Biomimetic Synthesis of Seven Halenaquinone Meroterpenoids

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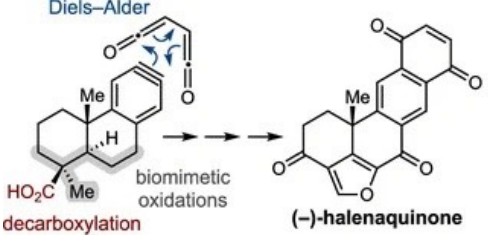


a strained diketofuran embedded within a decalin framework.

podocarpic acid: white solid in rimu timber

isolation on 180 g scale

(+)-13: podocarpic acid

base and triflation reagent critical

NaHMDS, NIS, THF, 0 °C *then* 2-PyNTf$_2$ 82%

14 (X-ray in SI)

n-BuLi, THF, −78 °C *then* aq. HCl; aq. NaOH; Me_2SO_4 89%

15

$LiAlH_4$, THF, 66 °C 97%

16

DDQ, H_2O, CH_2Cl_2, 0 °C [O] 94%

DMP, CH_2Cl_2 *then* conc; Zn, HCl, Et_2O, 35 °C 78%

Clemmensen-based deoxygenation

17

DDQ, H_2O, dioxane, 0 °C 93% [O]

18

a) $LiAlH_4$, THF, 66 °C b) Amberlyst 15, CH_2Cl_2, 40 °C 67% (2 steps)

19

20

CAN, H_2O, MeCN, 0 °C 69% [O]

O_2, *t*-BuOK, *t*-BuOH, 40 °C *then* conc; KOH, EtOH, 78 °C 90% [O]

DMP, MeCN *then* CAN, H_2O, 0 °C 68% [O]

CAN, H_2O, MeCN, 0 °C 69% [O]

(−)-21: *ent*-neopetrosiquinone B (32% overall yield)

22

"diosphenol motif"

(+)-3: *ent*-neopetrosiquinone A (45% overall yield)

(+)-2: *ent*-cyclozonarone (38% overall yield)

Ag_2O, HNO_3, 1,4-dioxane [O]

O_2, PhMe, 90 °C [O]

critical

O_2, Amberlyst 15, PhMe, 90 °C [O]

23

24

tautomerization

25

then filter; conc; *m*-CPBA, CH_2Cl_2; *then* conc; $CHCl_3$, 55 °C 91% [O]

27

a) I_2, DMSO, 40 °C *then* IBX, rt to 40 °C 89% [O] b) CAN, H_2O, MeCN, 0 °C 71% [O]

O_2, Amberlyst 15, PhMe, 90 °C [O] 61% (from **22**)

then conc; NIS, DMSO, 50 °C 71% [O]

CAN, H_2O, MeCN, 0 °C 84% [O]

(−)-5: *ent*-orhalquinone (38% overall yield)

26

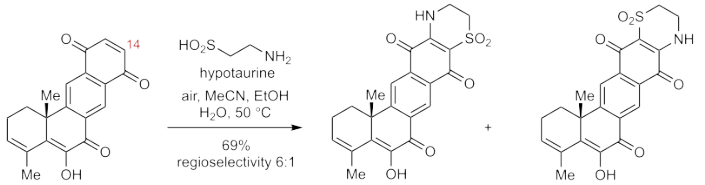
(−)-7: *ent*-xestoquinone (37% overall yield)

(−)-1: *ent*-halenaquinone (36% overall yield)

unstable

low yield

the optimized route to halenaquinone features seven consecutive oxidation events, exemplifying excellent redox economy.



(−)-5: *ent*-orhalquinone

(−)-30: *ent*-xestoquinolide B *revised structure*

31: *ent*-xestoquinolide C *anticipated natural product*

identical NMR

misinterpretation of mass spectral data, as this class of compounds undergoes facile SO 2loss upon ionization

excellent agreement with NMR

structure revision

(+)-9: xestoquinolide A Crews, 1993 *proposed structure*

(+)-5: orhalquinone Bourguet-Kondracki, 2010 δ_H 7.09 ppm

28 xestoquinolide B? Crews, 1993 *proposed structures*

or

29

structure revision

(+)-30: xestoquinolide B *revised structure*

(+)-10: noelaquinone Scheuer, 1998 *proposed structure*

structure revision

(+)-32: 3-ketoadociaquinone B Kingston, 2005