

Total Synthesis of Auripyrones A and B
and
Determination of the
Absolute Configuration of Auripyrone B

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Angew. Chem. Int. Ed. ASAP article

Nilesh Zaware

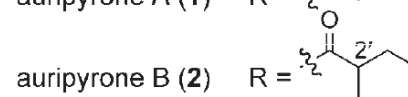
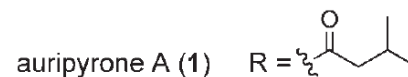
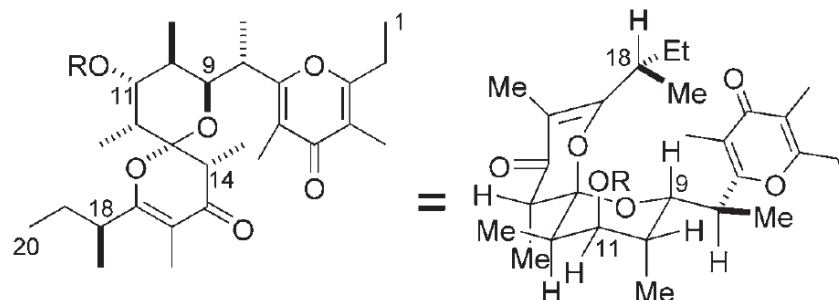
Current Literature

6th March 2010

Isolation and Activity of Auripyrones

- In 1996, auripyrones A (**1**) and B (**2**) were isolated from the sea hare *Dolabella auricularia* by Suenaga et al.

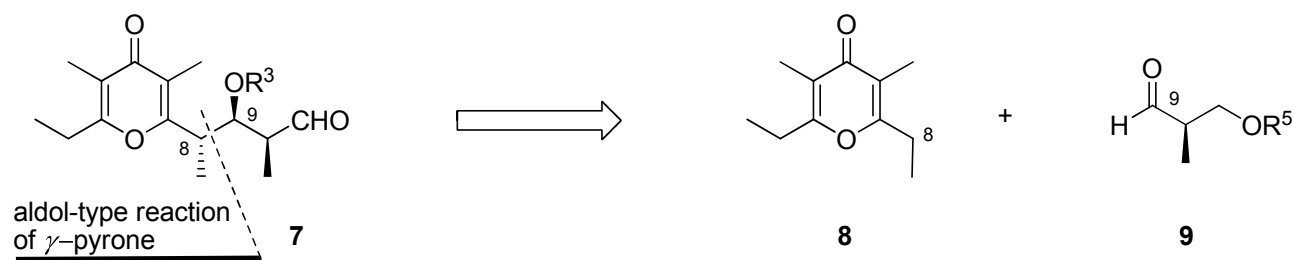
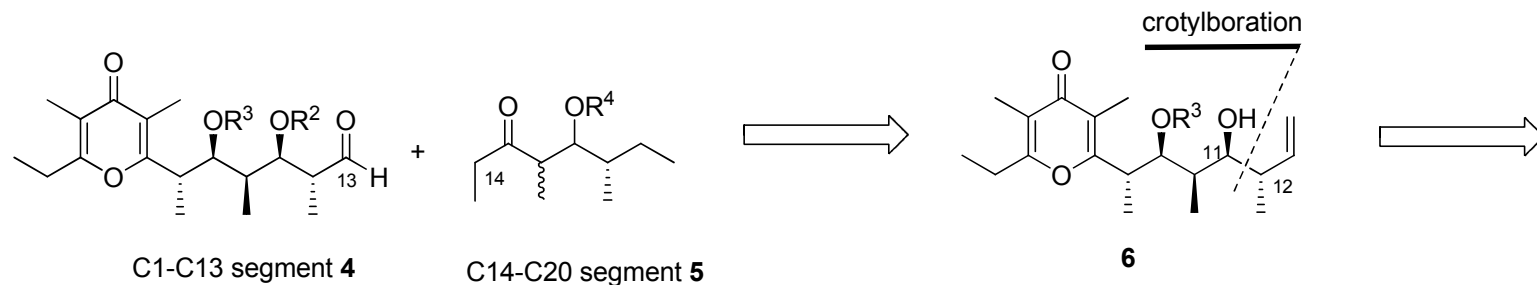
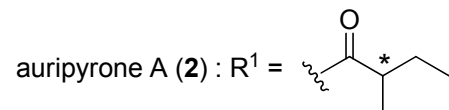
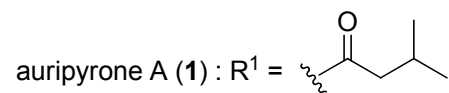
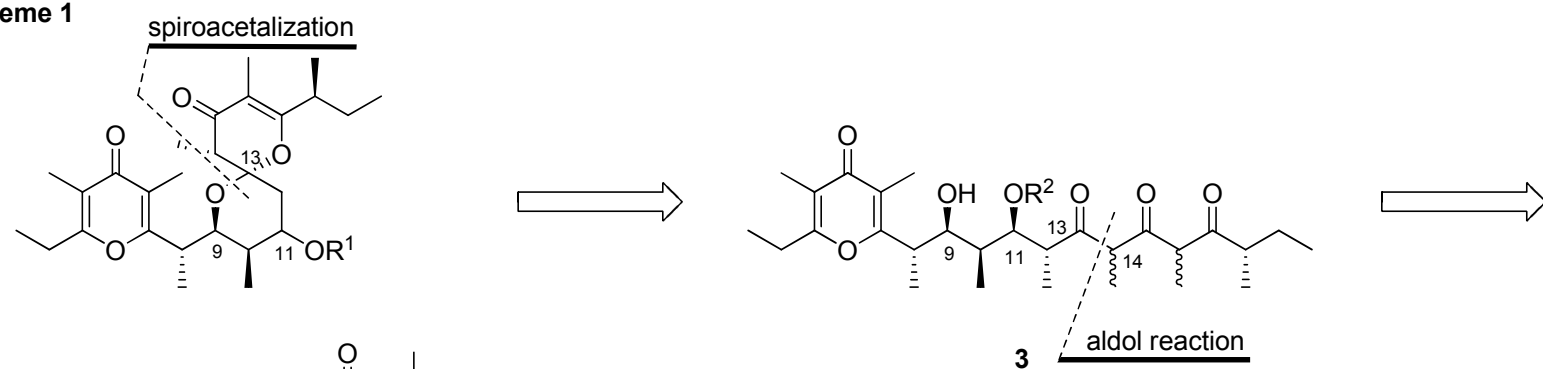
Tet. Lett. **1996**, 37, 5151-5154.



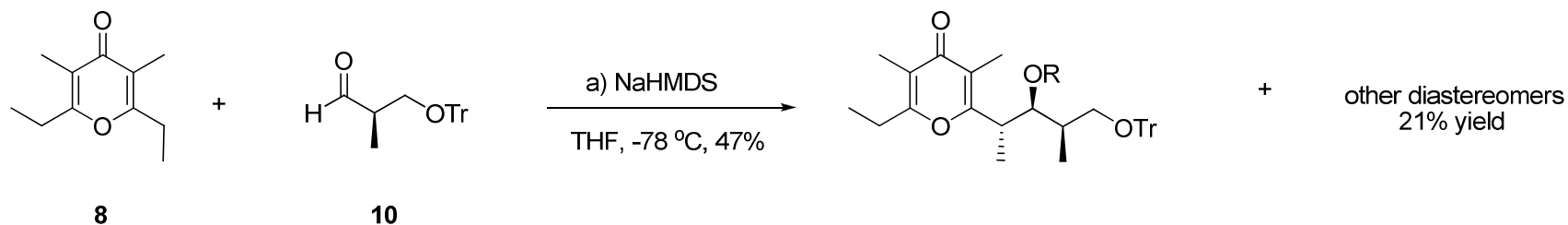
- Compounds **1** and **2** exhibit moderate cytotoxicity against HeLa S3 cells
 - Auripyrene A : $IC_{50} = 0.26 \mu\text{g/mL}$
 - Auripyrene B : $IC_{50} = 0.48 \mu\text{g/mL}$

- Structure indicates a spiroacetal dihydropyrone core tethered to a γ -pyrone ring
- Configuration at C2' of Auripyrene B was not known
- Reported syntheses of Auripyrones –
 - Lister et al. *Angew. Chem. Int. Ed.* **2006**, 45, 2560-2564 (Auripyrene A)
 - Jung et al. *Angew. Chem. Int. Ed.* **2009**, 48, 8766-8769 (Auripyrene A)
 - Kigoshi et al. *Angew. Chem. Int. Ed.* ASAP article. (Auripyrene A & B)

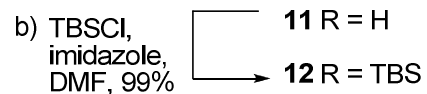
Scheme 1



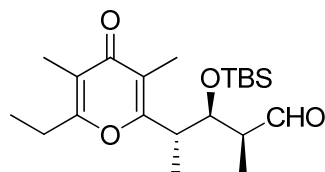
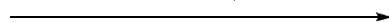
Scheme 2



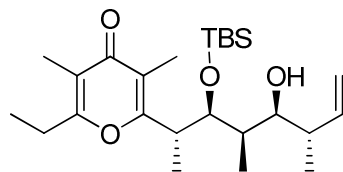
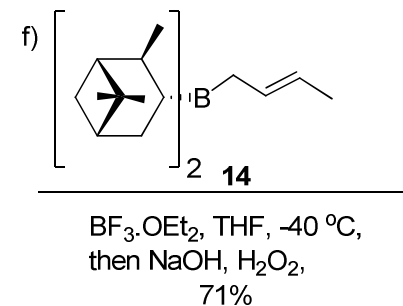
Tet. Lett. **2009**, *50*, 325-328



- c) HCO₂H, Et₂O, RT
 d) 25% NH₃ aq., MeOH, RT,
 92% yield over 2 steps
 e) (COCl)₂, DMSO, *i*Pr₂NEt, DCM,
 -78 °C then 0 °C, 99%

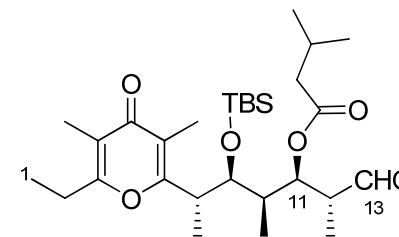


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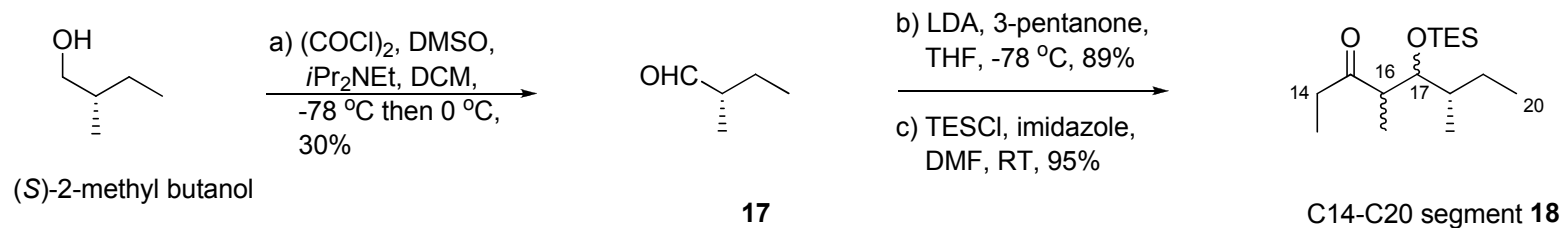
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- g) isovaleryl chloride, DMAP, pyr, RT,
 quantitative yield
 h) OsO₄, NMO, acetone/H₂O (1:1),
 RT, 90% yield
 i) NaIO₄, acetone/H₂O (1:1),
 RT, 72% yield

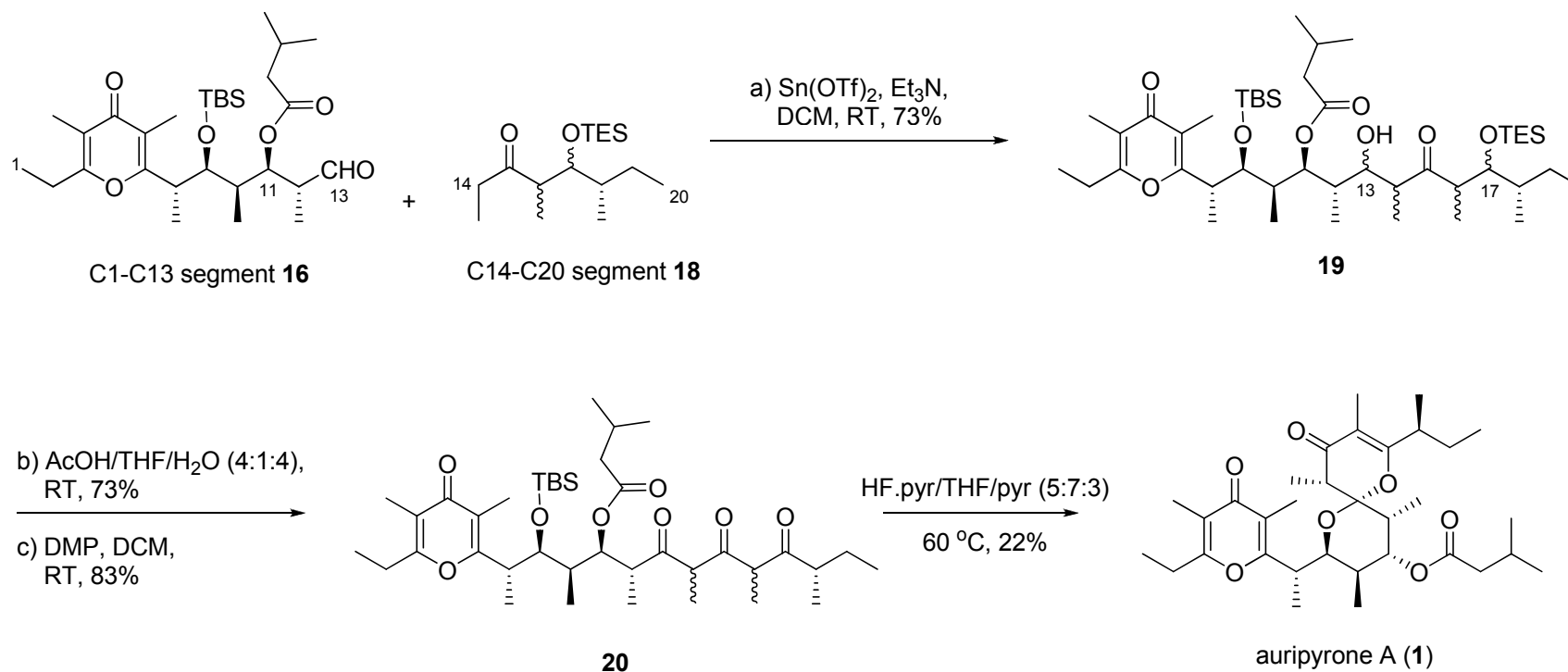


C1-C13 segment **16**

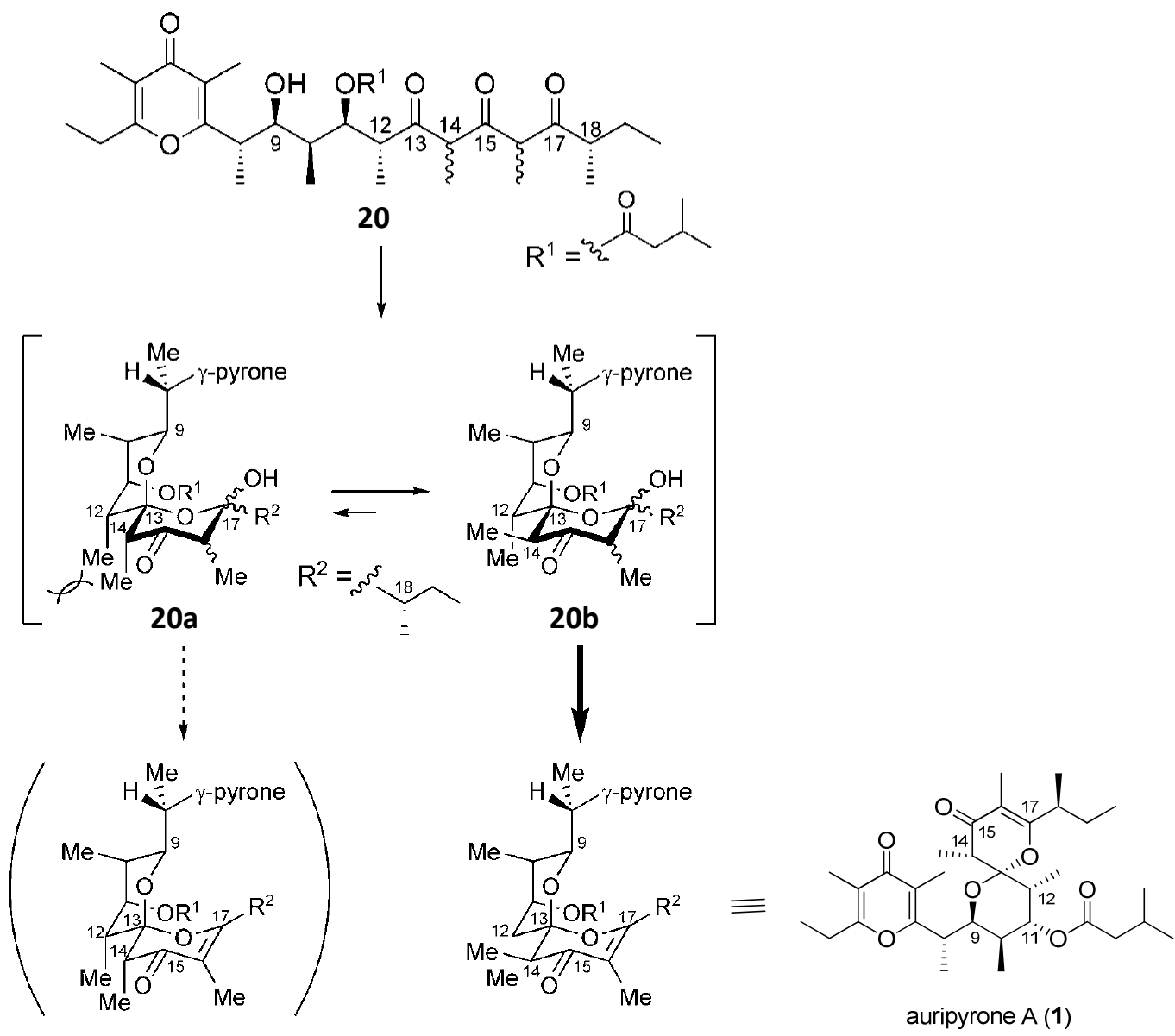
Scheme 3



Scheme 4

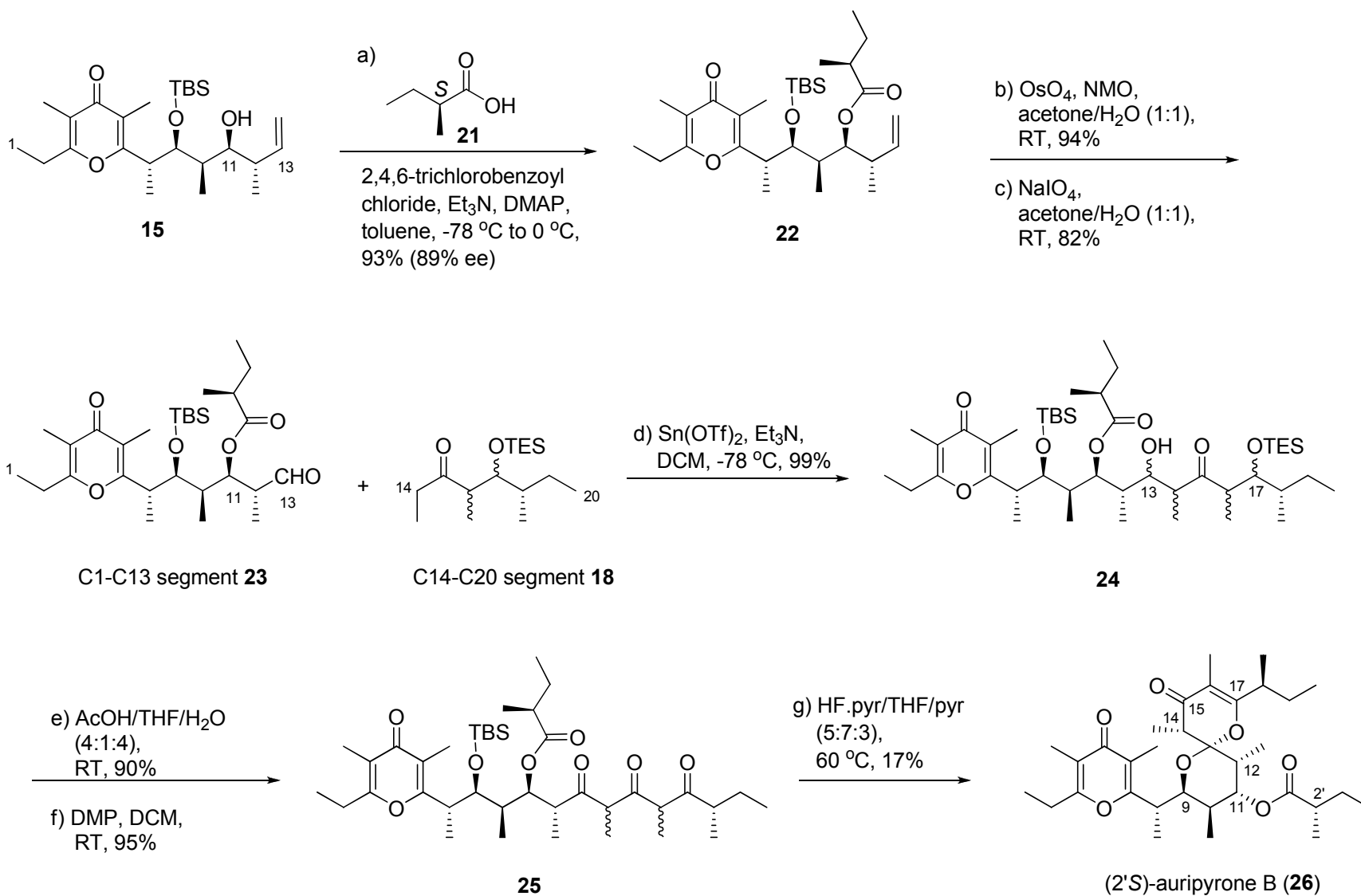


Scheme 5

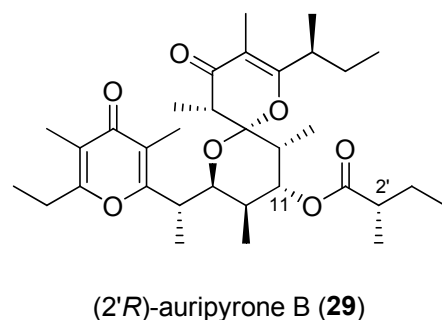
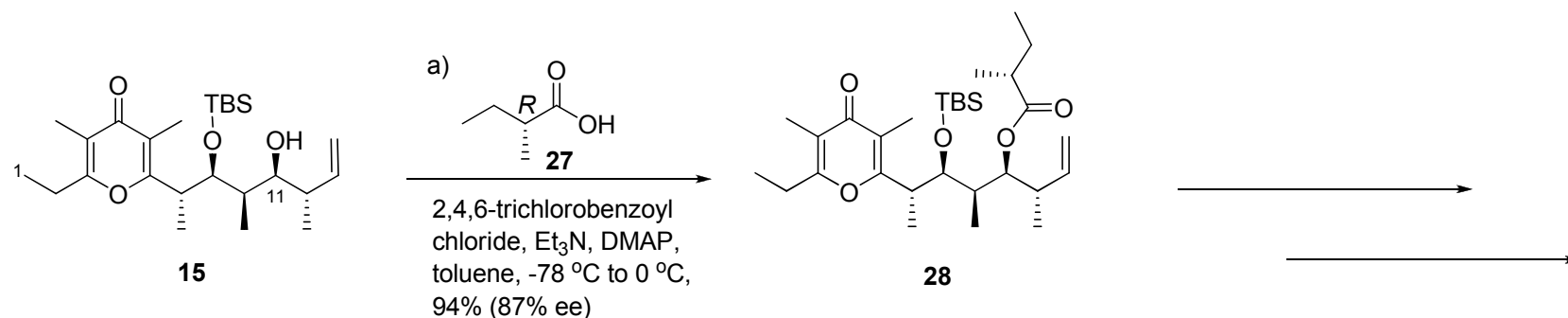


- Deacylation of Auripyrrone A for Auripyrrone B synthesis was unsuccessful

Scheme 6

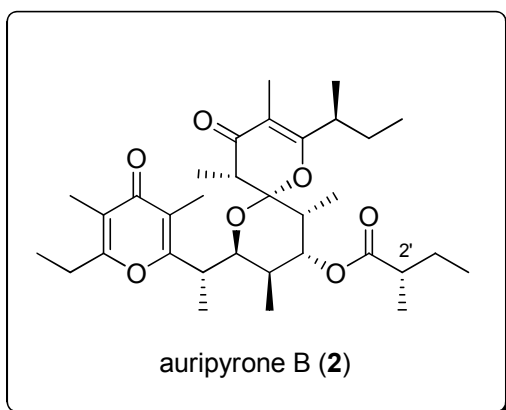


Scheme 7



The chemical shifts of the acyl protons (H4',H5') in (2'*R*)-auripyronone B (**29**) were clearly different from those of the natural auripyronone B (**1**)

The data for (2'*S*)-auripyronone B (**26**) were in good agreement with the natural ptd



Optical rotation of

-synthetic (2'*S*)-auripyronone B: $[\alpha]_D^{26} = +43$ ($c = 0.29$, CHCl₃)

-natural sample: $[\alpha]_D^{26} = +39$ ($c = 0.14$, CHCl₃)

Conclusion

- Total synthesis of Auripyrones A & B achieved; first synthesis of Auripyrone B
 - Auripyrone A (**1**; 2.6% overall yield in 13 steps)
 - Auripyrone B (**2**; 2.8% overall yield in 13 steps)
- Stereochemistry at C2' of Auripyrone B was established
- Key reactions
 - Diastereoselective aldol-type reaction with 2,6-diethyl-3,5-dimethyl-4-pyrone (**8**)
 - Spiroacetalization of triketones (**20**, **25**)
- Absolute configuration of Auripyrone B (**2**) determined