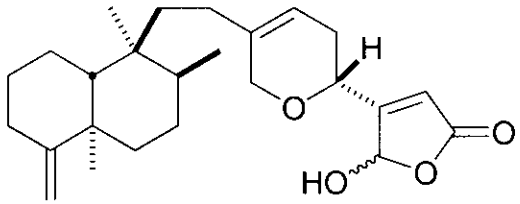
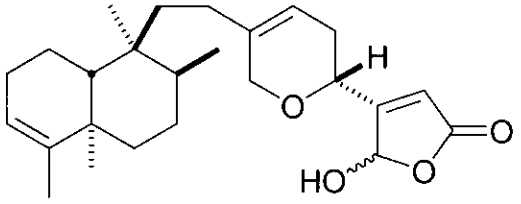
Total Syntheses of (+)- and (-)-Cacospongionolide B, Cacospongionolide E, and Related Analogues. Preliminary Study of Structural Features Required for Phospholipase A_2 Inhibition

Snapper, M. L.; Murelli, R.; Cheung, A. K. *J. Org. Chem.* **2004**, *ASAP*

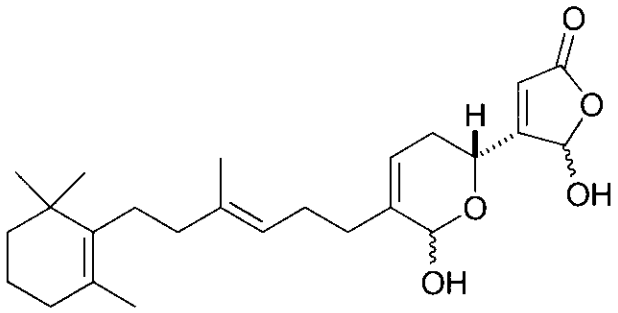
Representative Anti-inflammatory Marine Sponge Metabolites



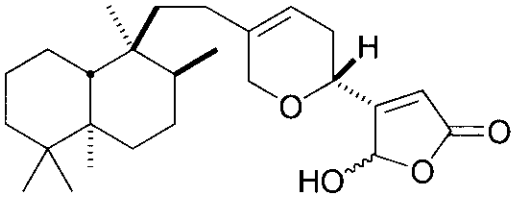
(+)-cacospongionolide B (**1**)



(+)-cacospongionolide E (**2**)



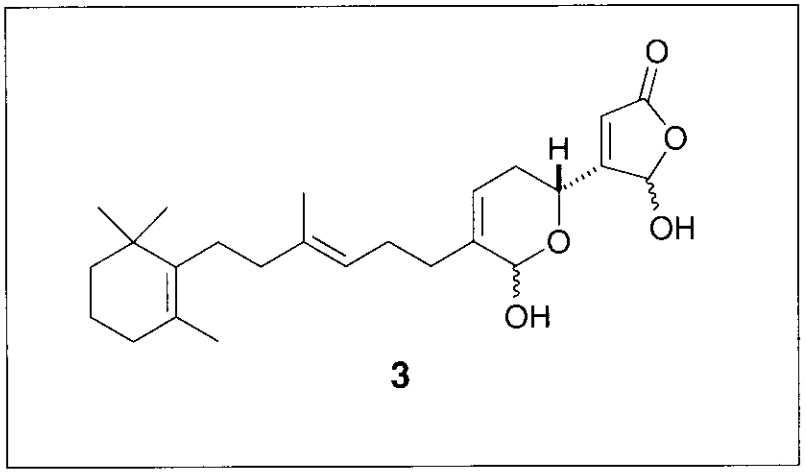
manoalide (**3**)



*(+)-cacospongionolide F (**4**)

*Damtew, D.; Forsyth, C. J. *Org. Lett.* **2003**, *5*, 991-4; synthesis

Manoalide



3

-isolated from the Pacific marine sponge *Luffariella variabilis* in 1979 by Scheuer and de Silva

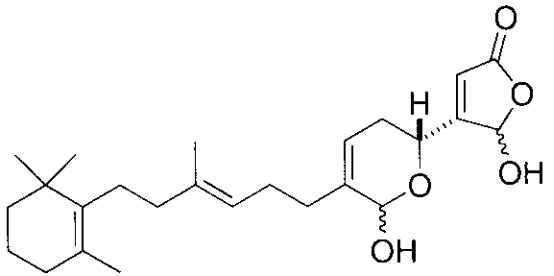
-irreversibly inhibits phospholipase A_2 (present in many neurotoxic venoms, plays an important role in phospholipid metabolism and prostaglandin synthesis)

-shows significant *in vitro* activity against Gram positive bacteria

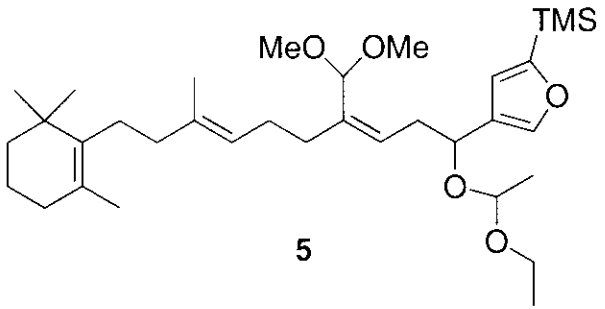
-possesses topical anti-inflammatory activity (NSAID-nonsteroidal anti-inflammatory drug)

-evaluated in phase II clinical trials for psoriasis

Retrosynthetic Analysis of Manoalide



manoalide (**3**)



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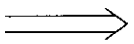
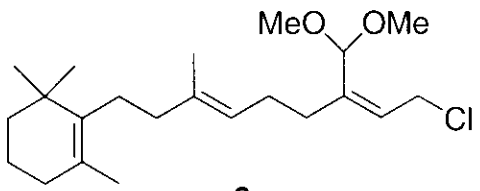
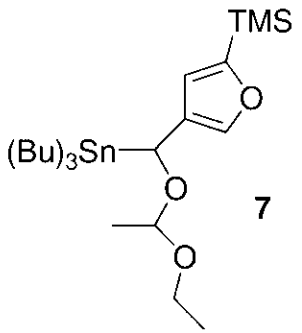




6

+

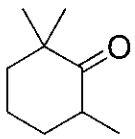


7

Katsumura, S.; Fujiwara, S,; Isoe, S. *Tetrahedron Lett.* **1985**, *26*, 5827

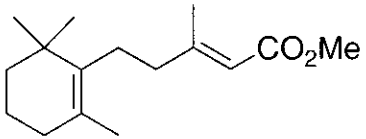
Katsumura, S.; Fujiwara, S,; Isoe, S. *Tetrahedron Lett.* **1986**, *29*, 1173: modification-Pd(0)-catalyzed coupling with CO

Synthesis of the Key Fragments



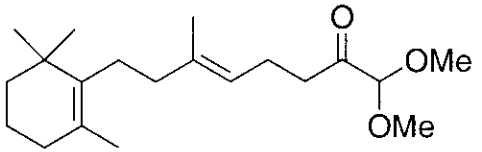
8

*5 steps



9

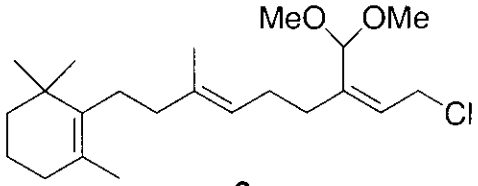
3 steps; 62%



10

1) Base, *t*-butyl 2-trimethylsilyl acetate; 95%
2) DIBAL, CH_2Cl_2

3) MsCl, LiCl; 90%



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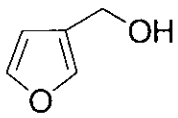
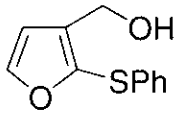


11

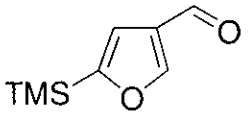
BuLi (2 eq), THF, -78 °C (1h) to 0 °C (2h);
then PhSSPh (1 eq), 0 °C; 91%



12

1) BuLi, THF, -78 °C to 0 °C; TMSCl, 0 °C
2) 1% HCl/THF, 0 °C, 5 min

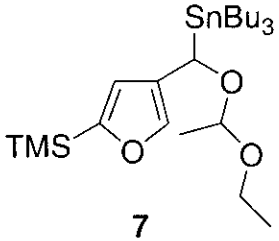
3) Raney-Ni, EtOH, reflux, 16h
4) $BaMnO_4$, CH_2Cl_2, 16h; 41%



13

1) Bu_3SnLi, THF, -78 °C, 1h

2) *alpha*-chloroethyl ethyl ether,
(i-Pr)$_2$NEt, CH_2Cl_2, 0 °C, 1h; 95%

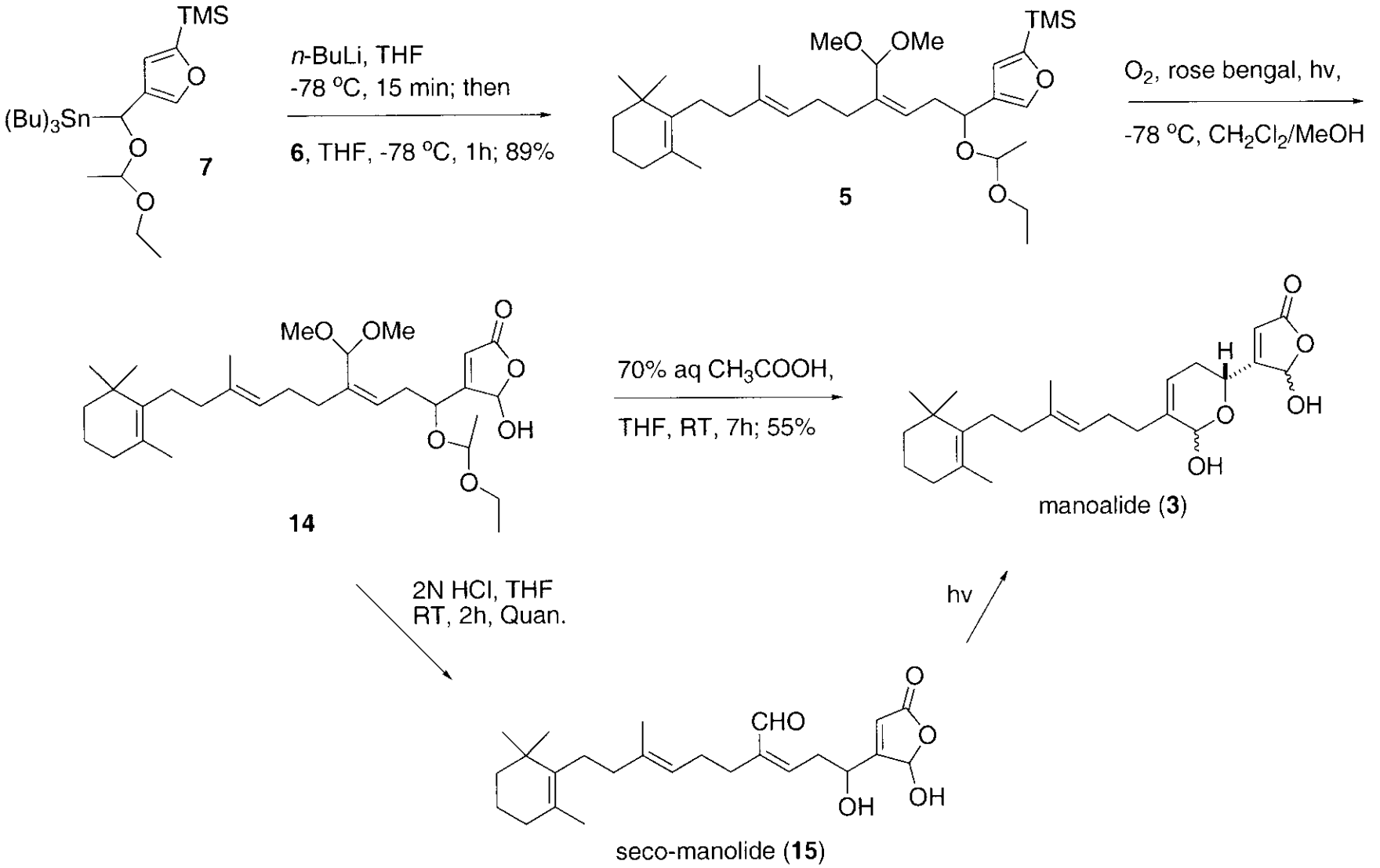


7

Katsumura, S.; Fujiwara, S,; Isoe, S. *Tetrahedron Lett.* **1985**, *26*, 5827

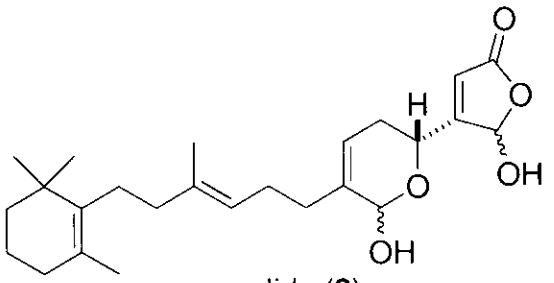
*Schmidt, C.; Chishti, N. H.; Breining, T. *Synthesis* **1982**, 391

Completion of the First Total Synthesis of Manoalide

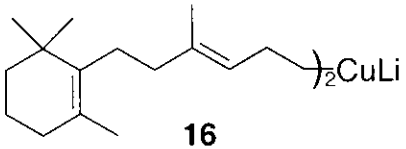


Katsumura, S.; Fujiwara, S.; Isoe, S. *Tetrahedron Lett.* **1985**, *26*, 5827

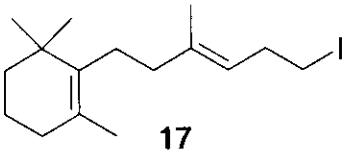
Retrosynthetic Analysis of Manoalide



manoalide (**3**)



16



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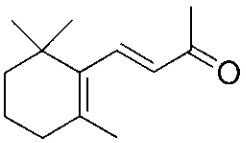
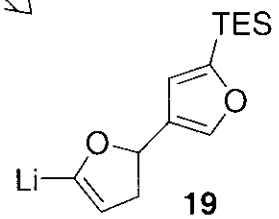


beta-ionone (**18**)



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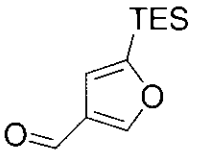
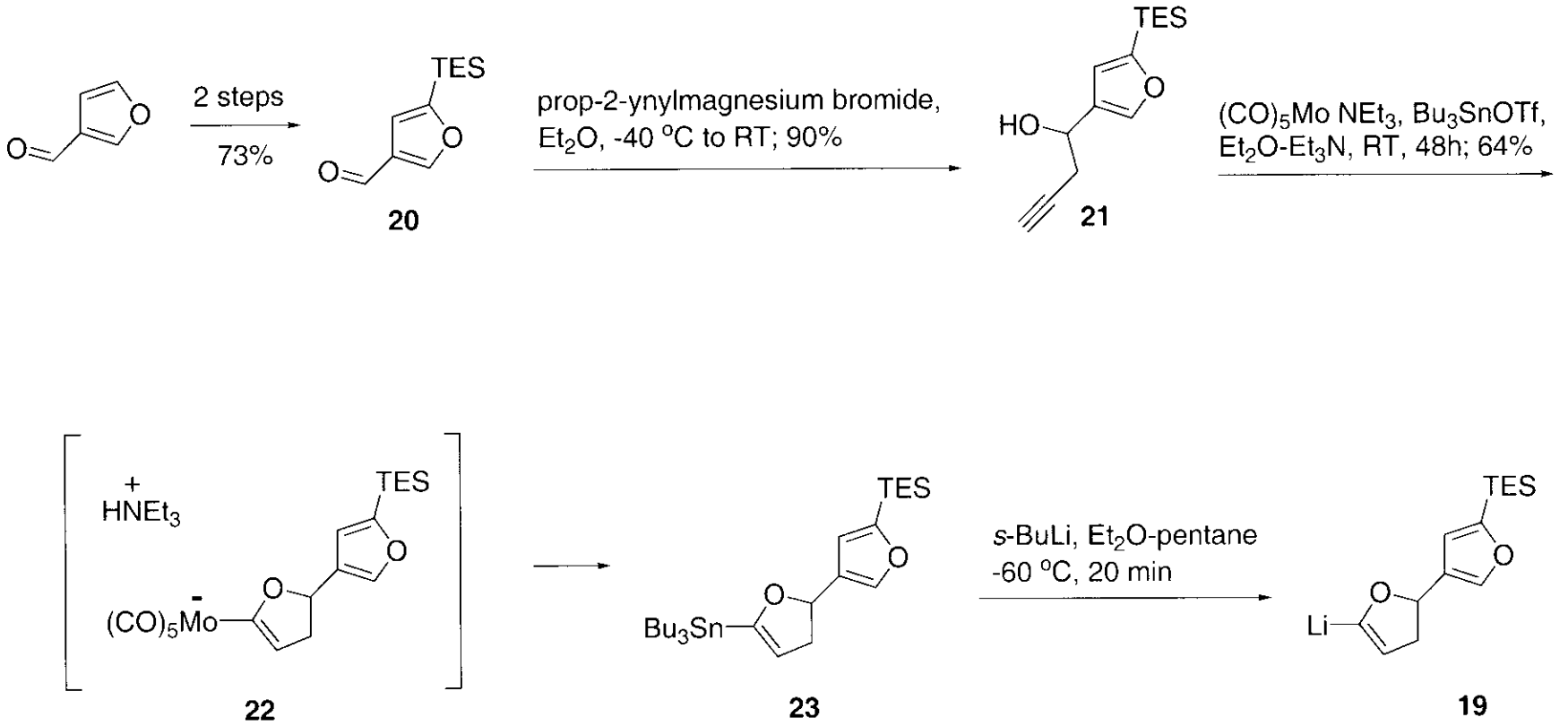


20

Pommier, A.; Kocienski, P. J. *Chem. Commun.* **1997**, 1139

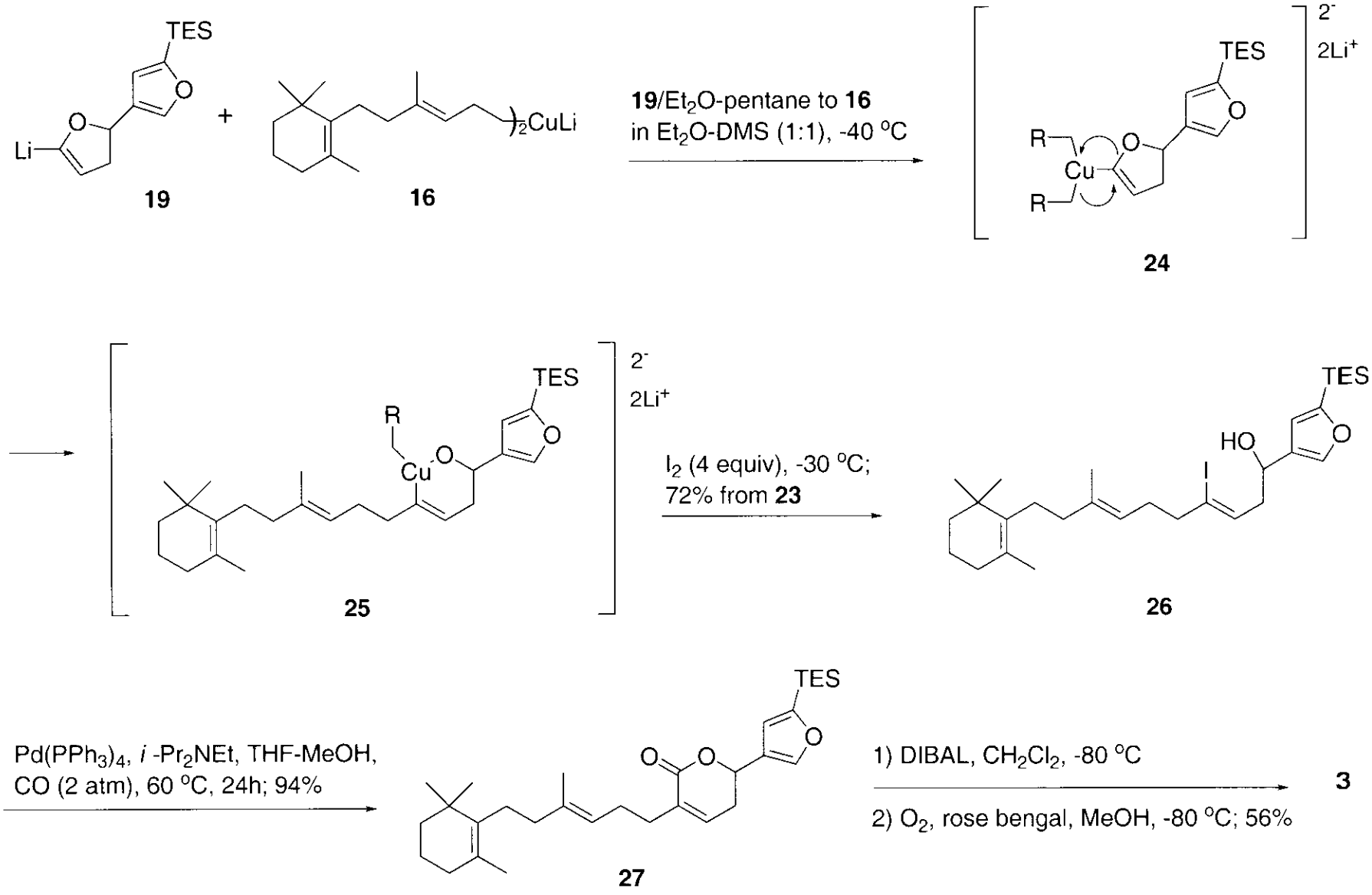
Bury, P.; Hareau, G.; Kocienski, P; Dhanak, D. *Tetrahedron* **1994**, *50*, 8793

Synthesis of Key Alkenyllithium



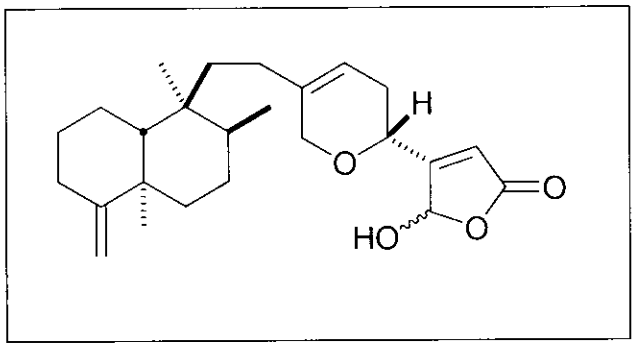
Pommier, A.; Kocienski, P. J. *Chem. Commun.* **1997**, 1139

Completion of the Total Synthesis of Manoalide



Pommier, A.; Kocienski, P. J. *Chem. Commun.* **1997**, 1139

Cacospongionolide B



-sesterterpenes isolated from Mediterranean region sponges of the Thorectidae family: B-1995; E-1998

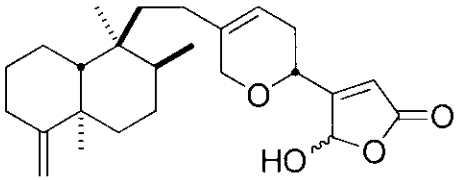
-possess cytotoxic, antimicrobial and anti-inflammatory activity

-anti-inflammatory activity: inhibition of secretory phospholipase A_2 (*s*PLA_2)

-irreversible inhibitor of recombinant human synovial PLA_2 *in vitro*

-offer promise for the treatment of diseases such as asthma, sepsis and rheumatoid arthritis

Retrosynthetic Analysis of (+)-Cacospongionolide B



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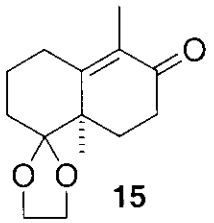

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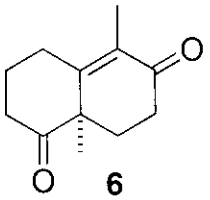

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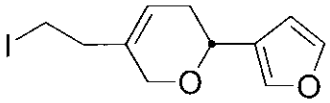

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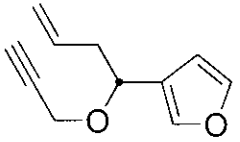

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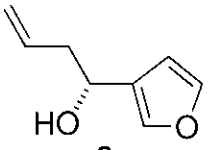
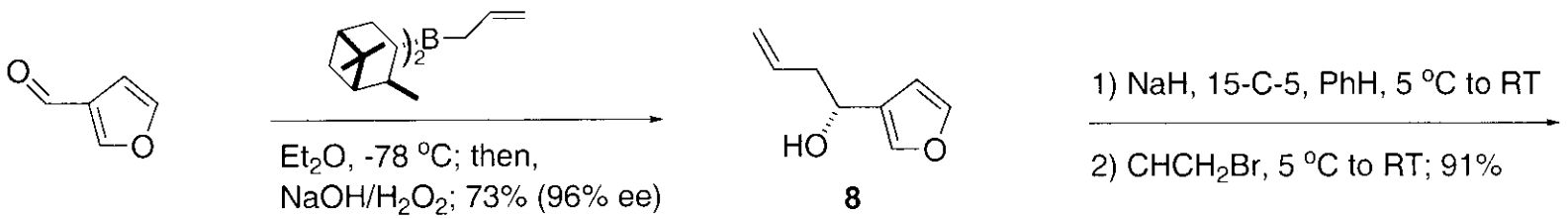


8

Construction of the Oxacyclic Fragment



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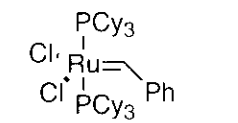
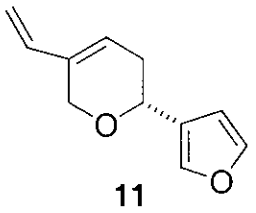
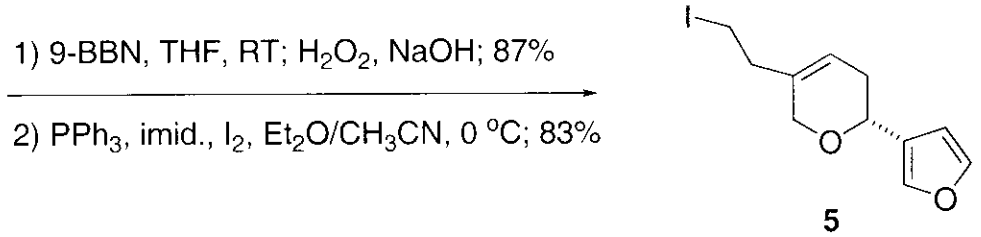




11

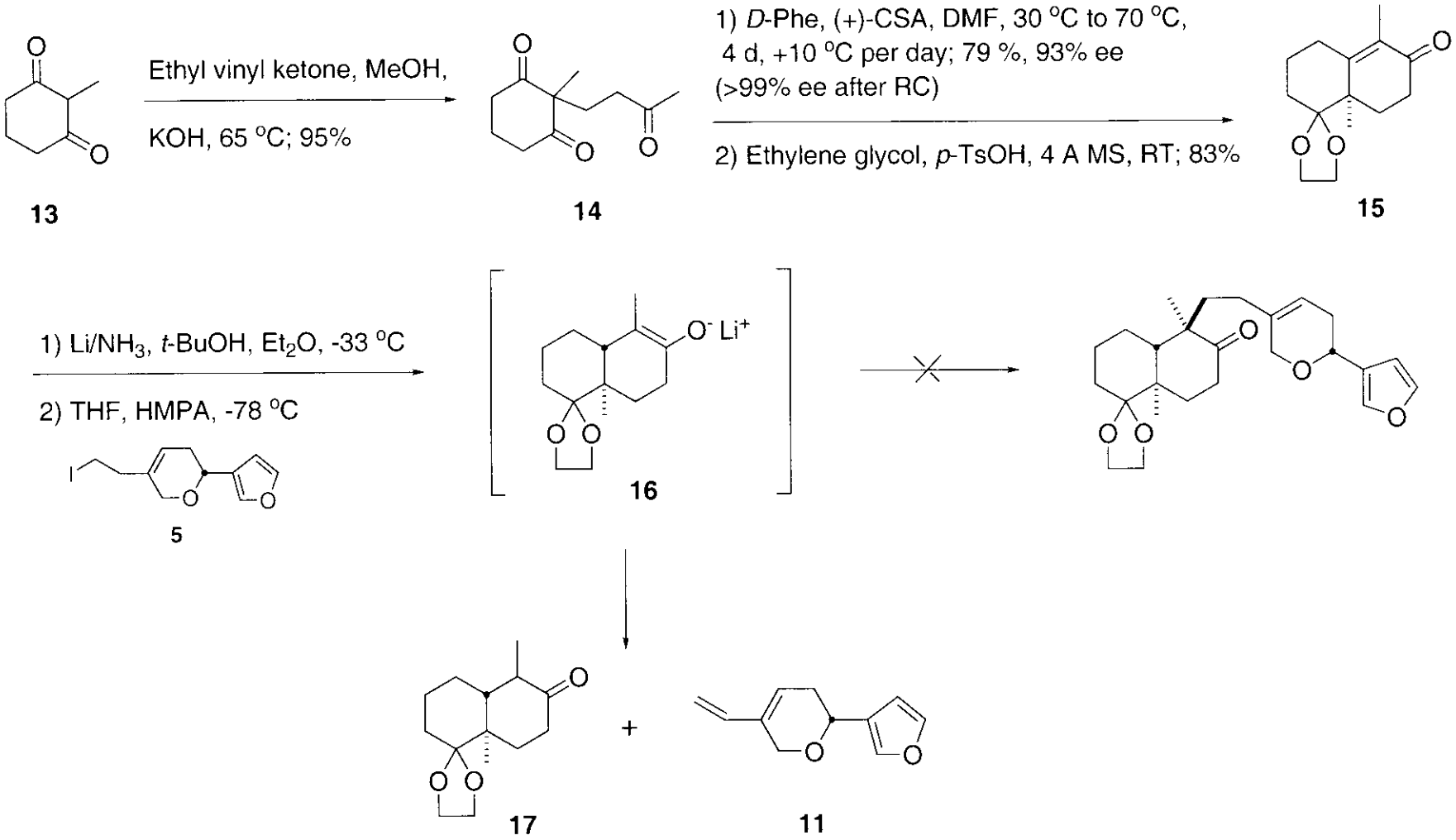
Intramolecular Enyne Ring-Closing Metathesis



5

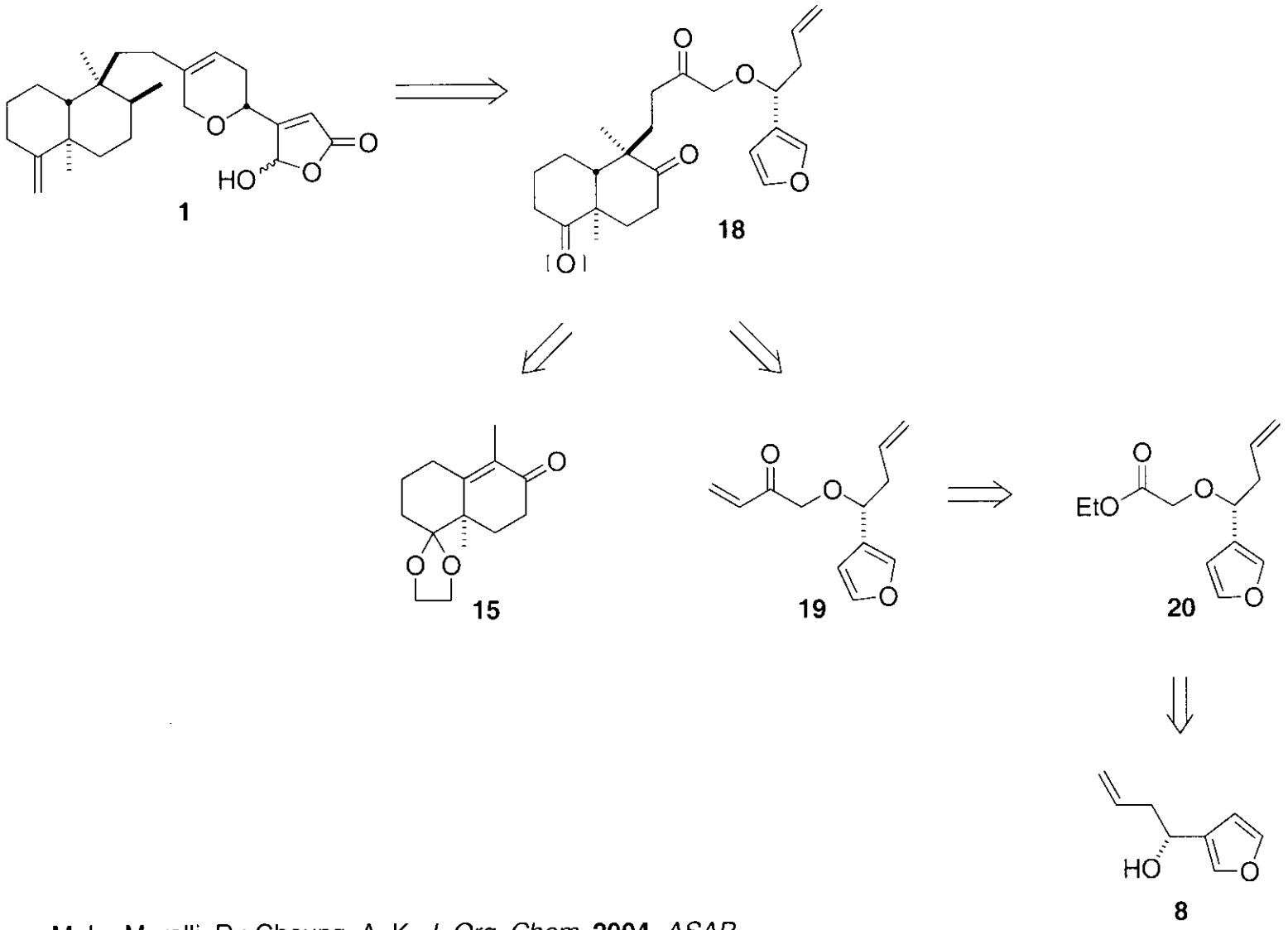
Snapper, M. L.; Murelli, R.; Cheung, A. K. *J. Org. Chem.* **2004**, *ASAP*

Synthesis of the Decalin Moiety and Investigation of the Key Reductive Coupling Reaction



Snapper, M. L.; Murelli, R.; Cheung, A. K. *J. Org. Chem.* **2004**, *ASAP*

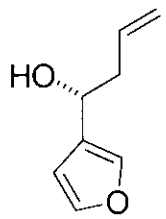
Revised Retrosynthetic Analysis of (+)-Cacospongionolide B



1 18 15 19 20 8

Snapper, M. L.; Murelli, R.; Cheung, A. K. *J. Org. Chem.* **2004**, *ASAP*

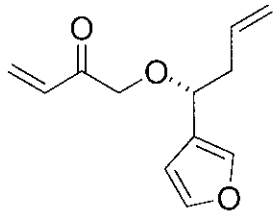
Synthesis of (+)-Cacospongionolide B Via A Key Michael Addition



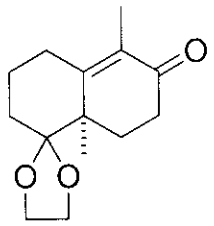
8

1) NaH, THF, 0 °C to RT; $BrCH_2CO_2C_2H_5$, 0 °C; 84% at 76% conversion
2) LiOH, MeOH/H_2O (3:1), RT

3) MeO(Me)NH HCl, DIC, DMAP, Et_3N, CH_2Cl_2, 0 °C to RT; 86% (2 steps)
4) vinyl Grignard, THF, -78 °C to 0 °C; 83%



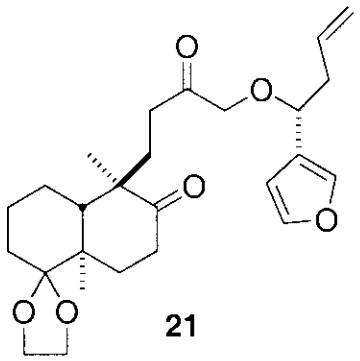
19



15

1) Li/NH_3, *t*-BuOH, Et_2O, -33 °C

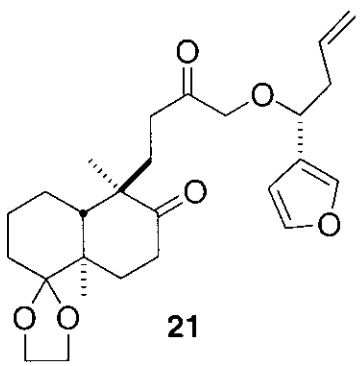
2) Et_2O, -78 °C, **19**; 70%



21

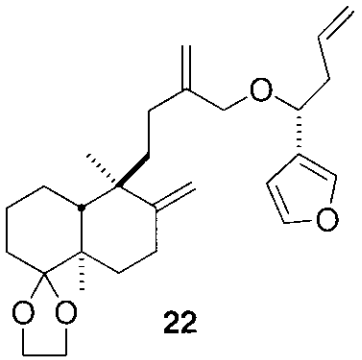
Snapper, M. L.; Murelli, R.; Cheung, A. K. *J. Org. Chem.* **2004**, *ASAP*

Completion of the Total Synthesis of (+)-Cacospongionolide B



21

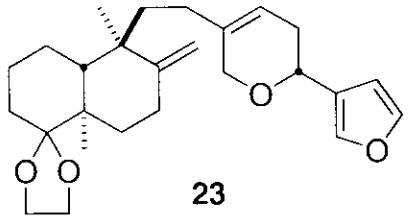
$Ph_3P{=}CH_2$, DMSO, 75 °C; 60%



22

$Cy_3P(iMes)(Cl)_2Ru{=}CHPh$

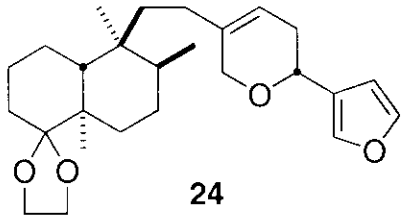
CH_2Cl_2, RT; 91%



23

Rh(I)/(***R***)-BINAP, 20 mol%, H_2 (3 atm),

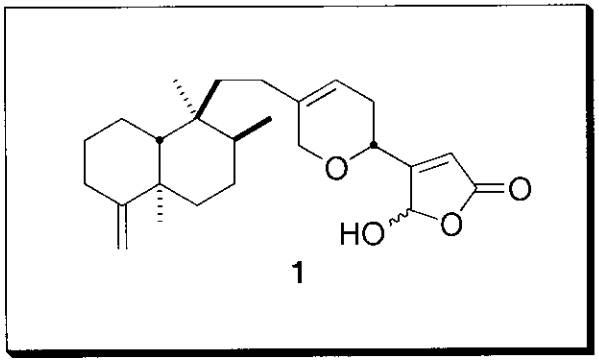
CH_2Cl_2, 30 °C; 91% at 76% conversion, *dr*-3.3:1



24

1) 1 N HCl/THF (1:2), RT; 90%
2) $Ph_3P{=}CH_2$, DMSO, 75 °C; 84%

3) $^1O_2$, rose bengal, *i*-Pr_2NEt, 150 W tungsten lamp, CH_2Cl_2, -78 °C; 69%



1

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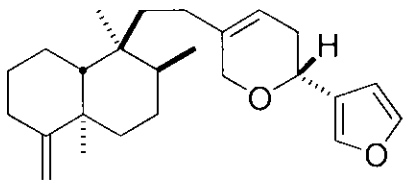
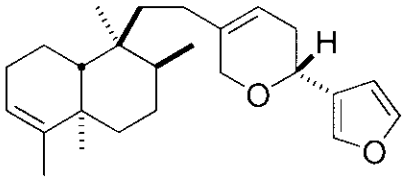
Total Synthesis of (+)-Cacospongionolide E



25

$RhCl_3\ H_2O$, EtOH/$CHCl_3$,

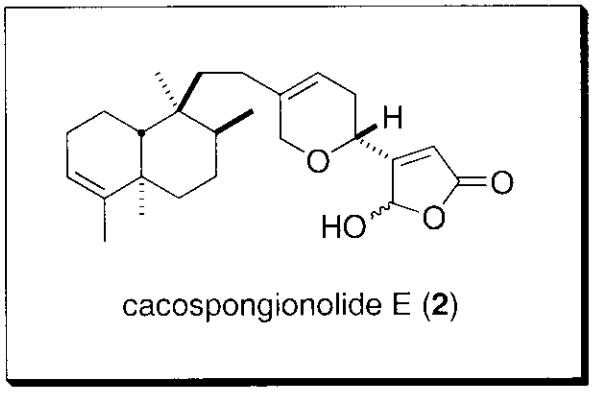
70 °C; 70%



26

$^1O_2$, rose bengal, *i*-Pr_2NEt

CH_2Cl_2, -78 °C; 54%



cacospongionolide E (**2**)

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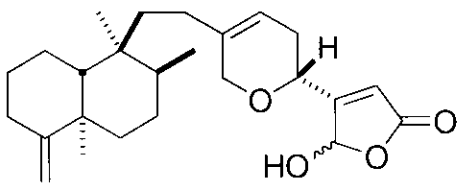
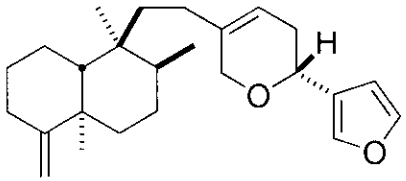
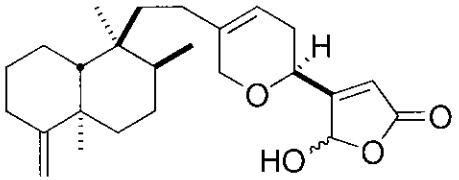
Natural and Unnatural Compounds Screened Against *s*PLA$_2$



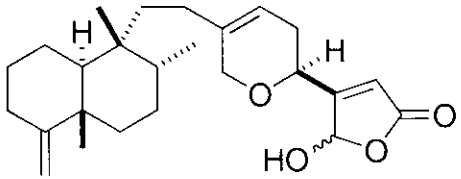
(+)-cacospongionolide B (**1**)



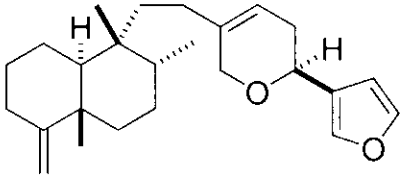
(+)-furan (**25**)



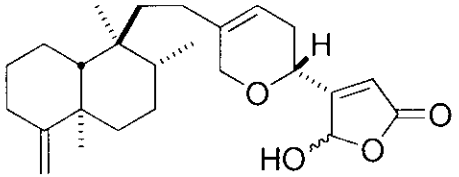
27



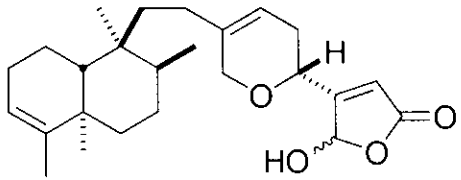
(-)-cacospongionolide B (**1**)



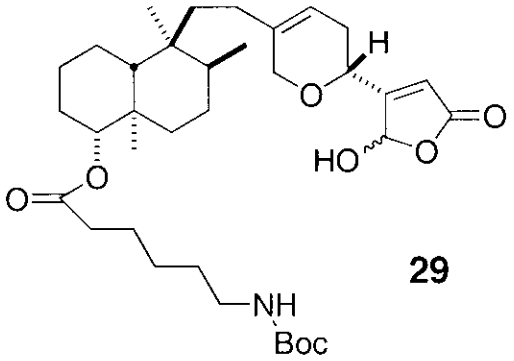
(-)-furan (**25**)



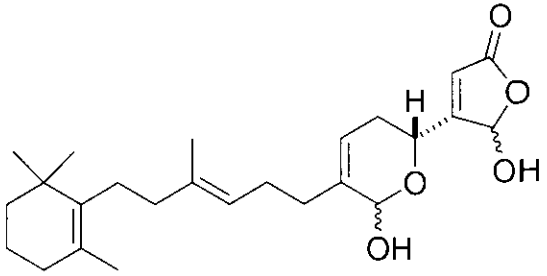
28



(+)-cacospongionolide E (**2**)



29



manoalide (**3**)

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Inhibition of Bee Venom *s*PLA$_2$

inhibitor	IC_{50} (μM)
manoalide (3)	38 (±3)
(+)-cacospongionolide B (1)	49 (±9)
(−)-cacospongionolide B (1)	114 (±7)
(+)-furan (25)	72 (±4)
(−)-furan (25)	167 (±32)
Cacospongionolide E (2)	27 (±7)
(*S*)-dihydropyran (27)	19 (±7)
C8-methyl diastereomer (28)	29 (±13)
C4-linker (29)	44 (±21)

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Inhibition of Bee Venom *s*PLA$_2$

(1) (+)-cacospongionolide B (natural)-2 times more potent than (-)-cacospongionolide B (unnatural): inhibition-enantiospecific

(2) (+)-25-greater potency than (-)-cacospongionolide B

(3) 27-most potent inhibitor (inversion of stereocenter on dihydropyran ring)

(4) diastereomeric methyl on decalin of 28-no adverse effect

(5) modification to C4 region (29)-problematic

(6) internal olefin of decalin of cacospongionolide E (2) -linked to more potent inhibition

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