Spirodiepoxides : Epoxomicin

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Why do we care?

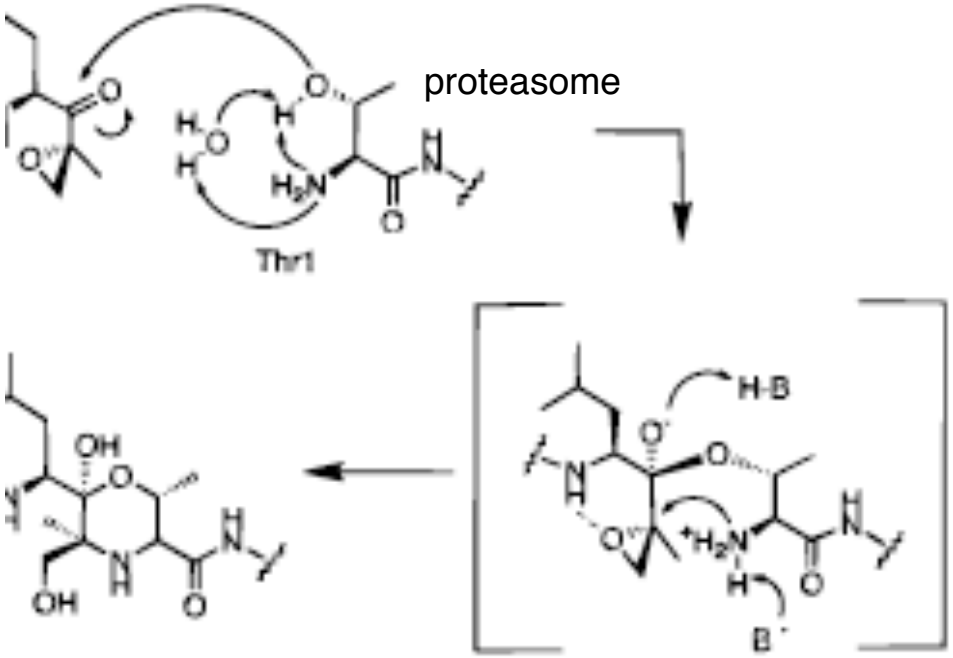
- Potent and irreversible proteasome inhibitor of S. cerevisiae 20S
- 20S proteasome inhibitors have been used as probes of proteasome function.
- Selective inhibitor: It does not touch calpain, papain, cathepsin B, chymotrypsin, and trypsin.
- Crystal structure published in 2000 crystallized in the binding pocket of 20S

Groll, M.; Kim, K; Kairies, N.; Huber, R.; Crews, C. *J. Am. Chem. Soc.* **2000**, 122, 1237-1238.

Nature of Irreversible Binding

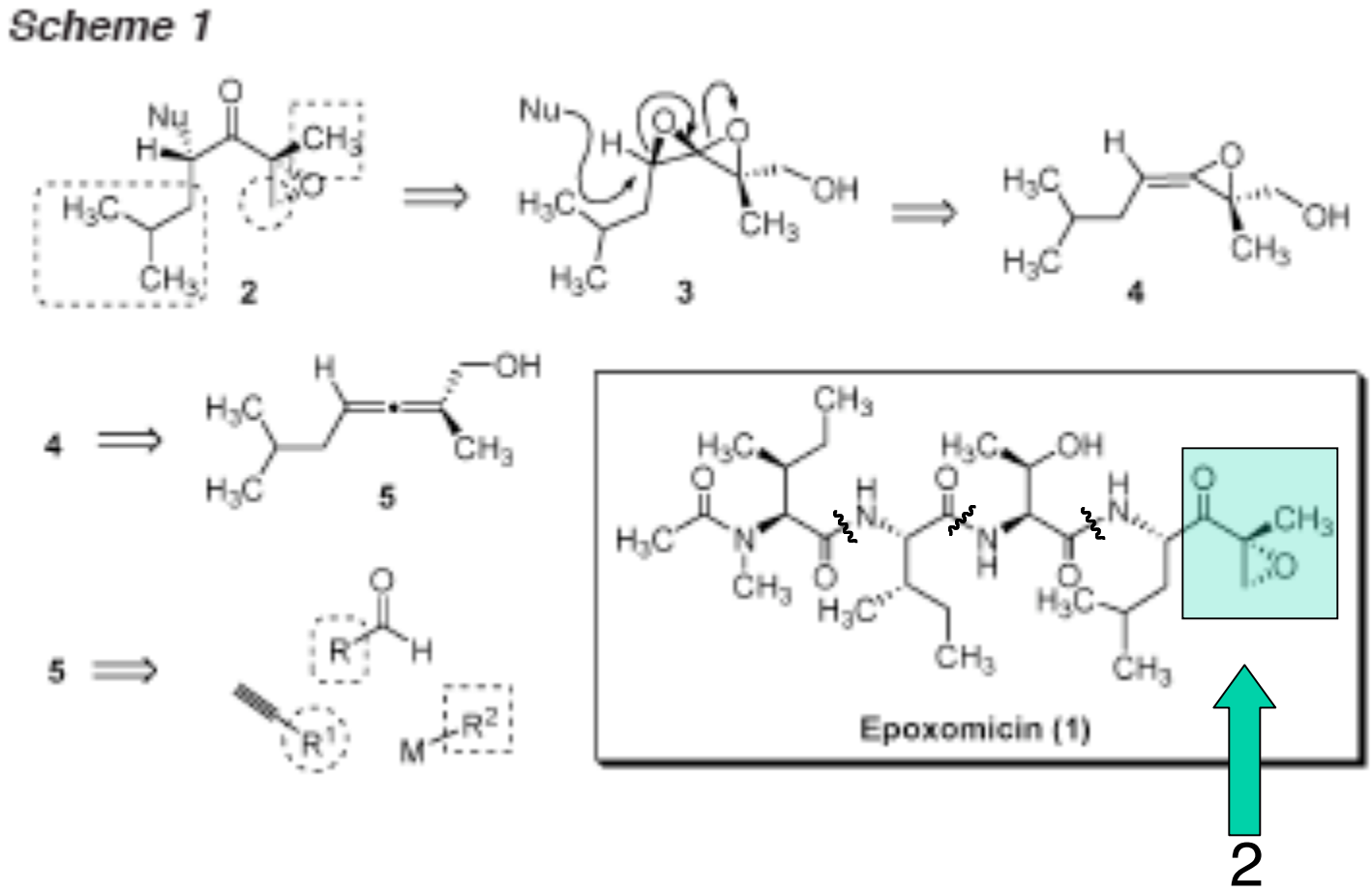
Epoxomicin

proteasome



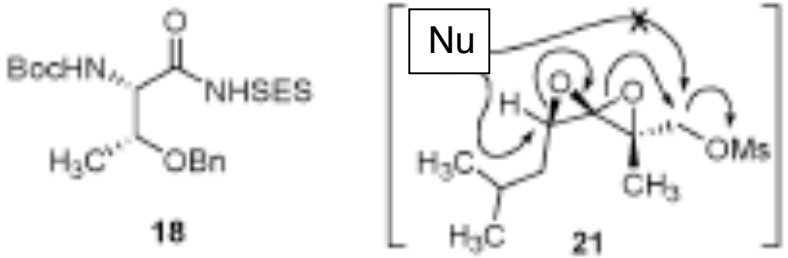
Groll, M.; Kim, K; Kairies, N.; Huber, R.; Crews, C. *J. Am. Chem. Soc.* **2000**, 122, 1237-1238.

Retrosynthesis



Katukojvala, S.; Barlett, K.; Lotesta, S.; Williams, L. *J. Am. Chem. Soc.* **2004**, 126 (47), 15348 - 15349.

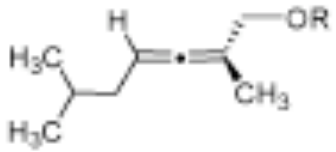
Did Not Work



Nu = 18 → Decomposition

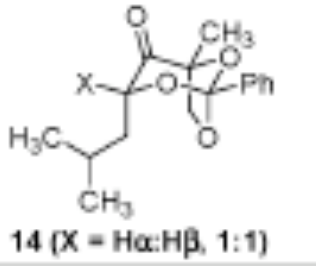
DIEA, K_2CO_3, LiHMDS, NaHMDS, or KHMDS

SES = $SO_2CH_2CH_2Si(CH_3)_3$.



R = Bz

ii →

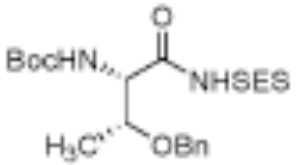


14 (X = Hα:Hβ, 1:1)

[a] Reagents and conditions: (i) DMDO, acetone, −40 to 23 °C, 2 h; then nucleophile (see Supporting Information); (ii) DMDO, acetone, −50 to 23 °C, 2 h; (iii) Bu_4NN_3, $CHCl_3$, −30 °C, 2 h; 30%. Major isomers shown.

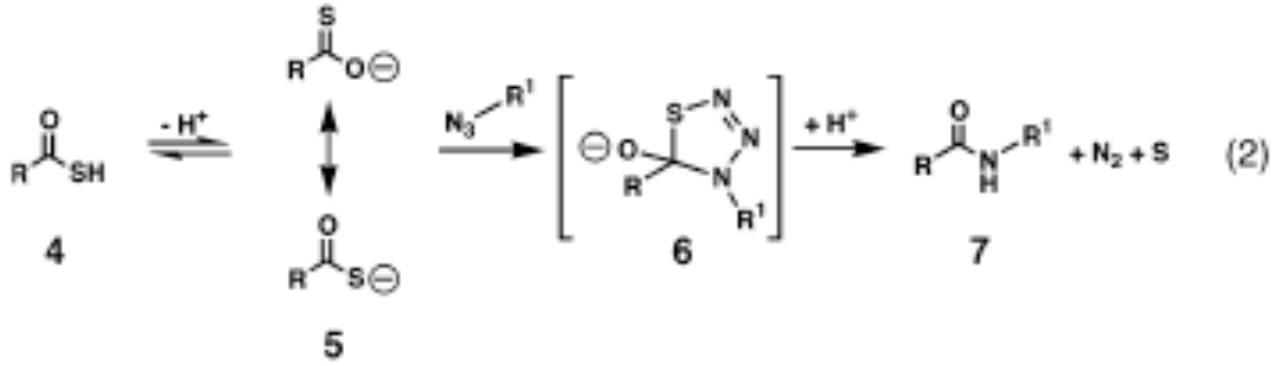
Katukojvala, S.; Barlett, K.; Lotesta, S.; Williams, L. *J. Am. Chem. Soc.* **2004**, 126 (47), 15348 - 15349.

Methods for Amide Formation



18

How was this made?



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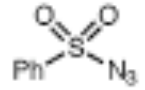
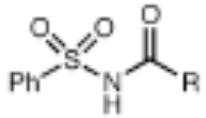
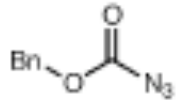
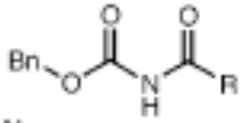
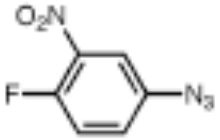
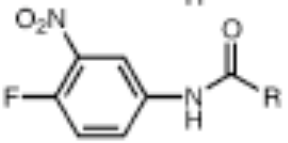
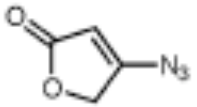
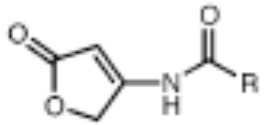
Shangguan, N.; Katukojvala, S.; Greenberg, R.; Williams, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 7754 - 7755.

Methods for Amide Formation

Table 1. Thio Acid/Azide Coupling in Polar Organic Solvent[a]

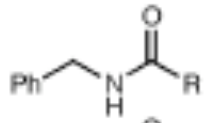
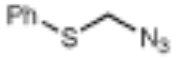
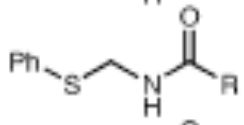
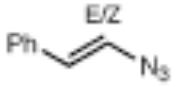
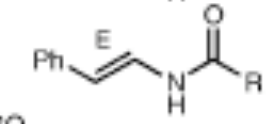
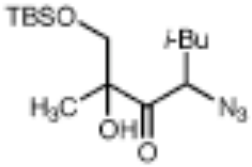
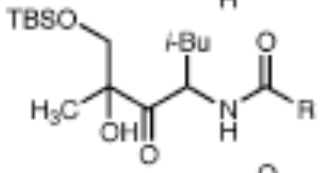
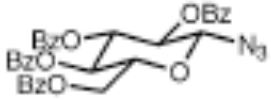
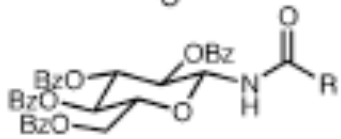
Entry	Azide	°C/time/solvent	Amide	Yield
1		a) 25/15 min/MeOH b) 25/15 min/MeOH		a) 98% b) 96%
2		a) 25/2 h/MeOH b) 25/2 h/MeOH		a) 99% b) 96%
3		a) 25/15 h/MeOH b) 25/15 h/MeOH		a) 95% b) 94%
4		a) 0/2 h/MeOH b) 0/2 h/MeOH		a) 98% b) 95%

[a] Conditions: 0.94−0.024 M azide; 1:1.3:1.3 azide:2,6-lutidine:thio acid. (a) Thiobenzoic acid, R = C_6H_5. (b) Thioacetic acid, R = CH_3.

Shangguan, N.; Katukojvala, S.; Greenberg, R.; Williams, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 7754 - 7755.

Methods for Amide Formation

Table 2. Thio Acid/Azide Coupling in Nonpolar Organic Solvent[a]

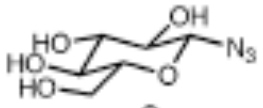
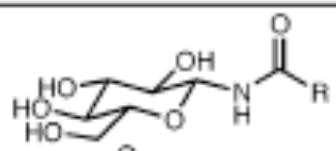
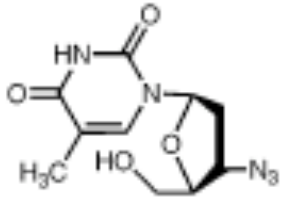
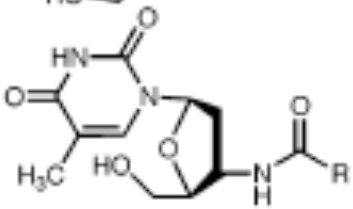
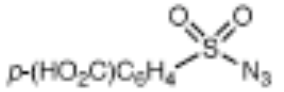
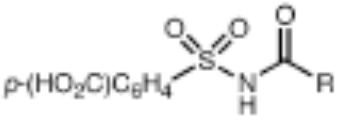
Entry	Azide	°C/time/solvent	Amide	Yield
1		a) 60/15 h/$CHCl_3$ b) 60/15 h/$CHCl_3$		a) 78% b) 86%
2		a) 60/15 h/$CHCl_3$ b) 60/15 h/$CHCl_3$		a) 77% b) 85%
3		a) 60/10 h/$CHCl_3$ b) 60/18 h/$CHCl_3$		a) 66% b) 79%
4		a) 25/30 h/$CHCl_3$ b) 60/24 h/$CHCl_3$		a) 94% b) 88%
5		a) 60/36 h/$CHCl_3$ b) 60/36 h/$CHCl_3$		a) 64% b) 97%

[a] Conditions: 1.0−0.18 M azide; 1:1.3−2.6:1.3−2.6 azide:2,6-lutidine: thio acid. (a) Thiobenzoic acid, R = C_6H_5. (b) Thioacetic acid, R = CH_3. For entry 5a, yield based on recovered starting material: 95%.

Shangguan, N.; Katukojvala, S.; Greenberg, R.; Williams, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 7754 - 7755.

Methods for Amide Formation

Table 3. Thio Acid/Azide Coupling in Water[a]

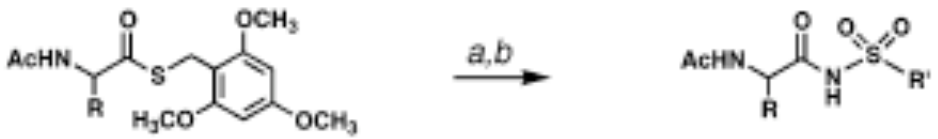
Entry	Azide	°C/time/solvent	Amide	Yield
1		a) 60/36 h/H_2O b) 60/36 h/H_2O		a) 83% b) 80%
2		a) 60/36 h/H_2O b) 60/36 h/H_2O		a) 68% b) 77%
3		a) 25/1 h/H_2O b) 25/1 h/H_2O		a) 93% b) 98%

[a] Conditions: 0.25−0.040 M azide; 1:1.3−5 azide:thio acid; entry 1, $NaHCO_3$(aq); entry 2, PBS buffer pH 7.4; entry 3, 1.8 equiv of 2,6-lutidine. (a) Thiobenzoic acid, R = C_6H_5. (b) Thioacetic acid, R = CH_3.

Shangguan, N.; Katukojvala, S.; Greenberg, R.; Williams, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 7754 - 7755.

Methods for Amide Formation

Table 4. Preparation of α-Aminoacyl Sulfonamide Derivatives[a]



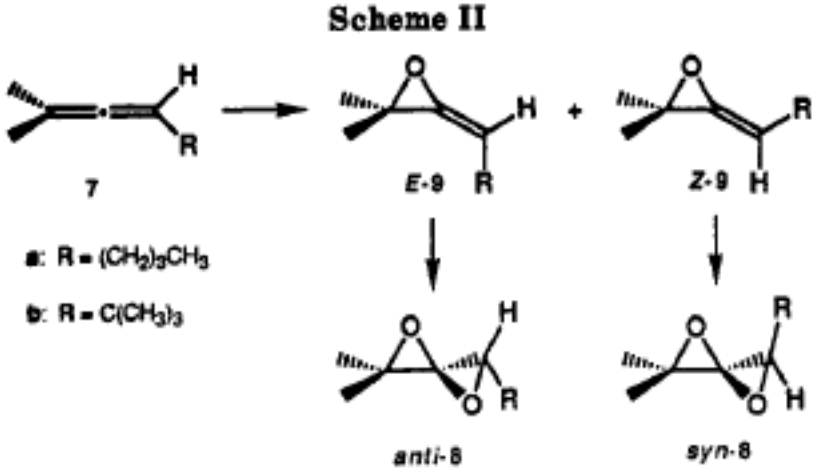
8 9

entry	8	R	azide	9	yield (two steps)
1	**a**	*i*-Bu	N_3-Bs	**9a**, *N*-Ac-Leu-NH-Bs	91%
2	**b**	(*R*)-*sec*-Bu	N_3-Ts	**9b**, *N*-Ac-alle-NH-Ts	87%
3	**c**	(*S*)-*sec*-Bu	N_3-Ts	**9c**, *N*-Ac-Ile-NH-Ts	72%
4	**d**	(*R*)-*sec*-Bu	N_3-dansyl	**9d**, *N*-Ac-alle-NH-dansyl	73%
5	**e**	*i*-Bu	N_3-dansyl	**9e**, *N*-Ac-Leu-NH-dansyl	73%

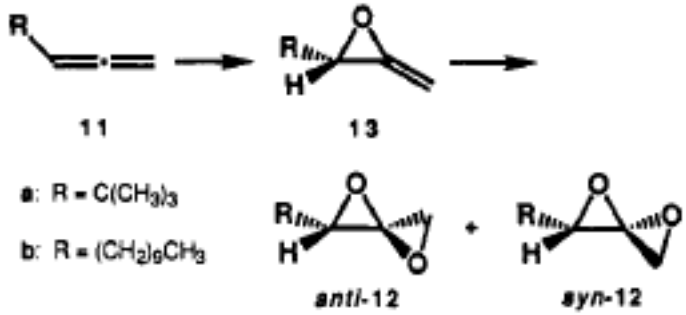
[a] Conditions: (a) TFA/DCM (40−80% v/v), $HSiEt_3$; (b) CH_3OH, 0.16−0.17 M thio acid; 2−5 equiv of azide, 3−6 equiv of 2,6-lutidine, room temperature.

Shangguan, N.; Katukojvala, S.; Greenberg, R.; Williams, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 7754 - 7755.

Preliminary Work



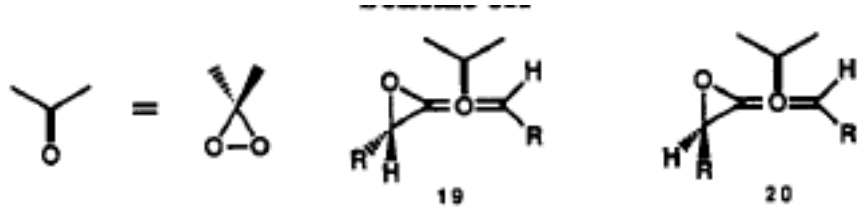
R=t-butyl = only product, 84 % yield
R=propyl=9:1 ratio, 95 % yield

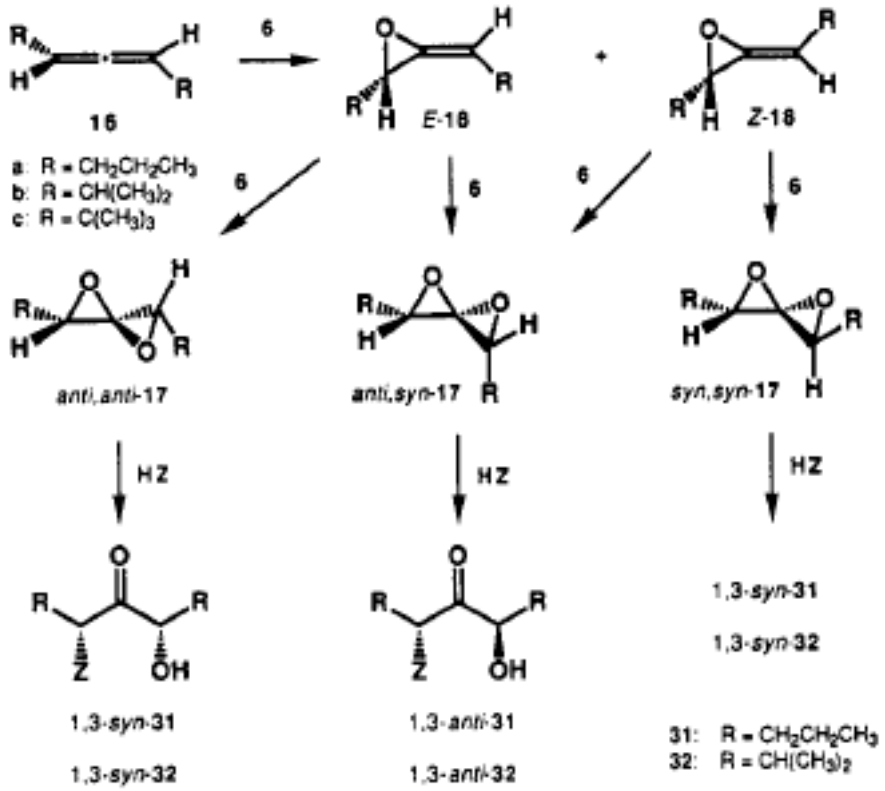


R=t-butyl =98 : 2, 78 % yield
R = propyl = 9 : 1, not reproducible

Crandal, J. K.; Batal, D. J.; Sebesta, D. P.; Lin, F. *J. Org. Chem.* **1991**, *56*, 1153 - 1166.

1,3-Disubstituted Allene





R = propyl,	1 : 1 : 0.15	Yield = ?
R= isopropyl,	2 : 1 : 0	Yield = ?
R= t-butyl,	1 : 0 : 0	Yield = ?

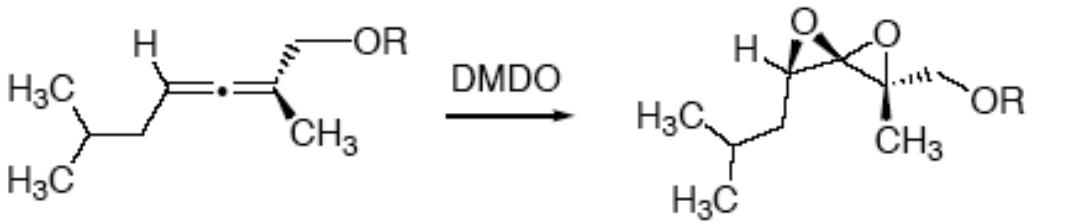
R = propyl

Z = OH	1.1 : 1	Yield = 78
Z = OAc,	1.4 : 1	Yield = 85
Z = Et_2NH	1.1 : 1	Yield = 85

No work done on 1,1,3-trisubstituted

Crandal, J. K.; Batal, D. J.; Sebesta, D. P.; Lin, F. *J. Org. Chem.* **1991**, *56*, 1153 - 1166.

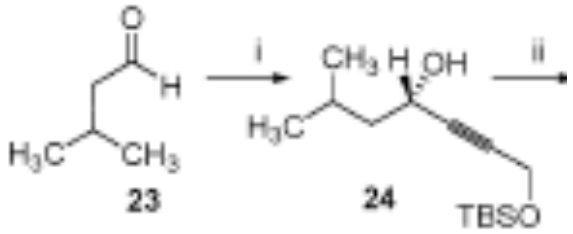
1,1,3-Trisubstituted

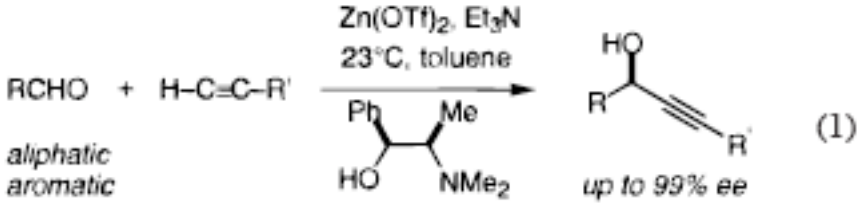


Allene	Approximate ratio of corresponding spirodiepoxide*
6: R = TBS	2:1
7: R = TMS	2:1
8: R = TIPS	2:1
9: R = TBDPS	2:1
10: R = t-Bu	1.5:1
11: R = Bn	1.5:1
12: R = BOM	1.5:1

Katukojvala, S.; Barlett, K.; Lotesta, S.; Williams, L. *J. Am. Chem. Soc.* **2004**, 126 (47), 15348 - 15349.

Epoxomicin





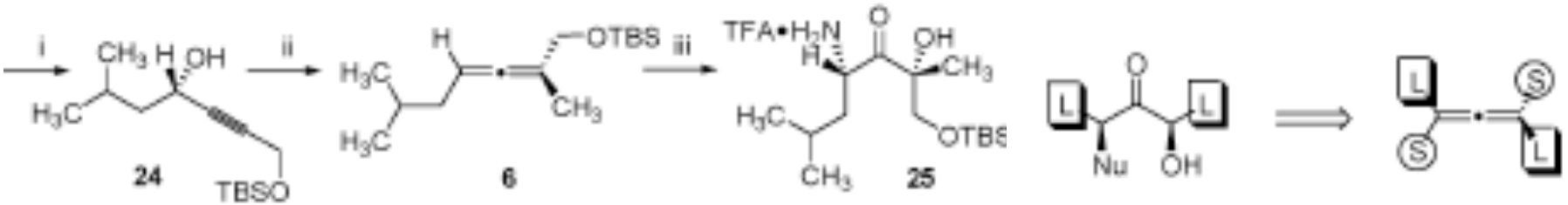
[a] Reagents and conditions: (i) (−)-*N*-methylephedrine, $Zn(OTf)_2$, Et_3N, toluene, rt, 2 h, $TBSOCH_2CCH$ then **23** 14 h, 93%, >95% ee; (ii) a. MsCl, Et_3N, DCM, −65 to 23 °C, 2 h; b. MeMgBr, CuBr, LiBr, THF/*tert*-butyl

Table 1. Enantioselective Additions of RC≡CH to Aldehydes[a]

Entry	Aldehyde	Alkyne	Time	Yield	ee[b,c]
1	*c*-C_6H_{11}	Ph	1h	99%	96%
2		$Ph(CH_2)_2$	4h	98%	99%[d]
3	*iso*-Pr	$Ph(CH_2)_2$	2h	90%	99%
4		Ph	2h	95%	90%
5	PhCH=CH	$Ph(CH_2)_2$	20h	39%	80%
6	*tert*-Bu	$Ph(CH_2)_2$	2h	84%	99%

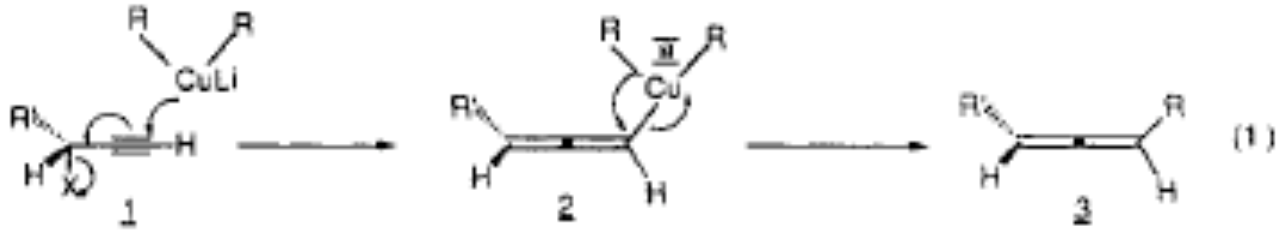
Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806 -1807.

Allene Formation



L = large substituent; S = small substituent

toluene, rt, 2 h, $TBSOCH_2CCH$ then **23** 14 h, 93%, >95% ee; (ii) a. MsCl, Et_3N, DCM, −65 to 23 °C, 2 h; b. MeMgBr, CuBr, LiBr, THF/*tert*-butyl ether, −65 to 23 °C, 2 h, 91%; (iii) a. DMDO, −40 to 23 °C, 1.5 h; b. Bu_4NN_3, $CHCl_3$, −20 to 23 °C, 1 h, 73% (3:1 dr); c. 10% Pd/C, H_2, $(Boc)_2O{\cdot}K_2CO_3$, EtOAc, rt, 12 h, 91%; d. TFA, 0 °C, 13 min; (iv) a. **26**,



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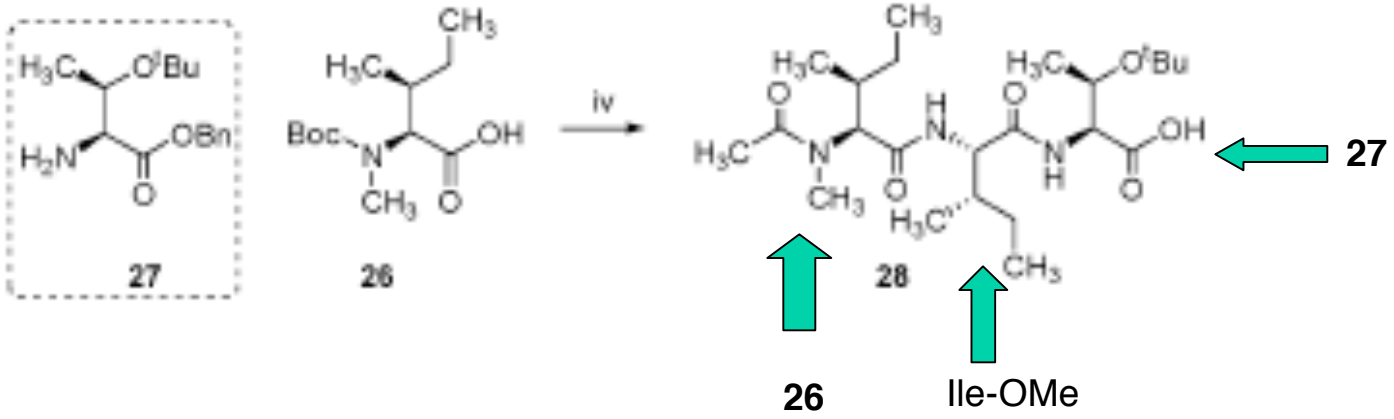
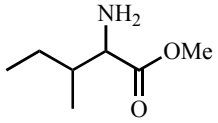
Peptide Coupling



$(Boc)_2O{\cdot}K_2CO_3$, EtOAc, rt, 12 h, 91%; d. TFA, 0 °C, 13 min; (iv) a. **26**, HCl·Ile-OMe, DCC, HOBT, Et_3N, DMF, 0 to 23 °C, 12 h, 93%; b. 25% TFA−DCM, 10 to 23 °C, 40 min; c. TEA, Ac_2O, DMAP, DCM, 0 to 23 °C, 3 h, 95%; d. 5% NaOH, MeOH−H_2O, rt, 2 h, 99%; e. **27**, DCC, HOBT, DCM−DMF, rt, 3 h, 92%; f. 10% Pd/C, H_2, MeOH, rt, 2 h, 100%; (v) **25**,



Ile-Ome = methyl isoleucinate

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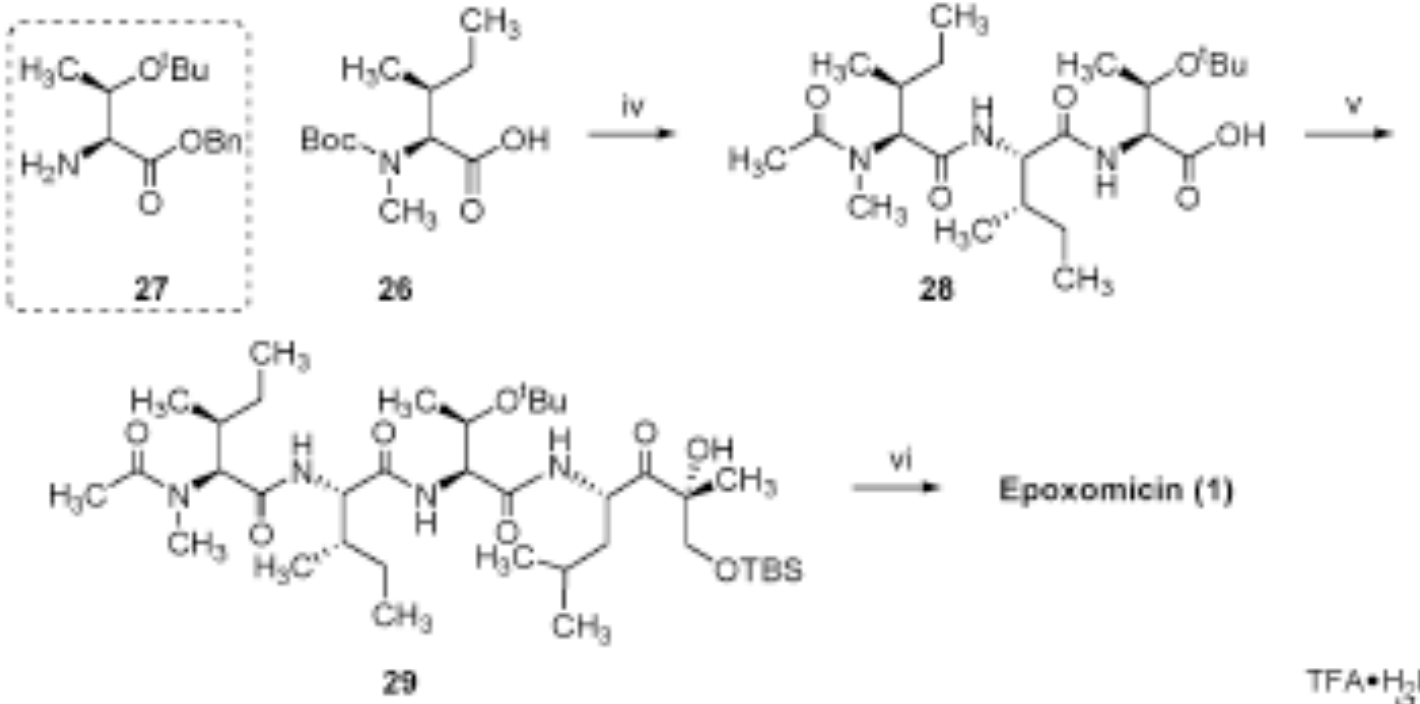
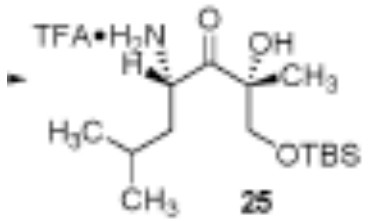
End Game



DCM−DMF, rt, 3 h, 92%; f. 10% Pd/C, H_2, MeOH, rt, 2 h, 100%; (v) **25**, DIEA, DCC, HOBT, DCM−DMF, rt, 4 h, 86%; (vi) a. TBAF, THF, 0 to 23 °C, 1 h, 89%; b. MsCl, DIEA, DCM, −40 to 23 °C, 1 h; c. K_2CO_3, THF−H_2O, rt, 3 h, 93%; d. TFA, 0 to 23 °C, 20 min, 88%.



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Thank you for your time!