Christian Gloor
Journal Club Group Meeting
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Enantioselective Total Synthesis of Hyperforin

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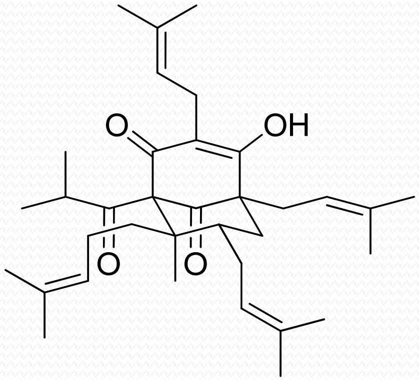
JACS **2013**, *135*, 644-647

Outline

- Isolation, structure and biological activity
- Biosynthesis proposal
- Synthesis of the Shair group
- Conclusion

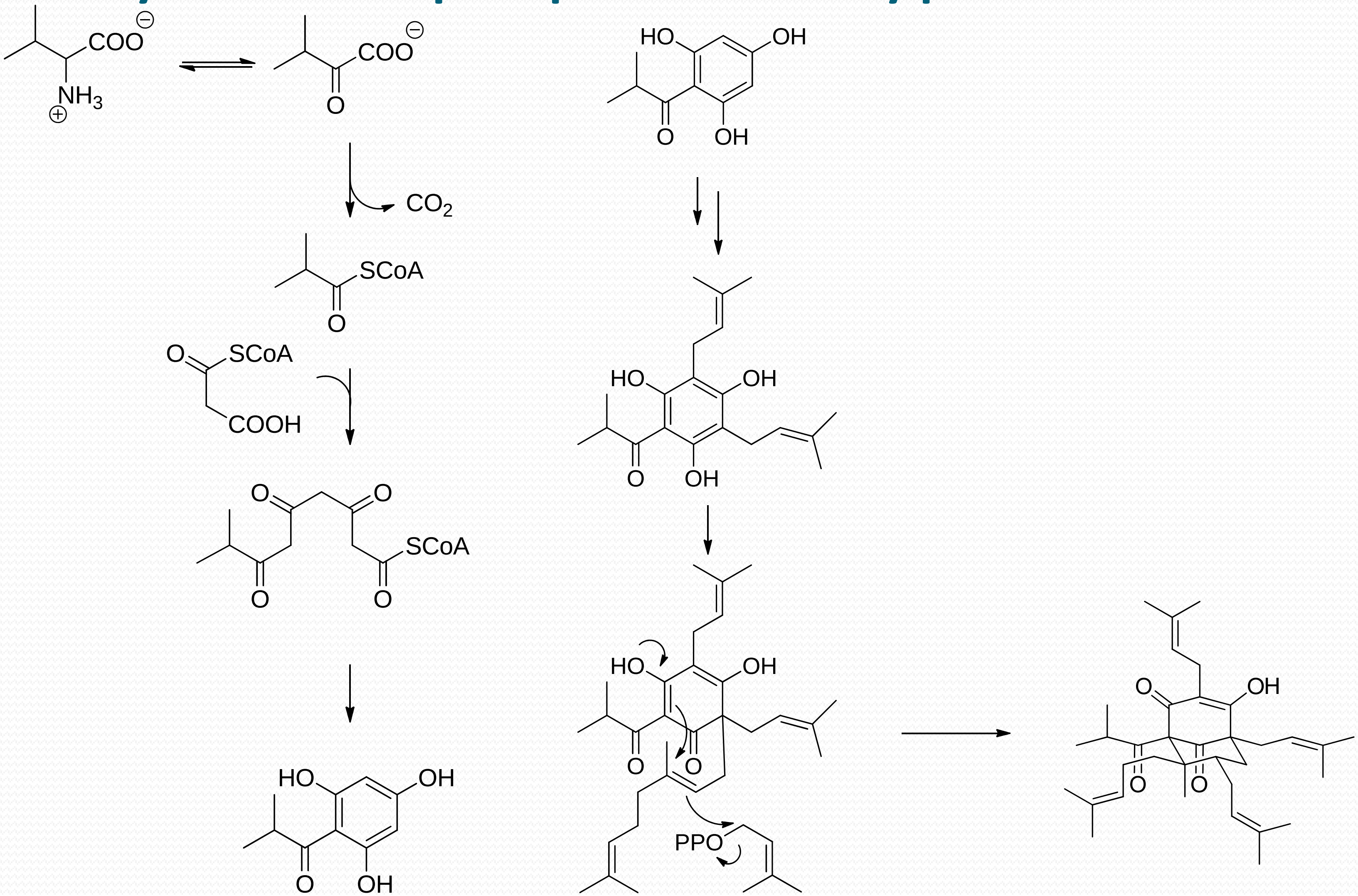
Isolation, Structure and biological activity

- Hyperforin was first isolated from the Saint John's wort in 1971



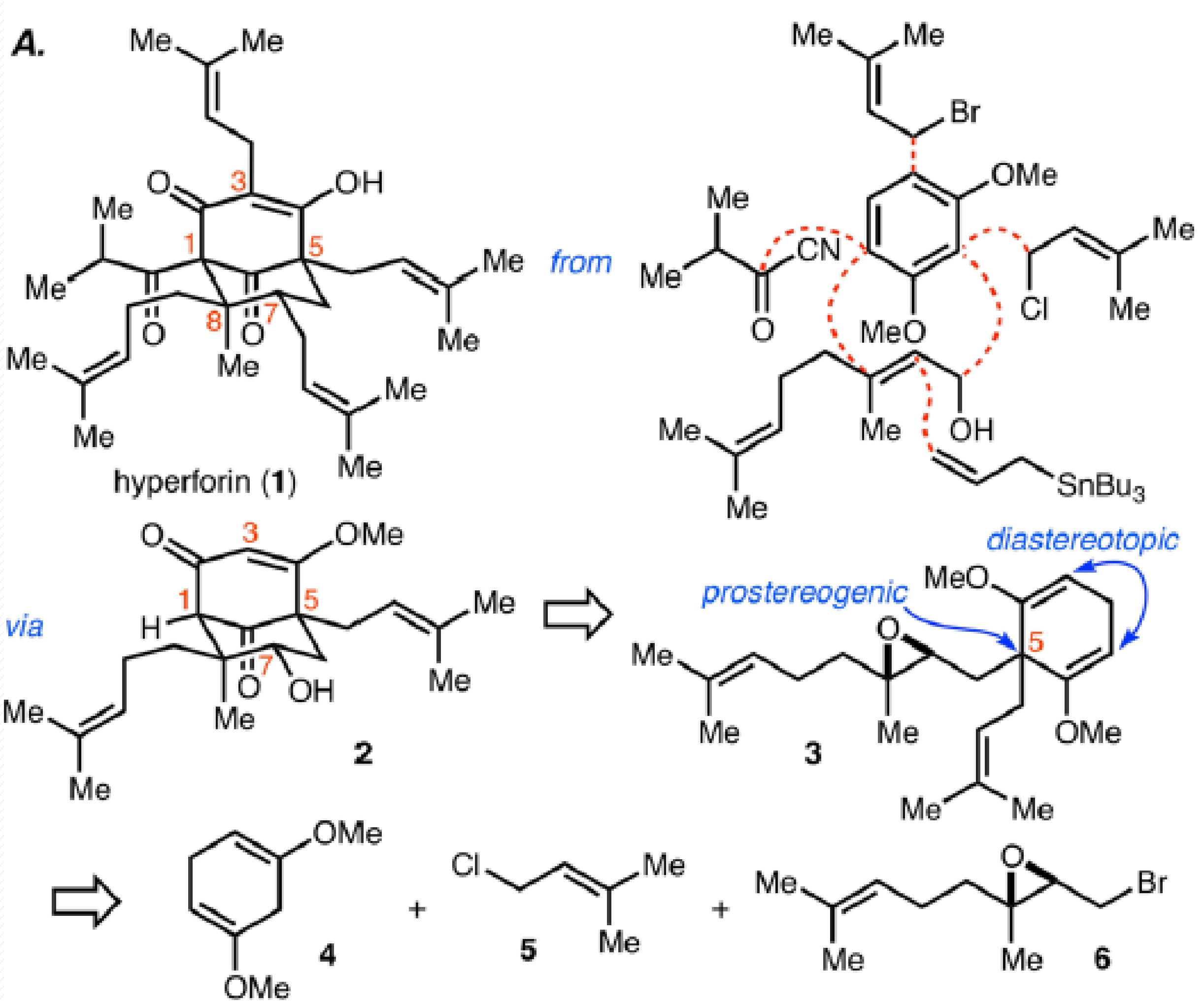
- Belongs structurally to the polycyclic polyprenylated acylphloroglucinol.
- Highly oxidized bicyclo[3.3.1]nonane core, substituted with terpenoid side chains
- Considered to be the constituent of the medicinal herb responsible for its antidepressant activity.

Biosynthesis proposal of hyperforin

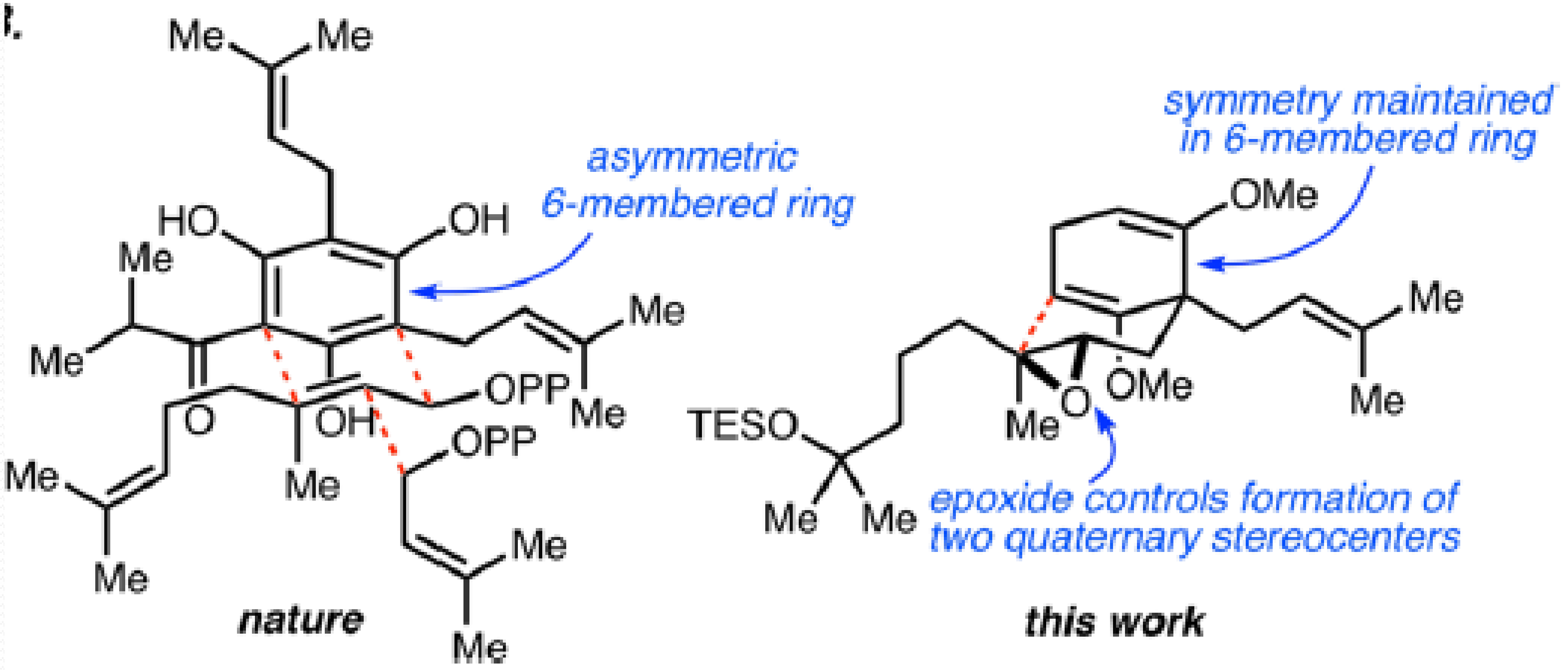


Adam, P.; Arigoni, D.; Bacher, A.;Eisenreich, W. *J. Med. Chem.* **2002**, *45*, 4786

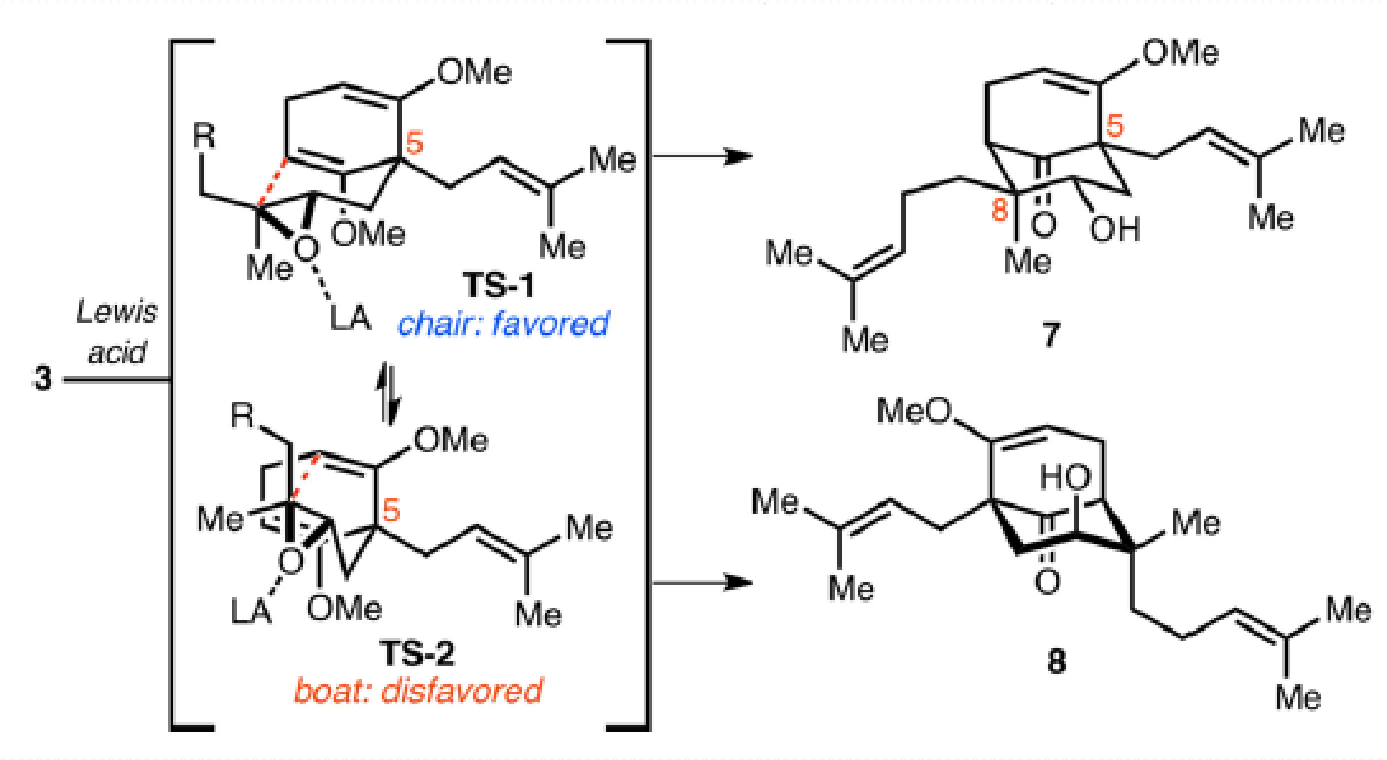
Retrosynthetic approach of Shair's group



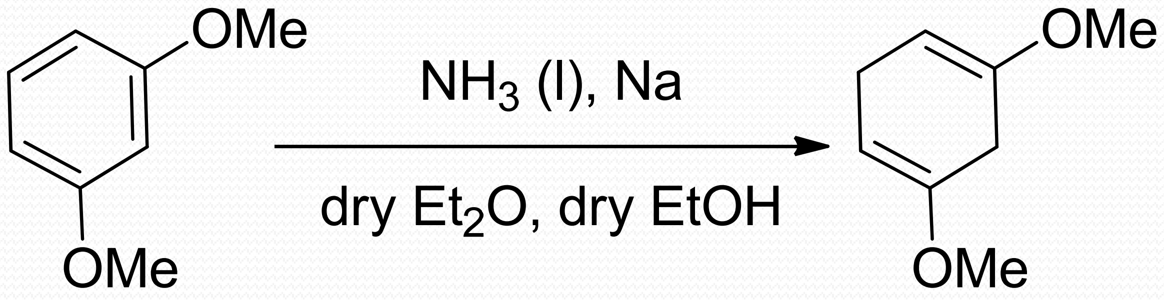
Retrosynthetic approach of Shair's group



Transition state for the cyclisation



Synthesis of Shair's group



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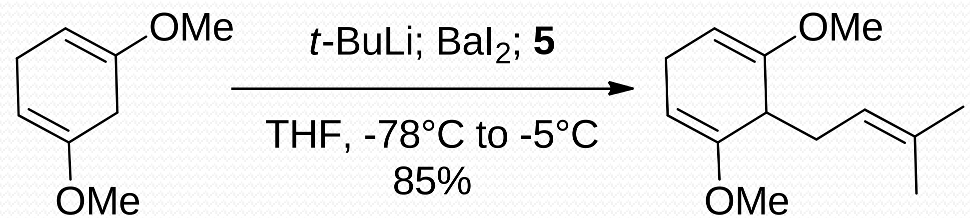
Piers, E.; Grierson, J. R. *J. Org. Chem.* **1977**, *42*, 3755

Synthesis of Shair's group



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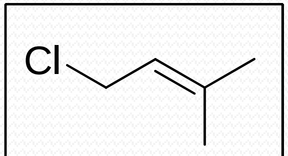

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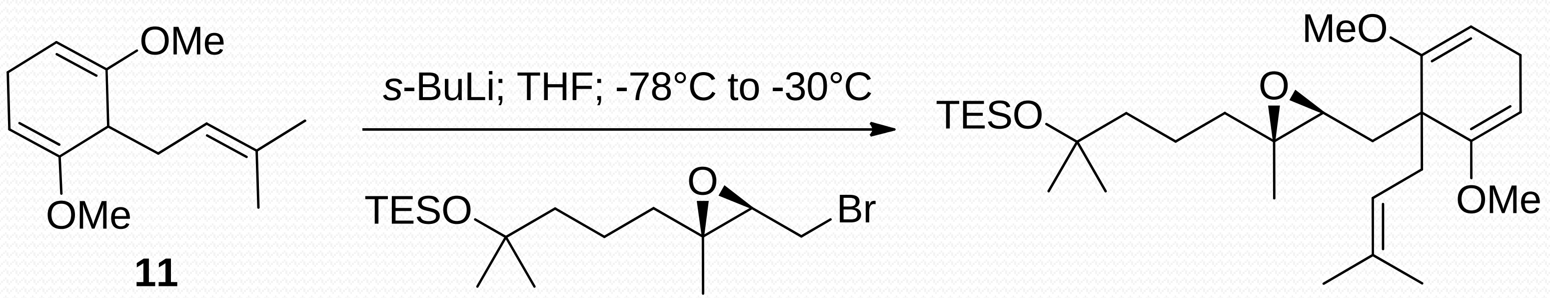

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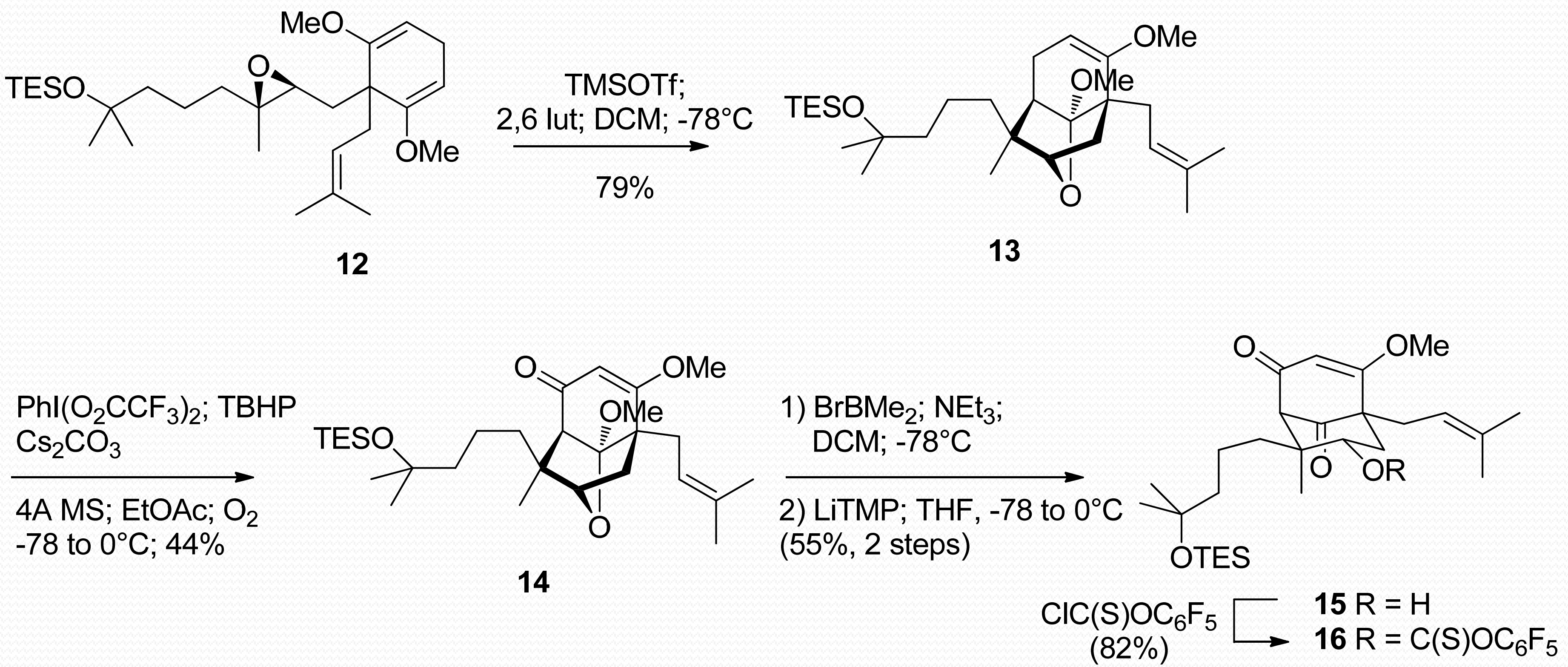
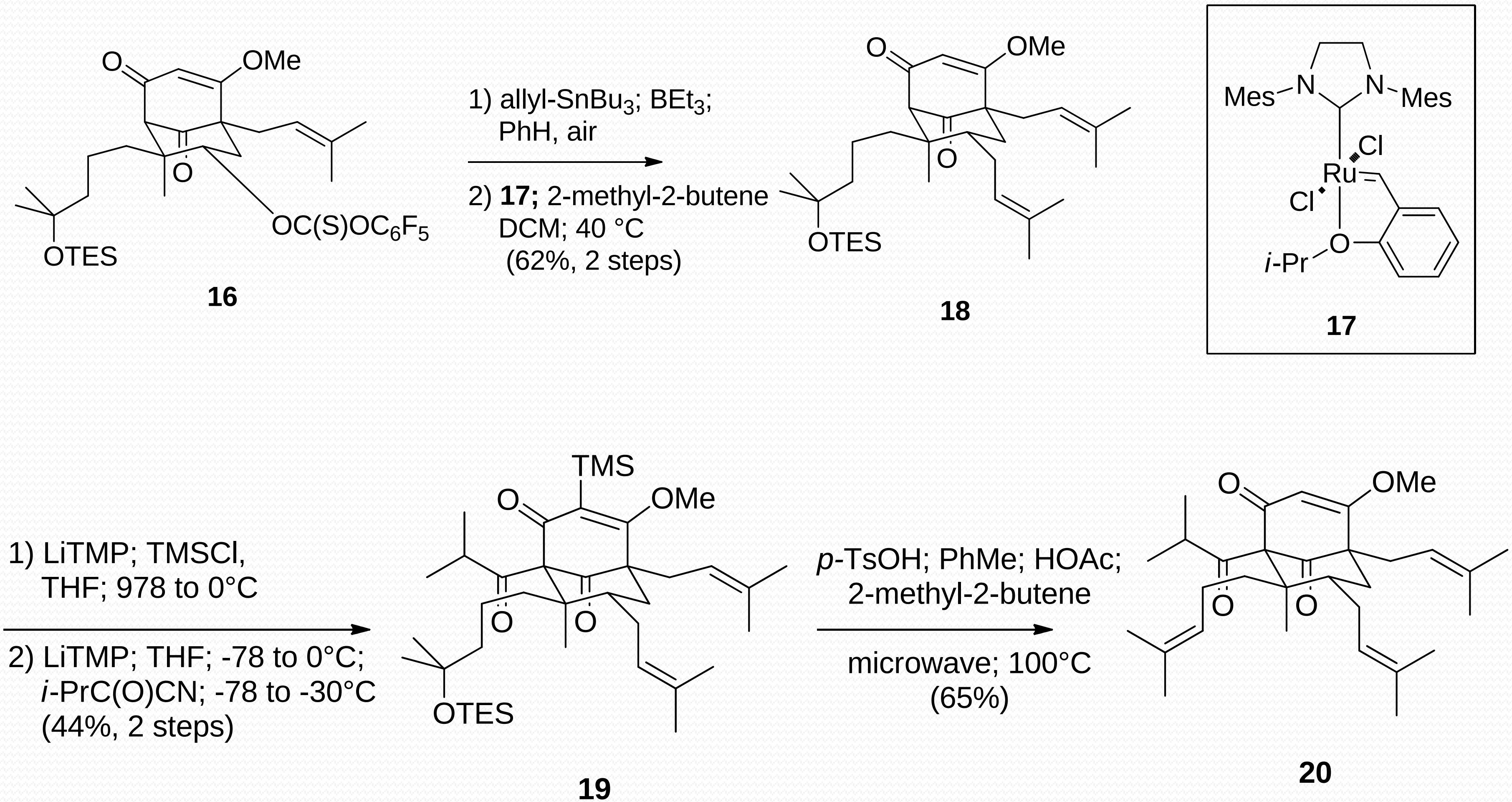
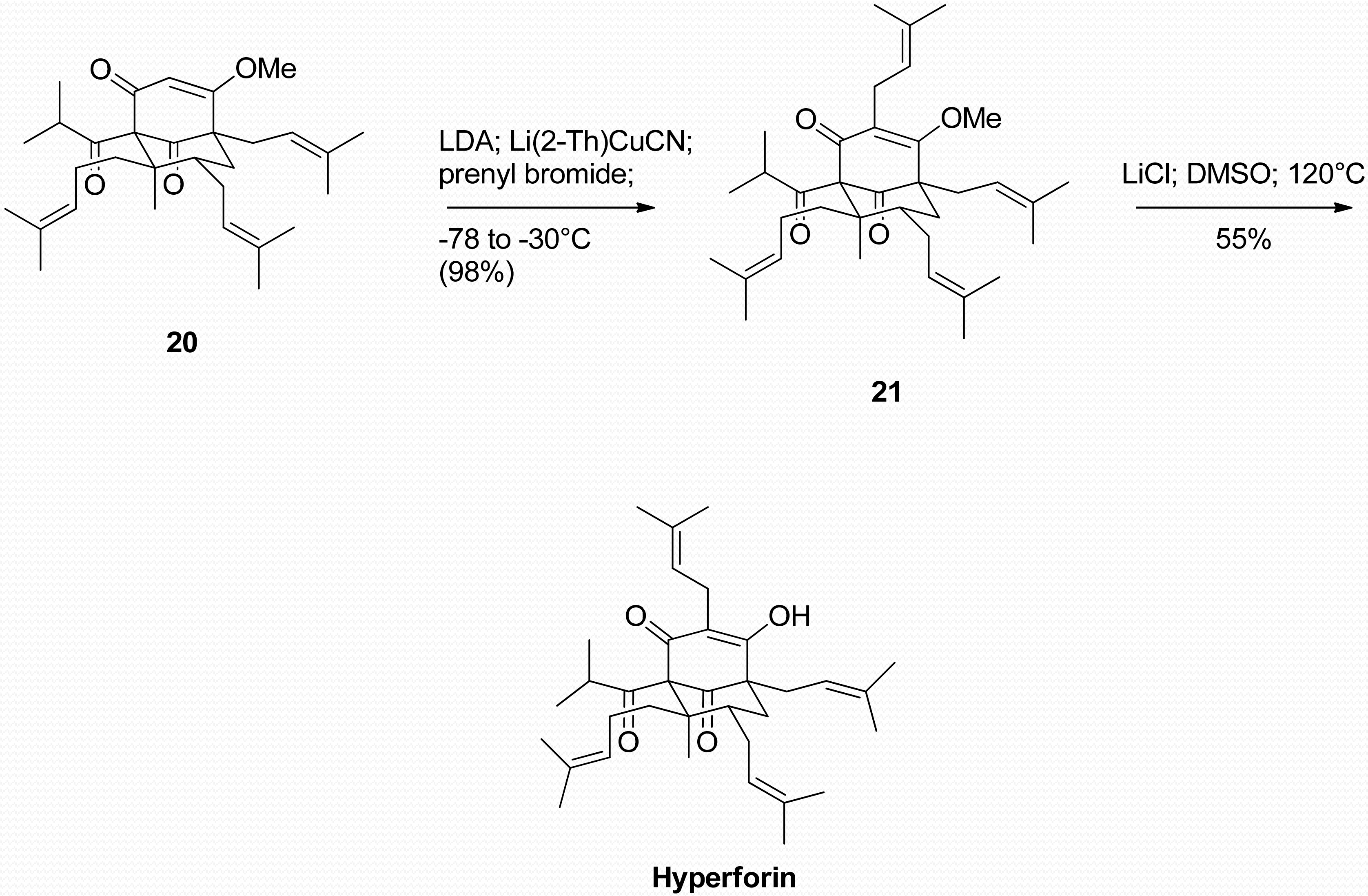
Synthesis of Shair's group



Synthesis of Shair's group



Synthesis of Shair's group



Conclusion

-Development of a short and enantioselective synthesis of hyperforin (18 steps longest linear sequence starting from geraniol).

-Overall yield of 0.76% for hyperforin

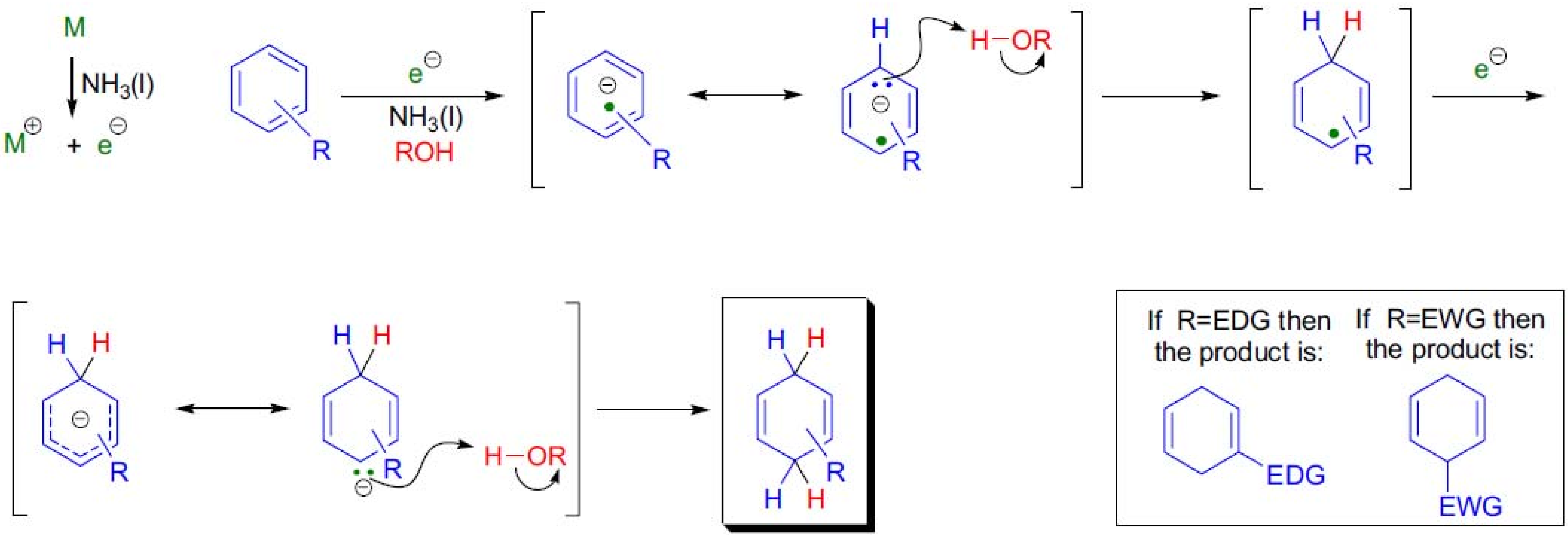
-Highly scalable (up to 40 mg were prepared)

-Utilisation of latent symmetry elements to quickly access the bicyclic core of hyperforin and to set the two quarternary stereocenters

-Practical route to create diverse hyperforin analogues for SAR studies

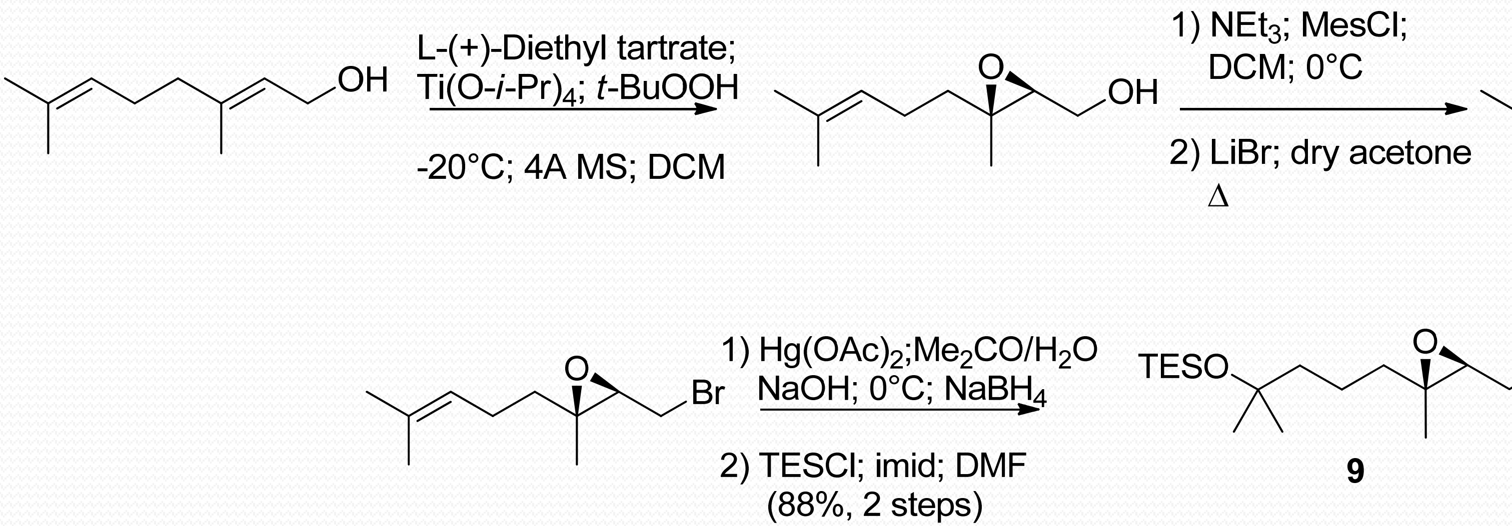
Thank you for your attention

Birch reduction



Kürti, L.; Czakó, B. Strategic Applications of named reactions in organic synthesis, Elsevier Inc. London **2005**, p. 308

Synthesis of **9**

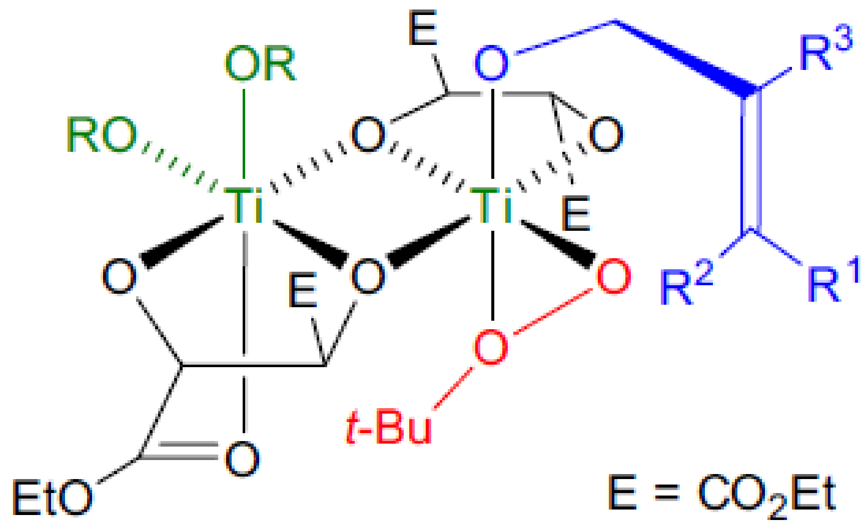


Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922

Gash, R. C.; MacCorquodale, F.; Walton J. C. *Tetrahedron* **1989**, *45*, 5531

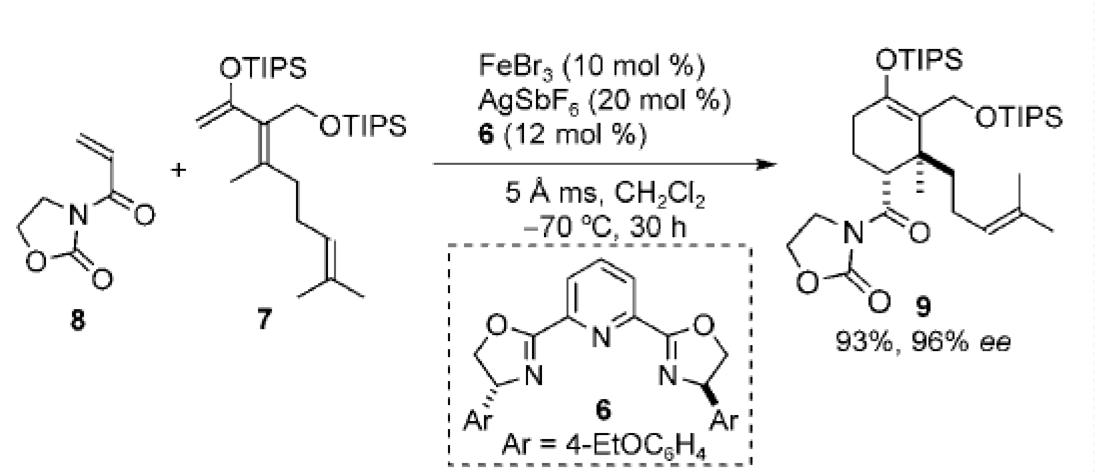
Sharpless epoxidation

Transition state of epoxidation:



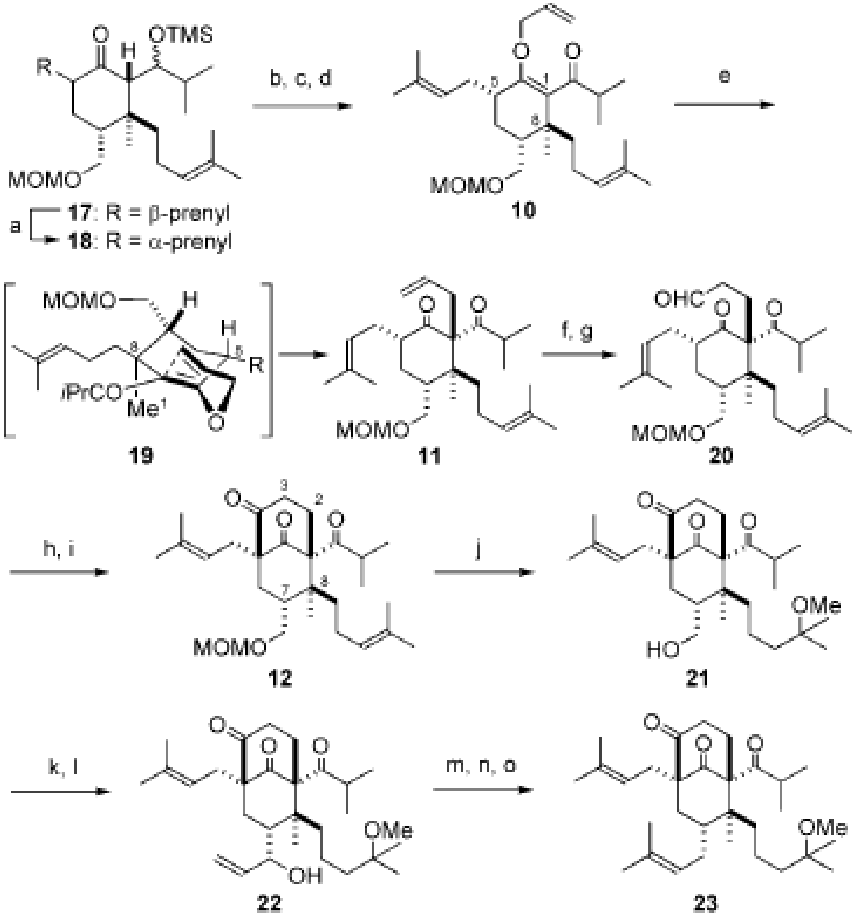
Kürti, L.; Czakó, B. Strategic Applications of named reactions in organic synthesis, Elsevier Inc. London **2005**, p. 308

Previous synthesis



Shibasaki, M. et al. *Angew. Chem. Int. Ed.* **2010**, *49*, 1103

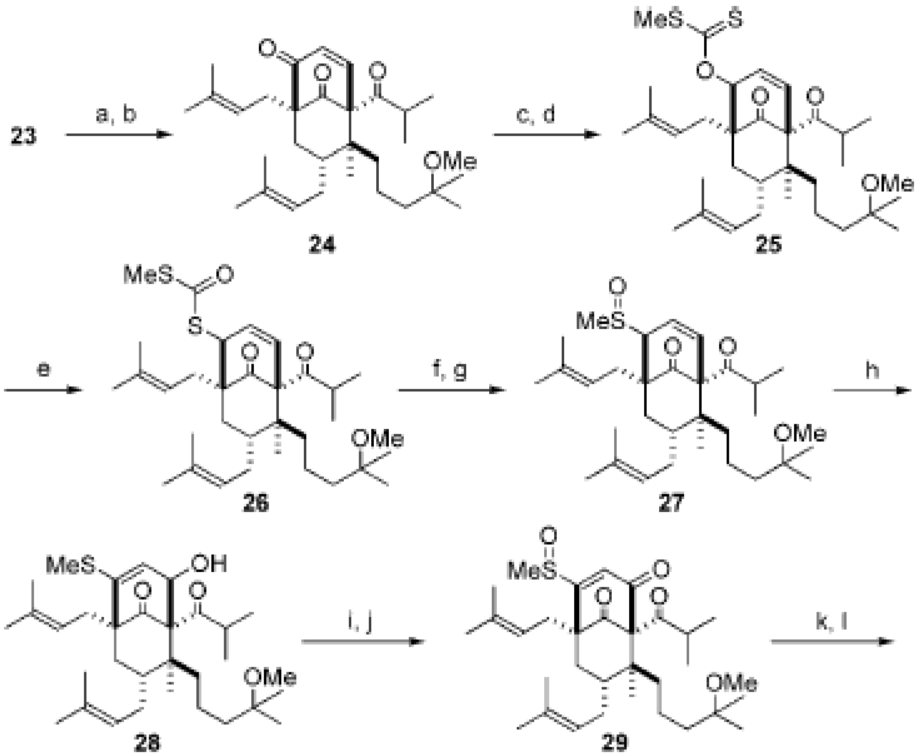
Previous synthesis

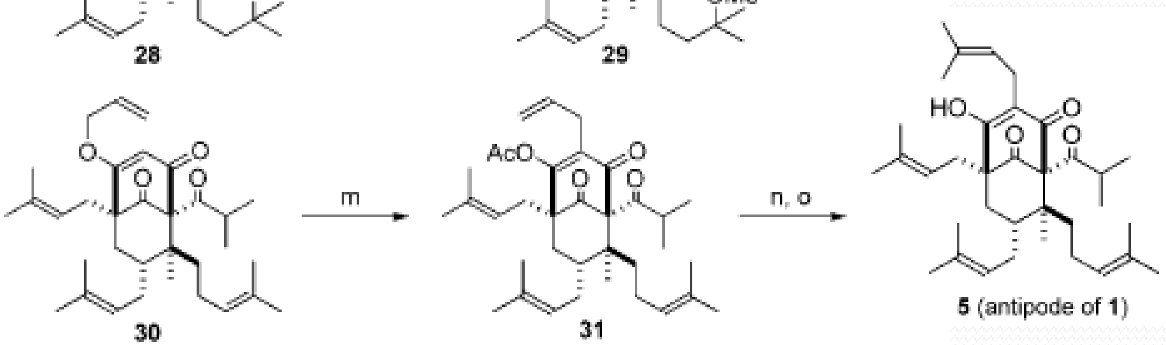


Scheme 4. Construction of the bicyclic core. Reagents and conditions: a) LDA, THF; aq NH_4Cl, 88% (d.r. > 33:1). b) HF·py, py, THF. c) DMP, CH_2Cl_2, 96% (over 2 steps). d) NaHMDS, allyl bromide, HMPA, THF, > 99%. e) toluene, *N*,*N*-diethylaniline, 170°C, > 99% (d.r. = 12:1). f) $(Sia)_2BH$, THF; aq H_2O_2, aq NaOH, EtOH, 81%. g) DMP, CH_2Cl_2, 91%. h) NaOEt, EtOH. i) DMP, CH_2Cl_2, 86% (over 2 steps). j) (+)-CSA, MeOH, 66% (over 3 cycles). k) $(COCl)_2$, DMSO, CH_2Cl_2; NEt_3, 95%. l) vinylmagnesium bromide, THF, 92% (d.r. > 33:1). m) Ac_2O, DMAP, iPr_2EtN, CH_2Cl_2, 98%. n) $[Pd(PPh_3)_4]$ (20 mol%), HCO_2NH_4, toluene, 95%. o) Hoveyda–Grubbs 2nd generation cat. (15 mol%), 2-methyl-2-butene, CH_2Cl_2, > 99%. DMP = Dess–Martin periodinane, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, CSA = camphorsulfonic acid, DMAP = 4-dimethylaminopyridine.

Shibasaki, M. et al. *Angew. Chem. Int. Ed.* **2010**, *49*, 1103

Previous synthesis





Scheme 5. Completion of the total synthesis. Reagents and conditions: a) TMSCl, NEt_3, DMAP, CH_2Cl_2, 84%. b) $Pd(OAc)_2$, DMSO, O_2, >99%. c) $NaBH_4$, MeOH, 95% (d.r.>33:1). d) CS_2, NaH, THF; MeI, >99%. e) toluene, 150°C. f) EtSLi, THF; MeI, NEt_3, 98% (over 2 steps). g) $NaBO_3 \cdot 4H_2O$, AcOH (d.r.=1.3:1), 95%. h) TFAA, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, −40°C; H_2O, 65% (d.r.>33:1). i) H_2O_2, HFIP, 87% (d.r.=9:1). j) DMP, CH_2Cl_2, 86%. k) Amberlyst 15 DRY, toluene, 55%. l) LiH, allyl alcohol, 67%. m) $[Pd_2(dba)_3]$ $CHCl_3$ (10 mol%), (*S*)-tol-binap (20 mol%), THF; Ac_2O, pyridine, 50%. n) Hoveyda–Grubbs 2nd generation cat. (15 mol%), 2-methyl-2-butene, CH_2Cl_2, 34%. o) K_2CO_3, MeOH, 94%. dba = *trans,trans*-dibenzylideneacetone, binap = 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl.

Shibasaki, M. et al. *Angew. Chem. Int. Ed.* **2010**, *49*, 1103