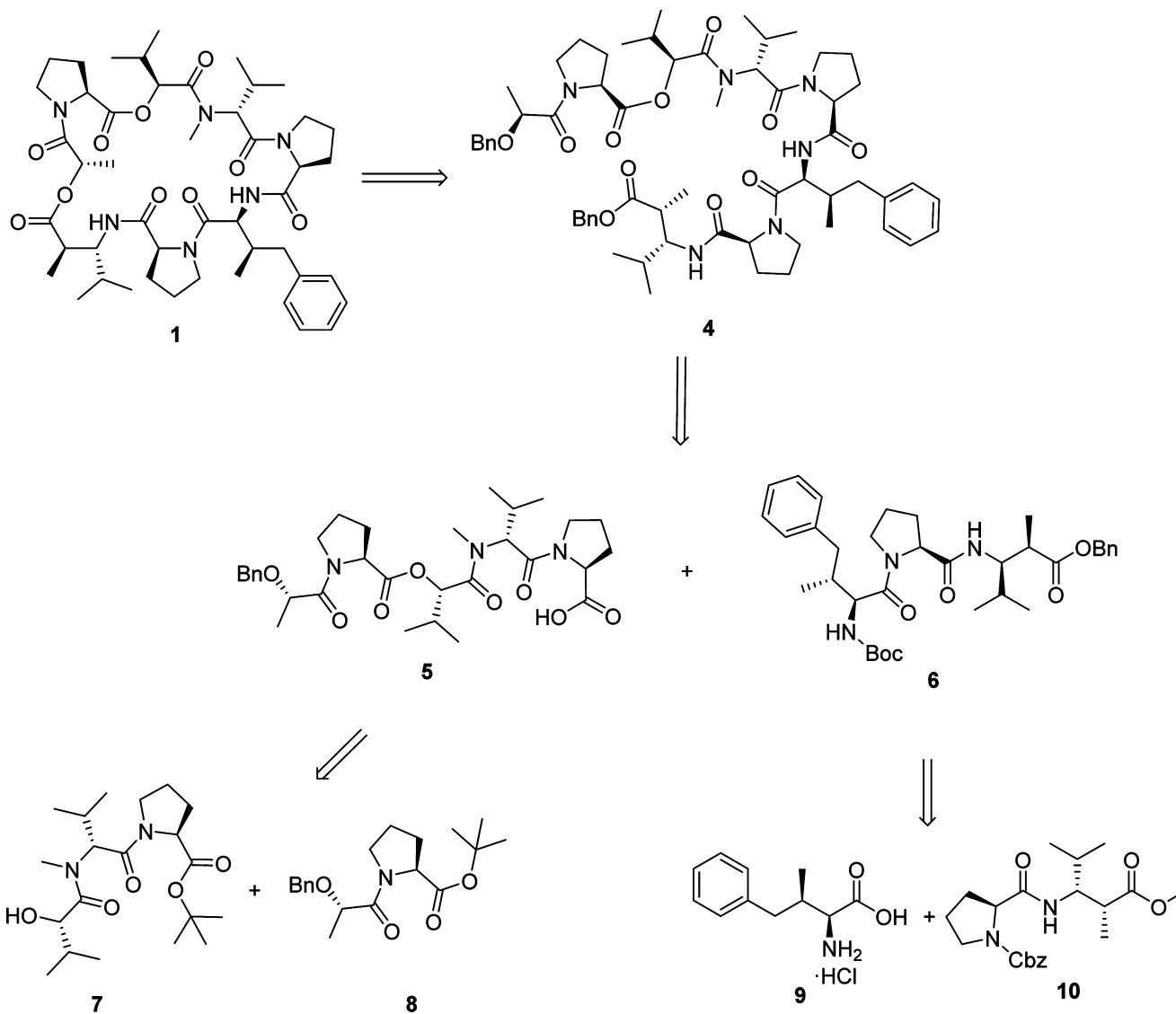




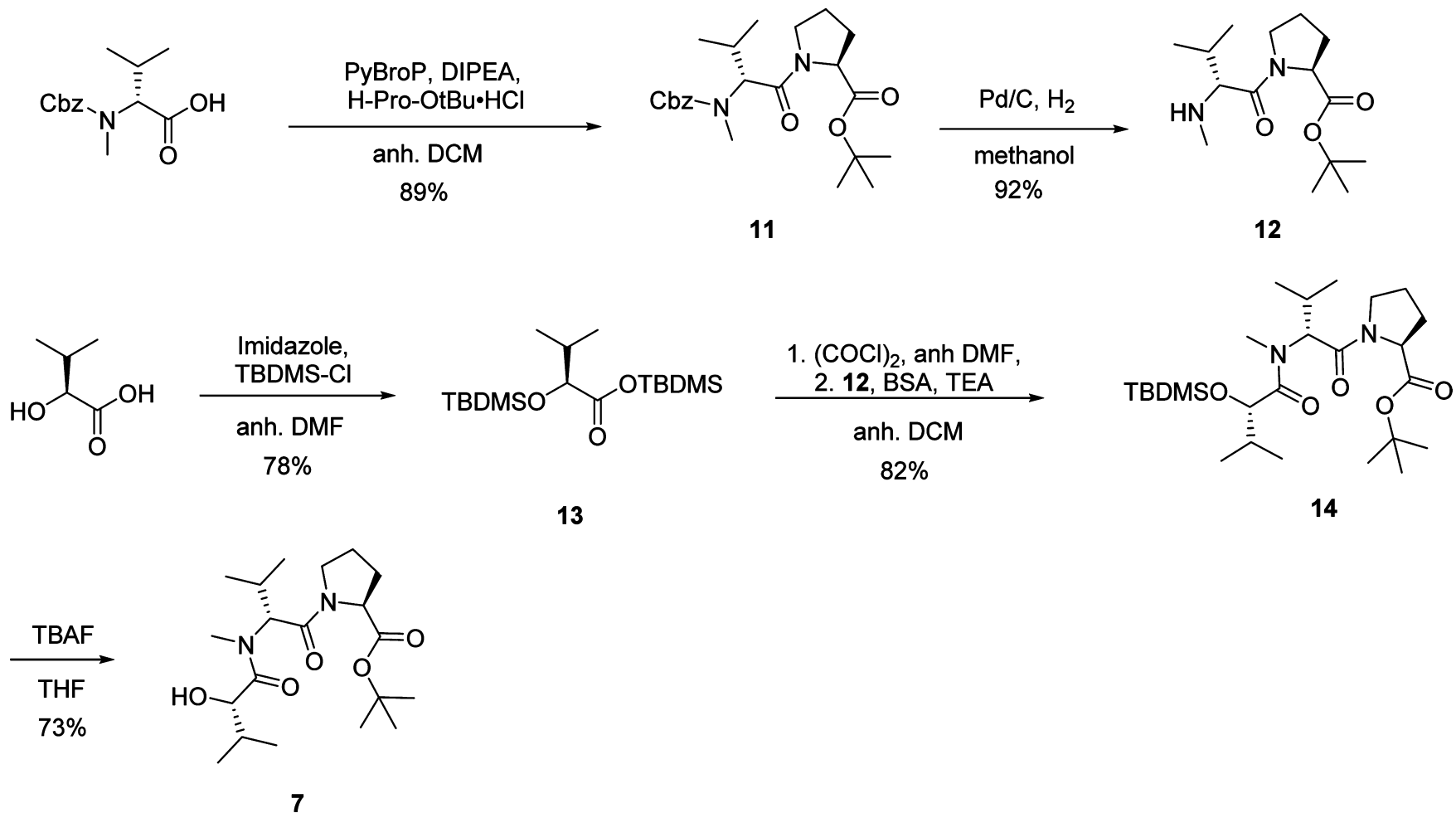




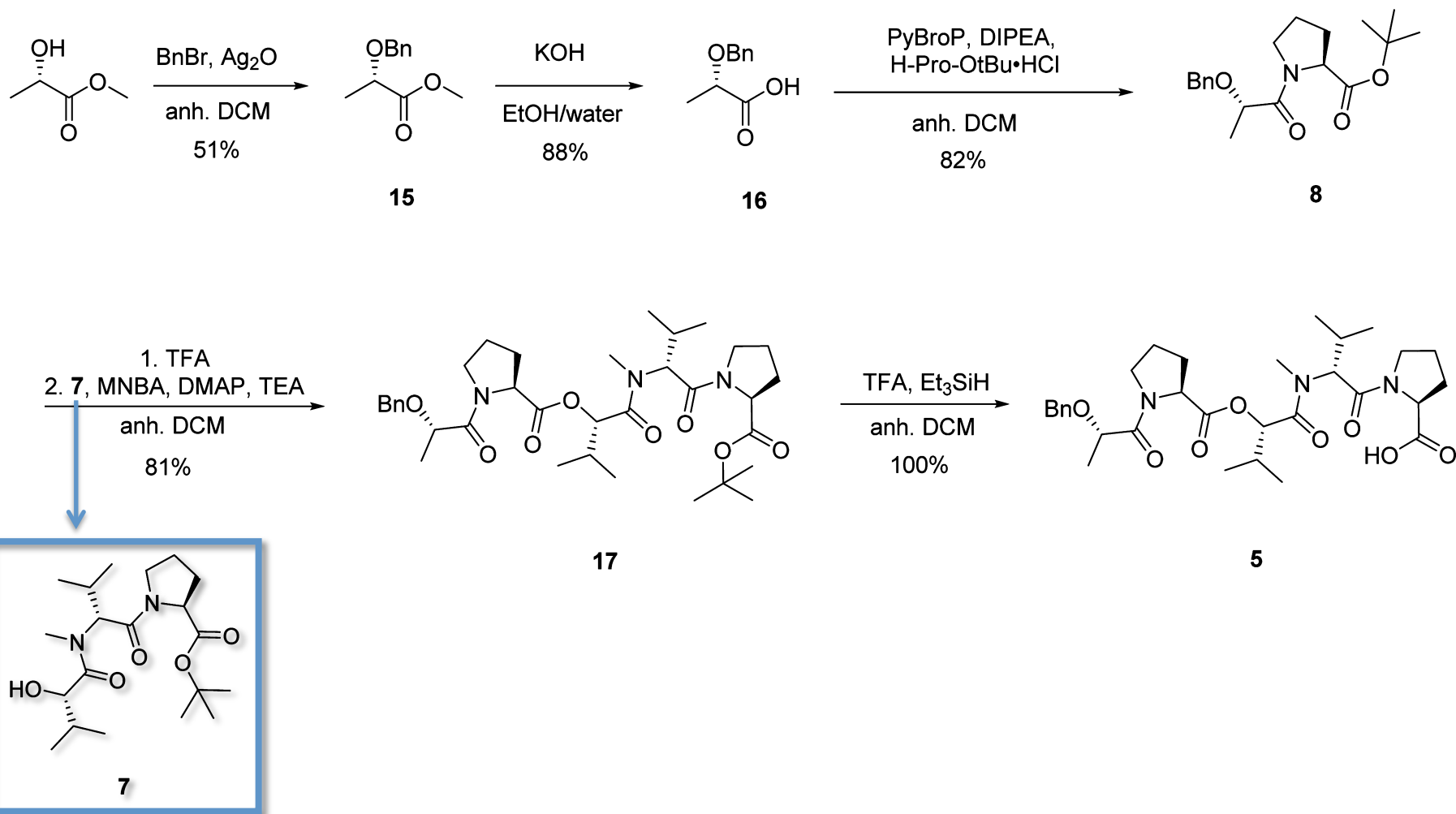
Retrosynthetic analysis of Dolastatin 16



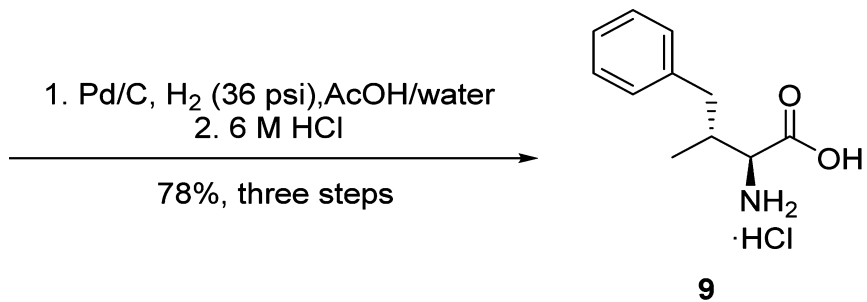
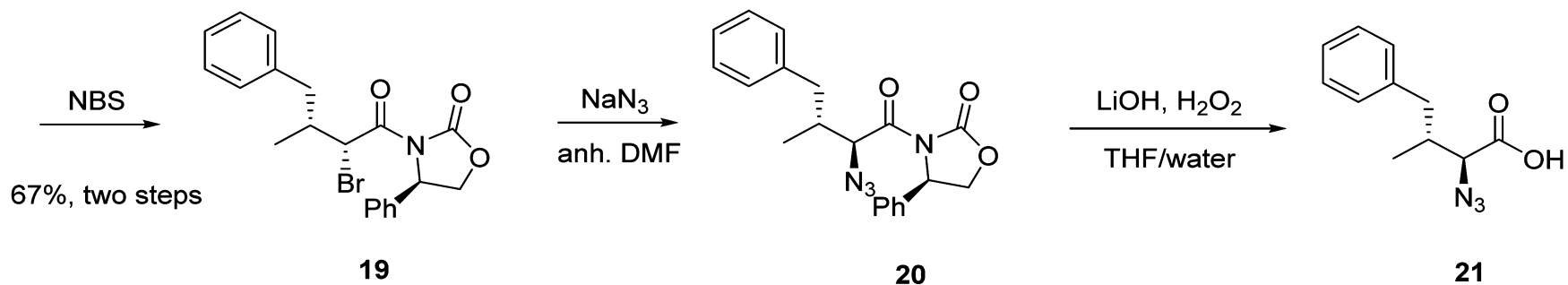
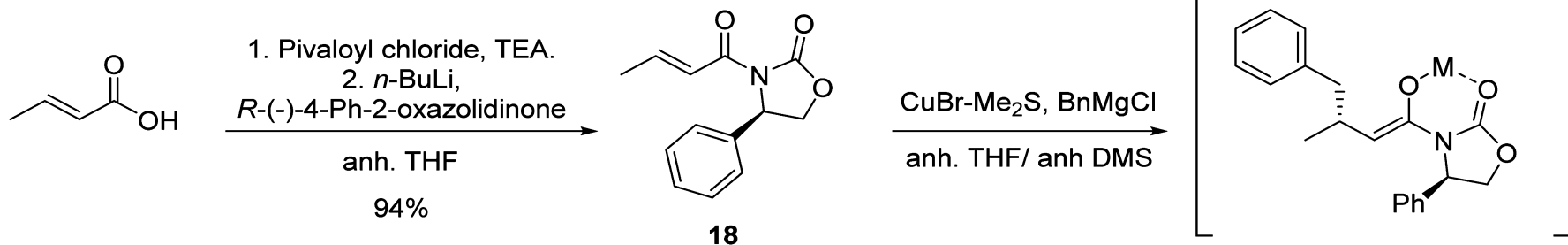
Synthesis of Intermediate 7 of Dolastatin 16



Synthesis of Intermediate 5

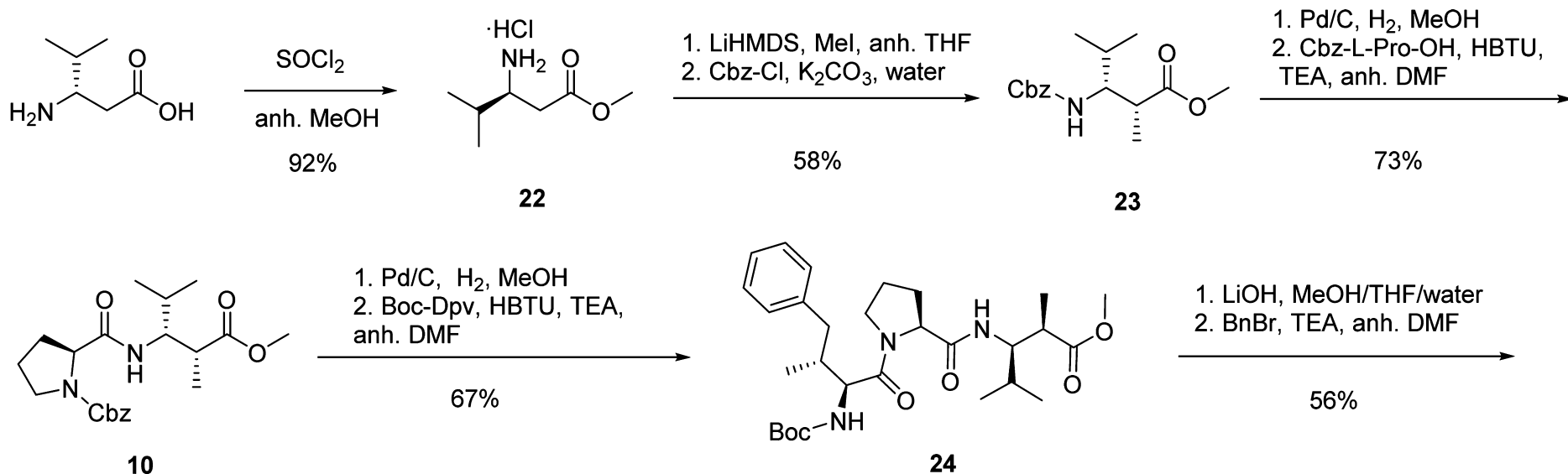


Synthesis of Intermediate 9

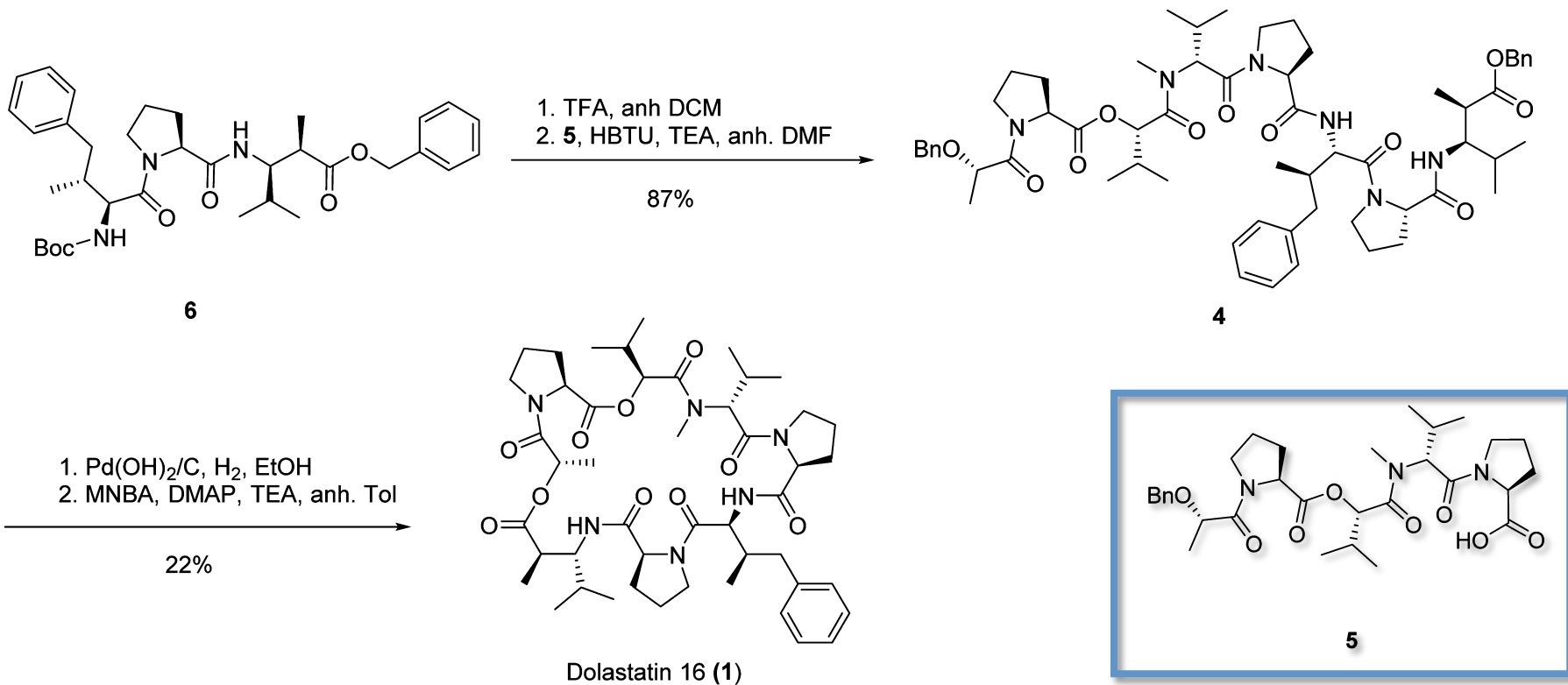


Dolophenvaline · HCl

Synthesis of Dolastatin 16



Synthesis of Dolastatin 16



Human Cancer Cell Growth Evaluation of Natural and Synthetic Dolastatin 16, GI₅₀ (μg/mL)

compound	solvent	cell line ^a					
		BXPC-3	MCF-7	SF-268	NCI-H460	KM20L2	DU-145
dolastatin 16 (natural)	DMSO	0.050	0.027	0.016	0.270	0.013	0.009
dolastatin 16 (synthetic)	DMSO	>10	>10	>10	>10	>10	>10
	MeOH	>10	>10	>10	>10	>10	>10

^aCancer cell lines in order: pancreas (BXPC-3); breast (MCF-7); CNS (SF-268); lung (NCI-H460); colon (KM20L2); prostate (DU-145).

Thank you for your attention!

