UNIVERSITÄT BERN

A Concise Total Synthesis of (–)-Berkelic Acid

Pruteanu Elena

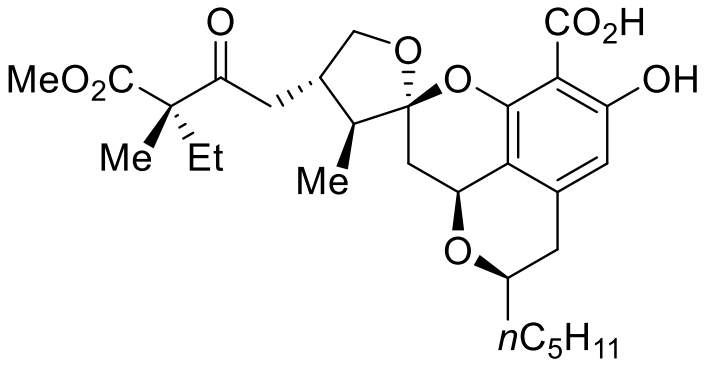
Journal club

02.06.2021

(-)-Berkelic acid

- Isolated in 2006 by Stierle and co-workers

from an extremophilic *Penicillium* species.

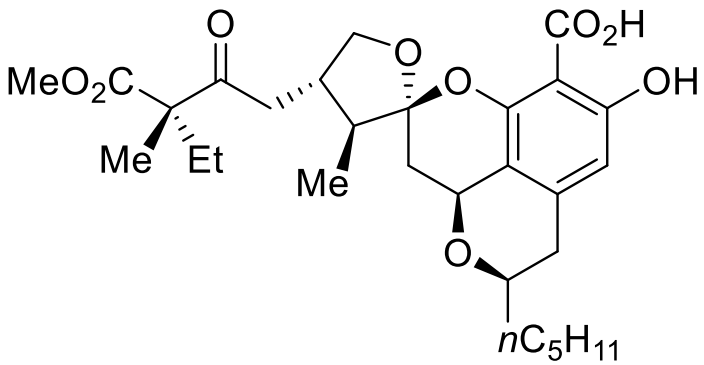


(-)-Berkelic acid **1**

Berkeley Pit Lake in Butte, Montana (USA)

Stierle, A. A.; Stierle, D. B.; Kelly, K. J. Org. Chem. 2006, 71, 5357–5360
Photo source : https://pitwatch.org/31-years-since-pumps-stopped/

Biological activity (under studies)



(-)-Berkelic acid **1**

Promising selectivity against:

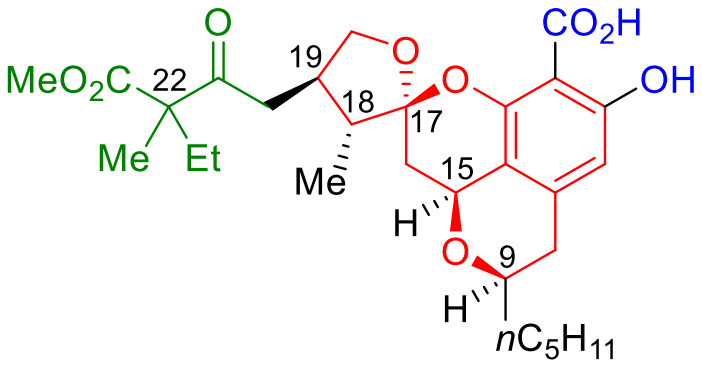
- human ovarian cancer cell line OVCAR-3 (GI50 91 nm),
- moderate inhibitory activity against the matrix metalloproteinase MMP-3 (1.87 µM),
- cysteine protease caspase-1 (98 µM).

Accessibility:

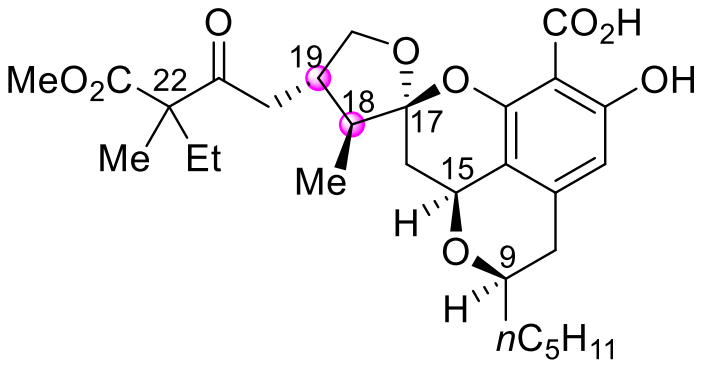
- limited from natural sources

Stierle, A. A.; Stierle, D. B.; Kelly, K. *J. Org. Chem*. **2006**, 71, 5357–5360
Wu, X.; Zhou, J.; **Snider**, B. B. *J. Org. Chem*. **2009**, 74, 6245–6252
T. Arto, I. S. de Santa-María, M.-D. Chiara, F. J. Fañanás, F. Rodríguez, *Eur. J. Org. Chem*. **2016**, 5876-5880.

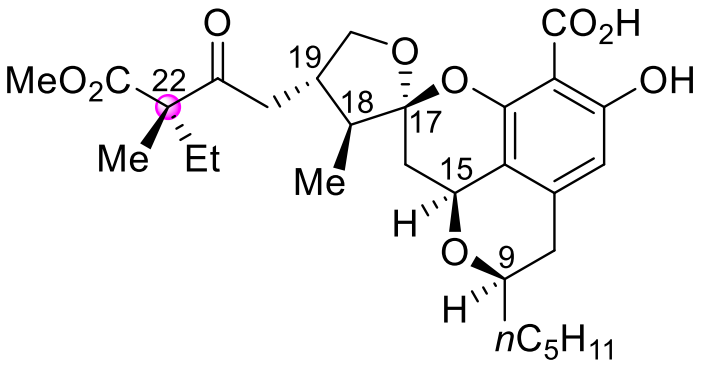
Structural feature



Stierle's original structure
of berkelic acid (2006)



Fürstner's revised structure
of berkelic acid (2008)



Snider's revised structure
of berkelic acid (2009)

- unique tetracyclic isochroman/chroman spiroketal structure,
- a pentasubstituted phenyl ring with a free hydroxyl group and carboxylic acid,
- 6 stereogenic centers, including 1 quaternary carbon centre.

Fürstner et all, Angew. Chem. Int. Ed. 2008, 47, 8450-8454; Angew. Chem. 2008, 120, 8578-8582
Wu, X.; Zhou, J.; **Snider**, B. B. J. Org. Chem. 2009, 74, 6245–6252

Barry B. Snider
Chair, Chemistry Department, Brandeis University (USA), 1992-1995, 2013-present

Angewandte Chemie
GDCh Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Zuschrift | Full Access

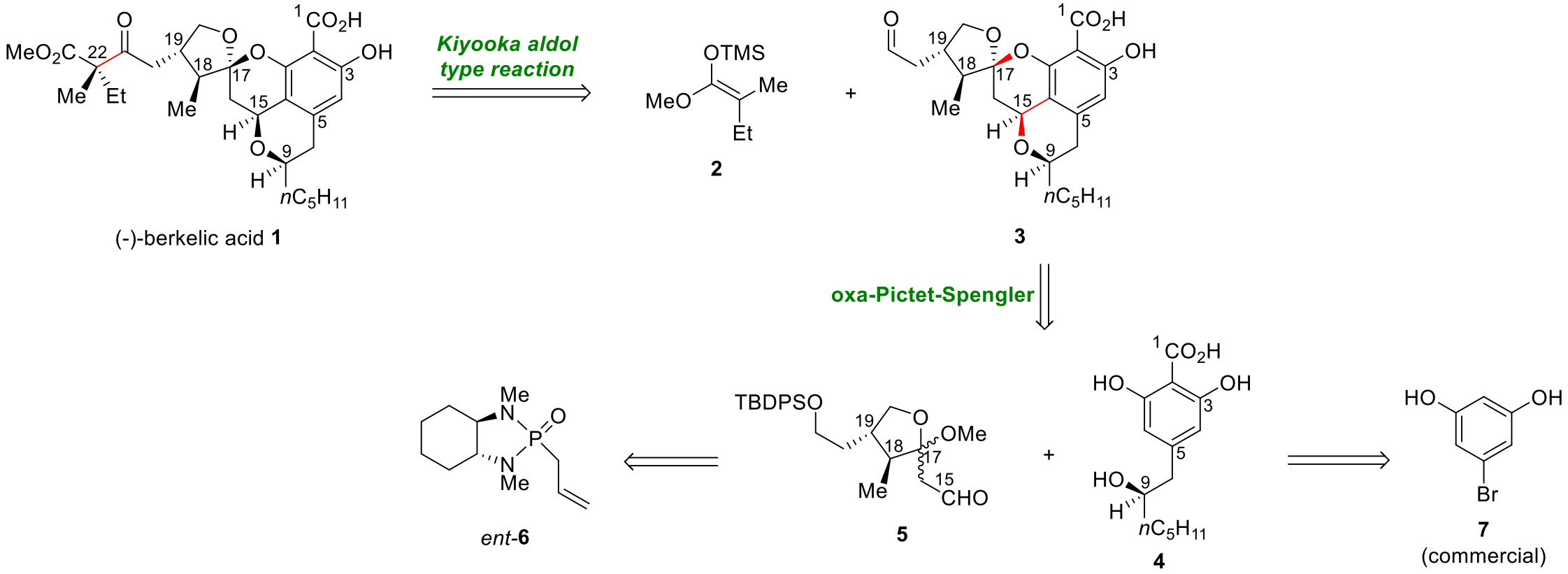
Synthesis of (−)-Berkelic Acid†

Xiaoxing Wu, Jingye Zhou Dr., Barry B. Snider Prof.

First published: 26 January 2009 | https://doi.org/10.1002/ange.200805488 | Citations: 17

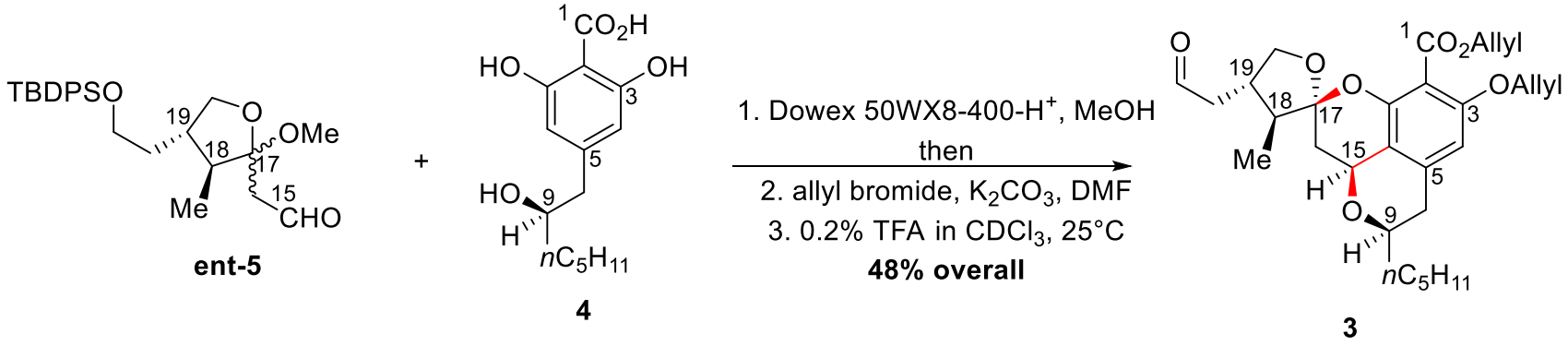
1. J. Zhou, B. B. Snider, *Org. Lett.* **2007**, *9*, 2071-2074 (investigation of the Oxa-Pictet-Spengler Cyclization);
2. X. Wu, J. Zhou, B. B. Snider, *Angew. Chem. Int. Ed.* **2009**, *48*, 1283-1286; *Angew. Chem.* **2009**, *121*, 1309-1312 (total synthesis report);
3. Wu, J. Zhou, B. B. Snider, *J. Org. Chem.* **2009**, *74*, 6245-6252 (aldol condensation and full assignment).

Snider 1st Synthesis – Retrosynthetic approach

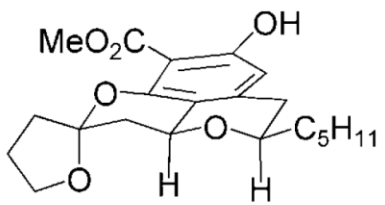


X. Wu, J. Zhou, B. B. **Snider**, *Angew. Chem. Int. Ed*. **2009**, 48, 1283-1286; *Angew. Chem*. **2009**, 121, 1309-1312

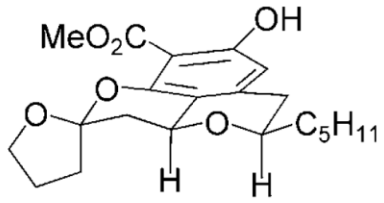
oxa-Pictet-Spengler :



Relative strain energies:
28.9 : 31.3 : 32.8 : 33.3 kcal mol^{-1}



A (most stable)



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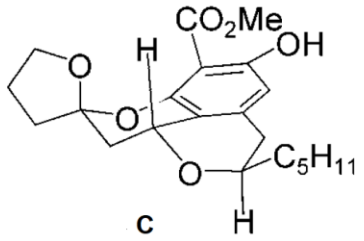
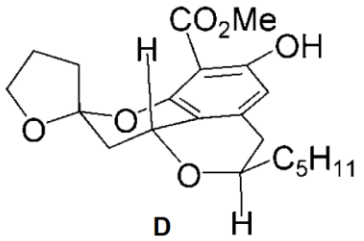
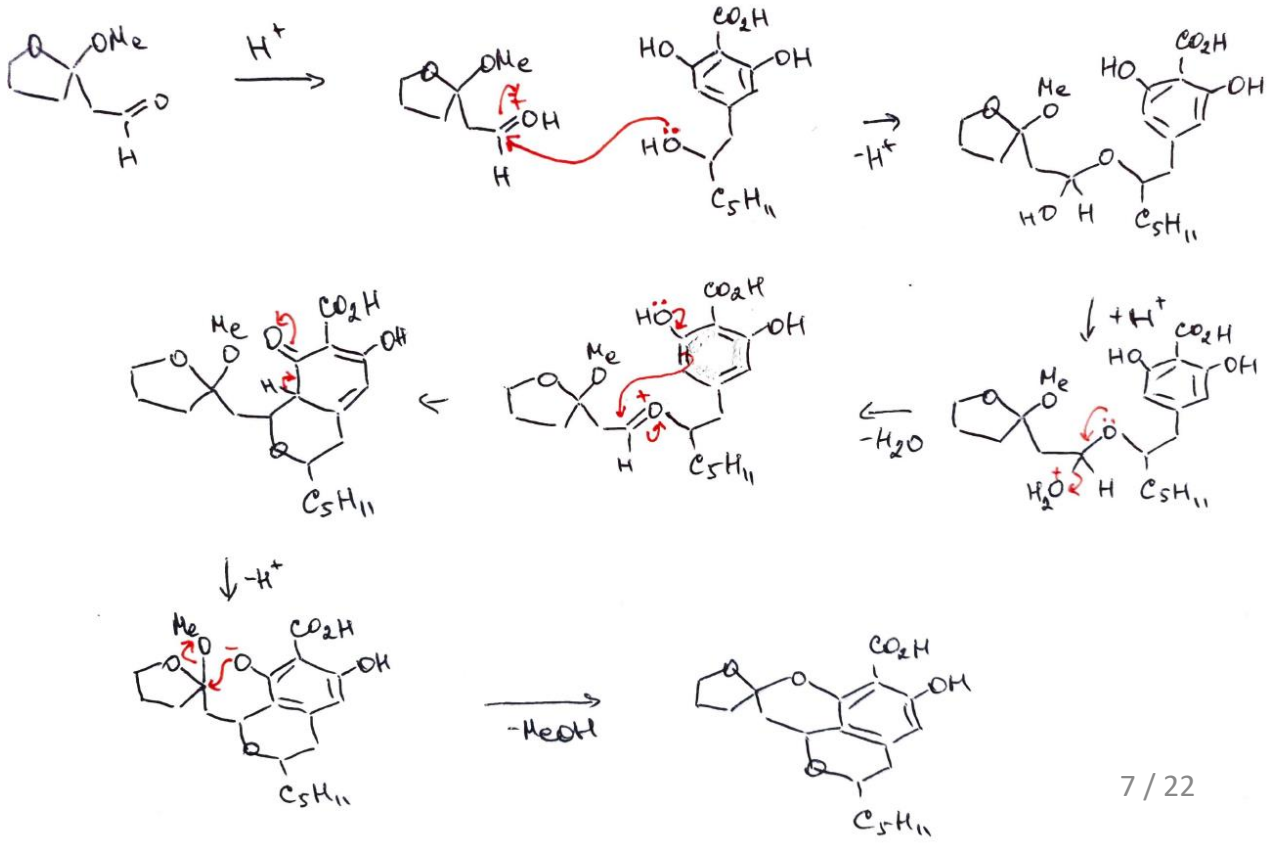


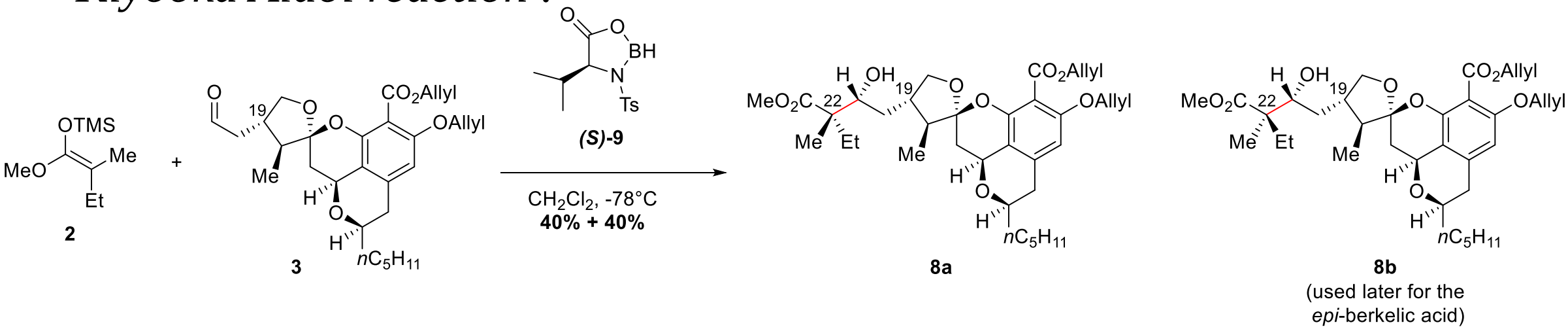
C

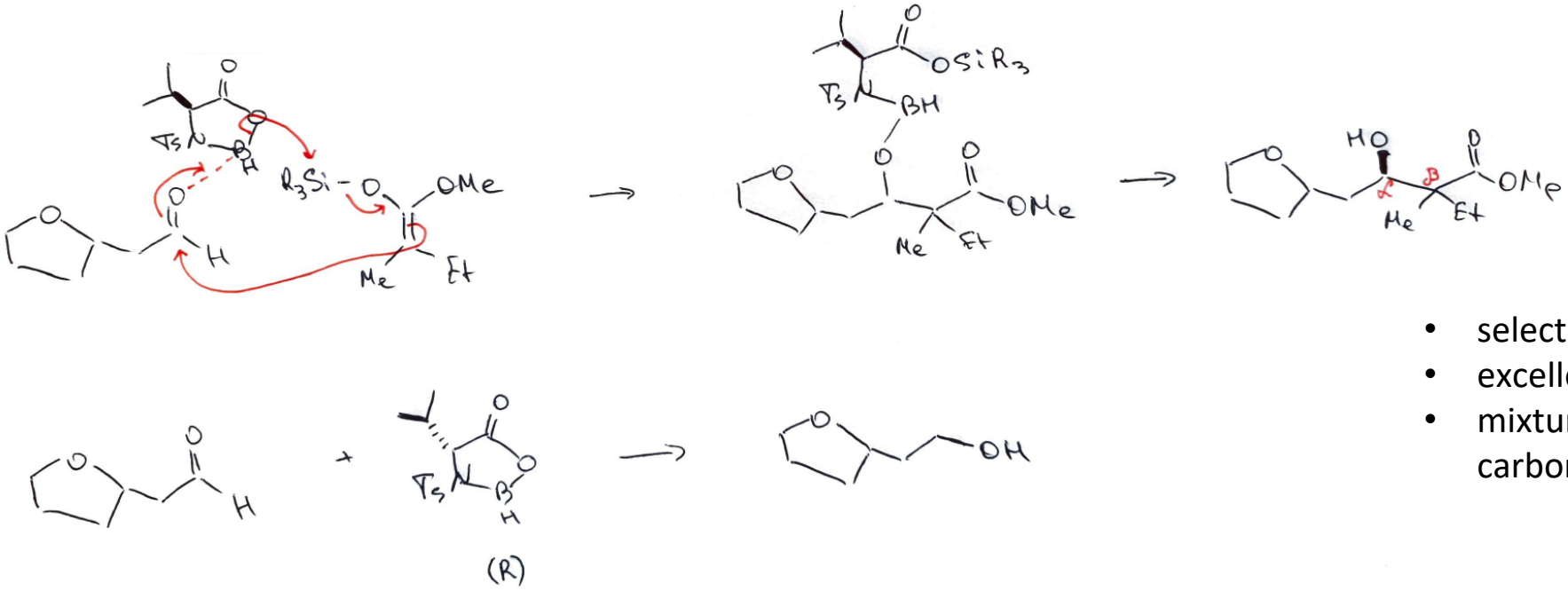


D



Kiyooka Aldol reaction :

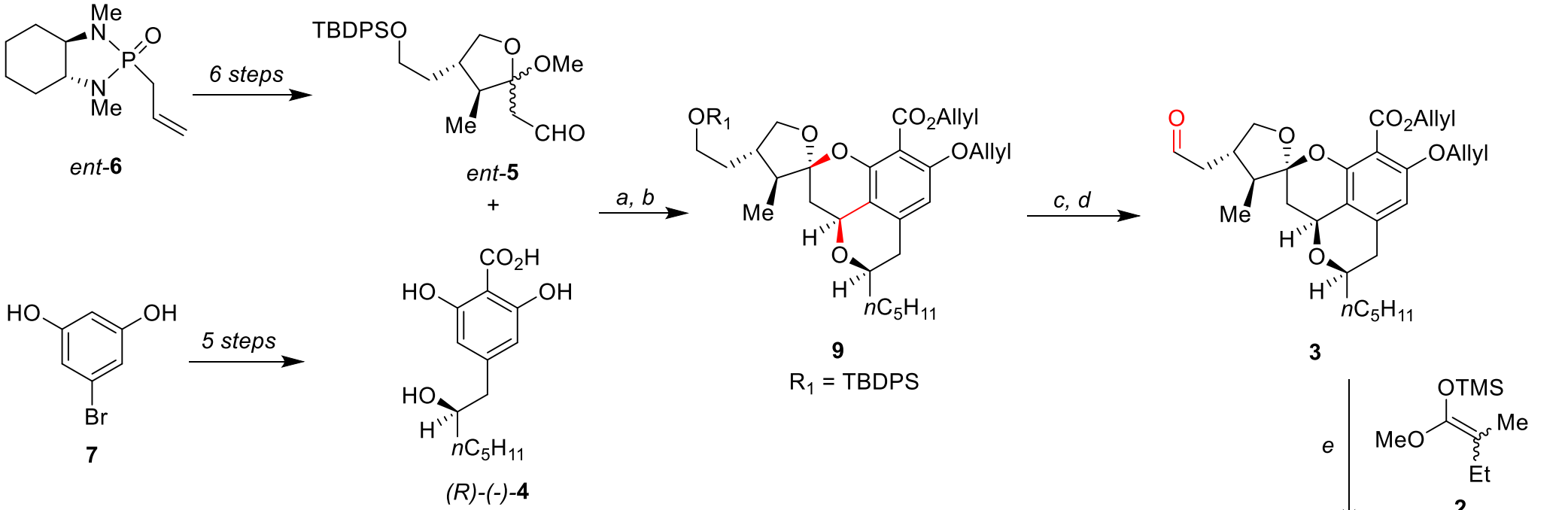




- selective for the *Si* face affording
- excellent control at the β-carbon
- mixtures of isomers at the α-carbon centre

Wu, J. Zhou, B. B. Snider, *J. Org. Chem.* **2009**, *74*, 6245-6252 (aldol condensation and full assignment)
Bülow, L., Naini, A., Fohrer, J. and Kalesse, M., *Organic letters*, **2011**, 13(22), 6038-6041.

Snider 1st Synthesis : 13 steps, 2% overall yield



Reagents and conditions: a) Dowex 50WX8-400-H^+, MeOH; b) allyl bromide, K_2CO_3, DMF (32%); c) TBAF/AcOH (1:1) in THF (86%); d) Dess–Martin (88%); e) N-Ts-(*S*)-valine, BH_3·THF, CH_2Cl_2 (40%); f) Dess–Martin (85%); g) [$Pd(Ph_3P)_4$] (0.2 equiv), HCO_2H (40 equiv), Et_3N (40 equiv), THF, (78%).

X. Wu, J. Zhou, B. B. **Snider**, *Angew. Chem. Int. Ed*. **2009**, 48, 1283-1286; *Angew. Chem*. **2009**, 121, 1309-1312

Félix Rodríguez
Associate Professor
University of Oviedo (Spain)
2009 -present

Angewandte International Edition Chemie
GDCh A Journal of the German Chemical Society

Communication | Full Access

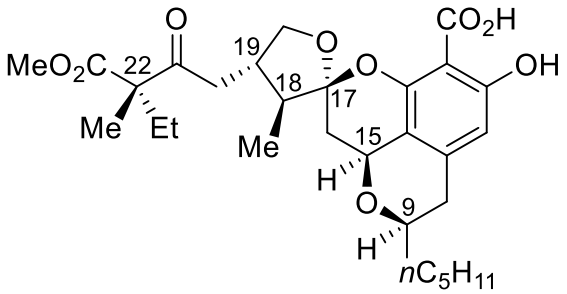
Scalable Total Synthesis of (−)-Berkelic Acid by Using a Protecting-Group-Free Strategy†

Prof. Dr. Francisco J. Fañanás, Dr. Abraham Mendoza, Tamara Arto, Dr. Baris Temelli, Prof. Félix Rodríguez

First published: 04 April 2012 | https://doi.org/10.1002/anie.201109076 | Citations: 49

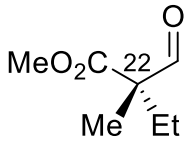
1. J. F. J. Fananas, A. Mendoza, T. Arto, B. Temelli, F. Rodriguez, *Angew. Chem. Int. Ed.* **2012**, 51, 4930-4933; *Angew. Chem*. **2012**, 124, 5014-5017 (total synthesis report);
2. T. Arto, I. S. de Santa-María, M.-D. Chiara, F. J. Fañanás, F. Rodríguez, *Eur. J. Org. Chem*. **2016**, 5876-5880 (studies of activity on 23 related molecules).

Rodriguez Scalable route – Retrosynthetic approach

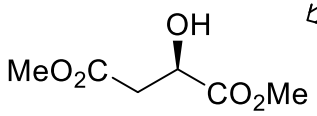


(-)-berkelic acid **1**

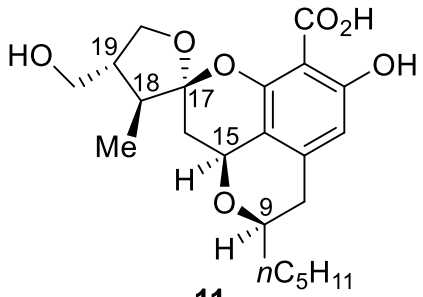
Umpolung alkylation



10

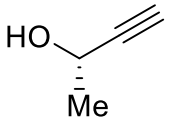


Dimethyl-D-malate
(commercial)

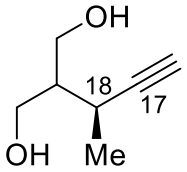


11

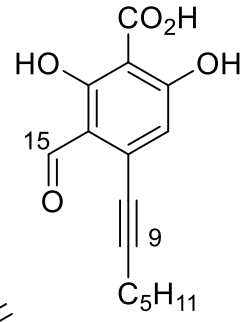
Ag catalyzed cascade polycyclisation



(S)-3-butyn-2-ol
(commercial)



12



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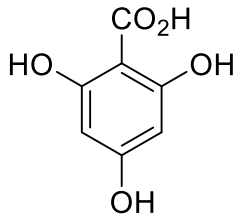
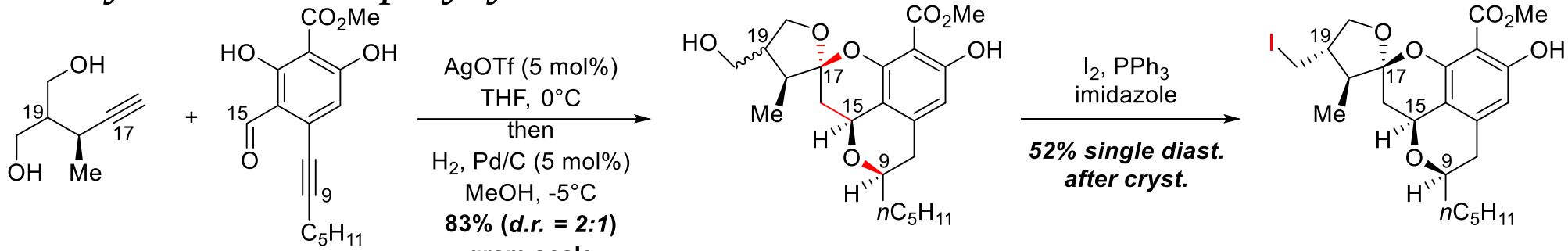


Methyl 2,4,6-trihydroxybenzoate
(commercial)

F. J. Fananas, A. Mendoza, T. Arto, B. Temelli, F. **Rodriguez**, *Angew. Chem. Int. Ed*. **2012**, 51, 4930-4933; *Angew. Chem*. **2012**, 124, 5014-5017

Ag catalysed cascade polycyclisation

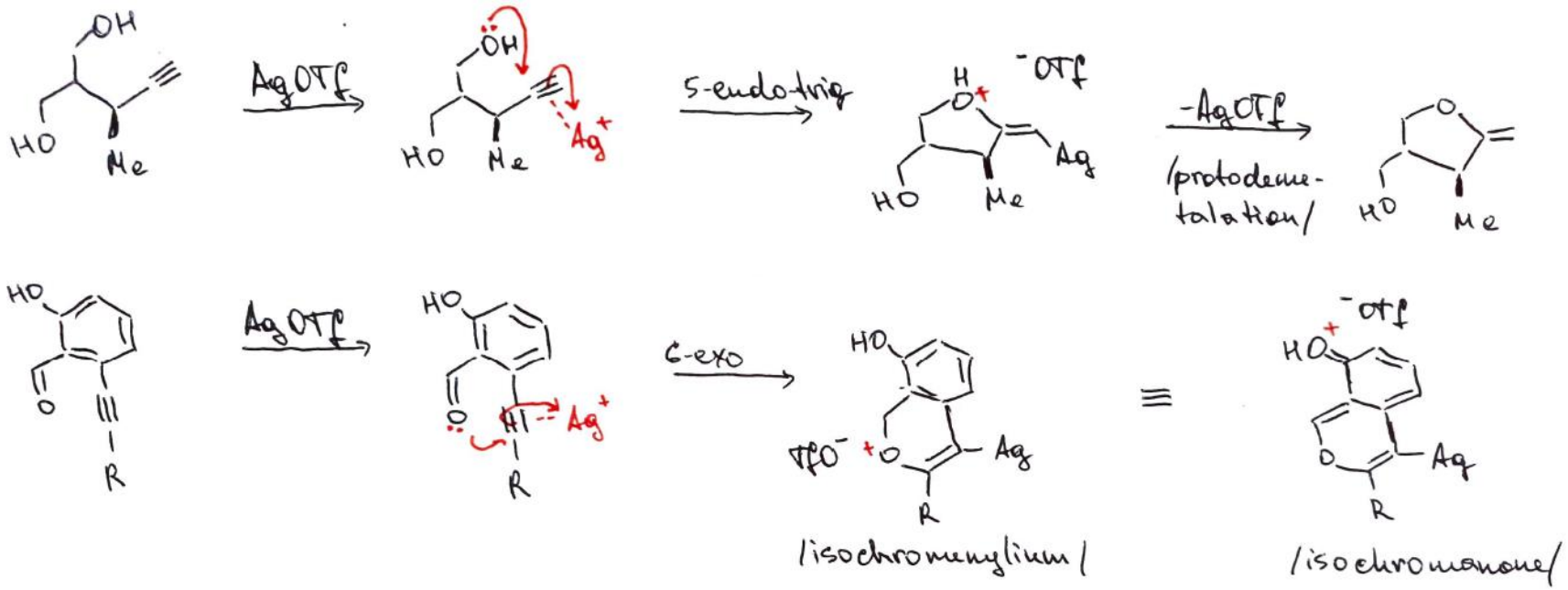


12
1 equiv

13
1 equiv

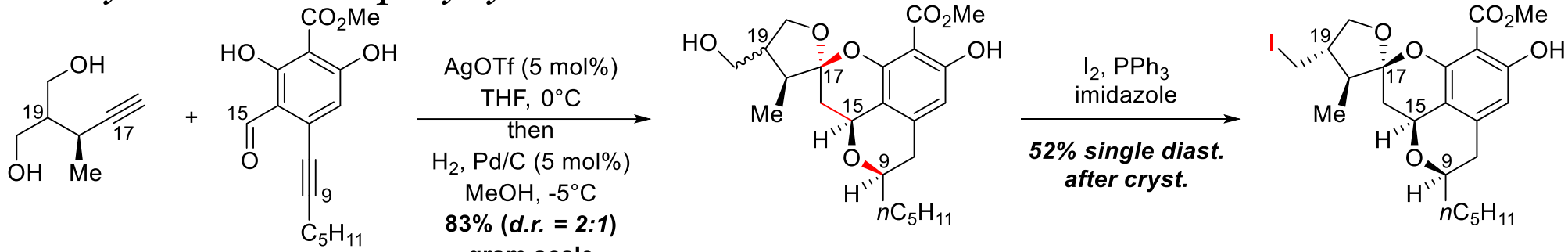
11

14



Gold(I) catalysis : T. Arto, F. J. Fañanás, F. Rodríguez, *Angew. Chem*. **2016**, 128, 7334-7337
Pd(II) catalysis : Barluenga, J., Mendoza, A., Rodriguez, F., Fananas, F. J., *Angew. Chem. Int. Ed*. **2009**, 48(9), 1644-1647.

Ag catalysed cascade polycyclisation

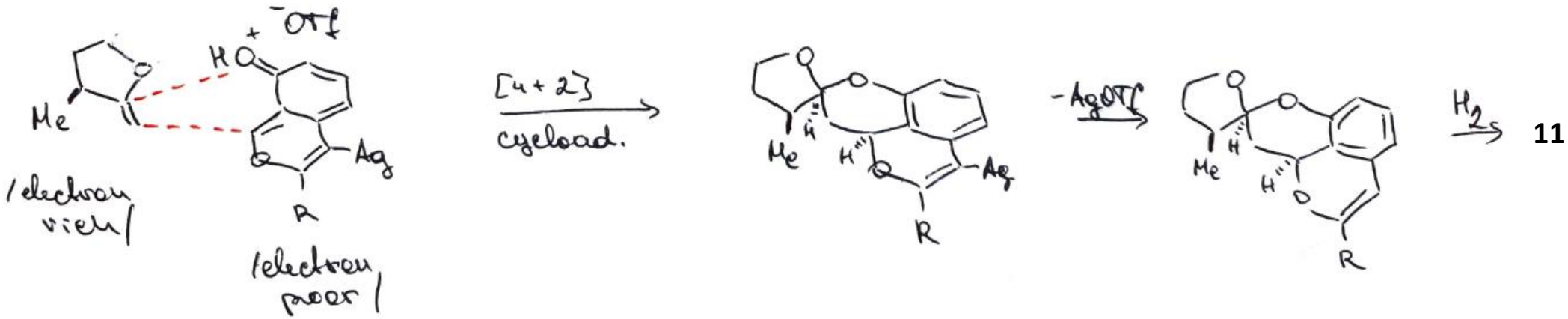


12
1 equiv

13
1 equiv

11

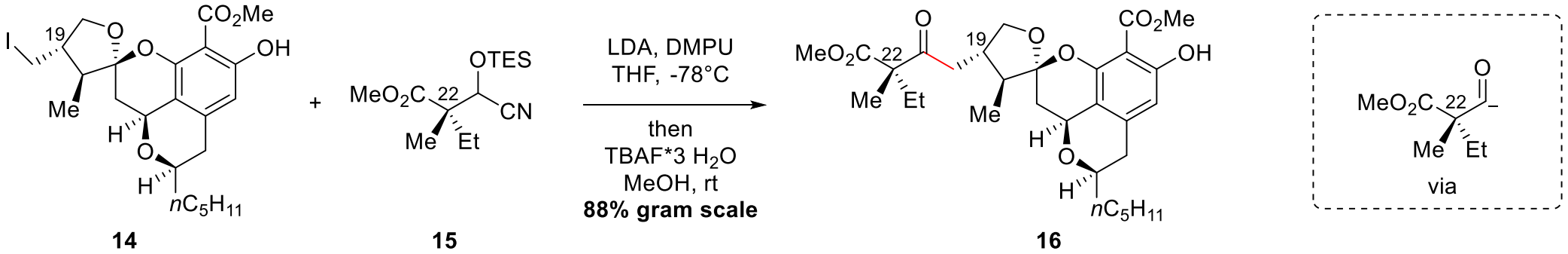
14



Gold(I) catalysis : T. Arto, F. J. Fañanás, F. Rodríguez, *Angew. Chem*. **2016**, 128, 7334-7337

Pd(II) catalysis : Barluenga, J., Mendoza, A., Rodriguez, F., Fananas, F. J., *Angew. Chem. Int. Ed*. **2009**, 48(9), 1644-1647.

Umpolung alkylation

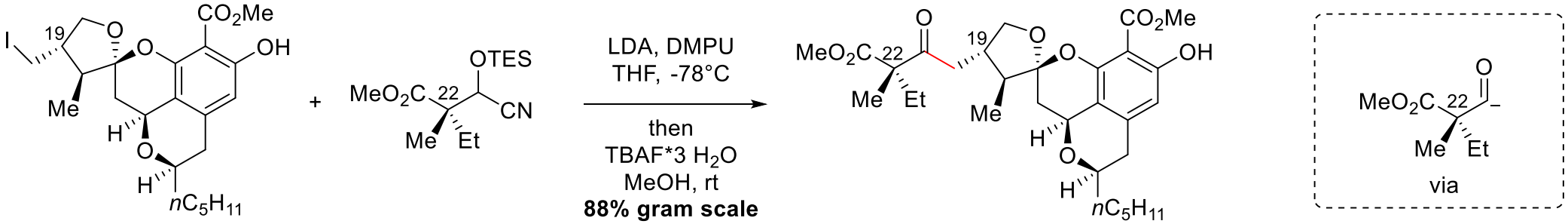


14 **15** **16**

Use of cyanohydrins : S. D. Rychnovsky, S. S. Swenson, *J. Org. Chem*. **1997**, 62, 1333 – 1340.
For silylcyanation : M.-A. Lacour, N. J. Rahier, M. Taillefer, *Chem. Eur. J.* **2011**, 17, 12276 – 12279

X-ray confirmation

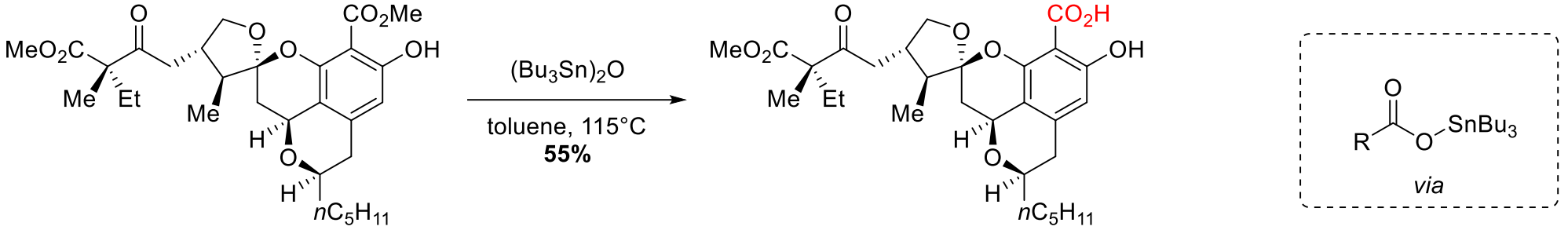
Umpolung alkylation



14 **15** **16**

Use of cyanohydrins : S. D. Rychnovsky, S. S. Swenson, *J. Org. Chem*. **1997**, 62, 1333 – 1340.
For silylcyanation : M.-A. Lacour, N. J. Rahier, M. Taillefer, *Chem. Eur. J.* **2011**, 17, 12276 – 12279

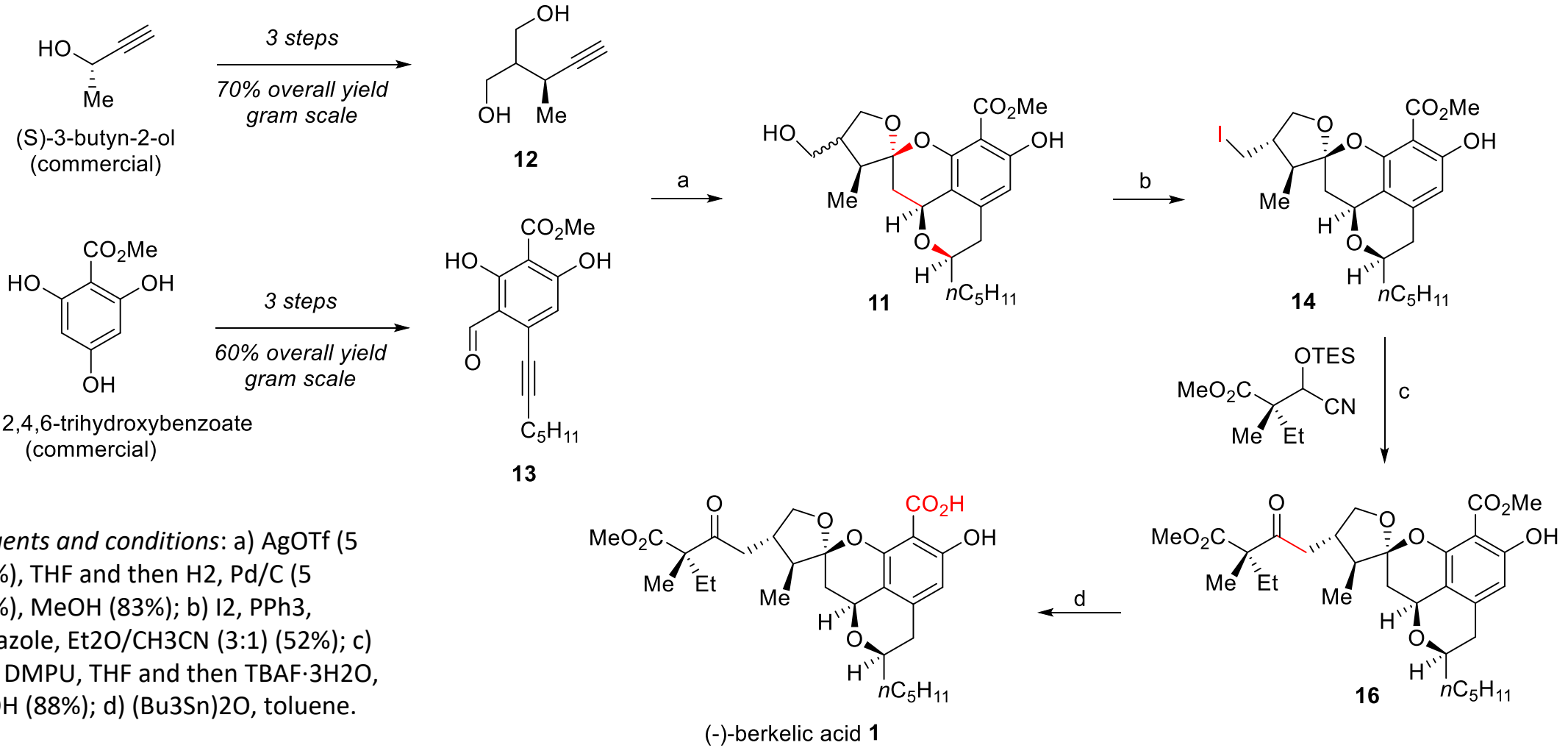
Sn hydrolysis of carboxylic esters



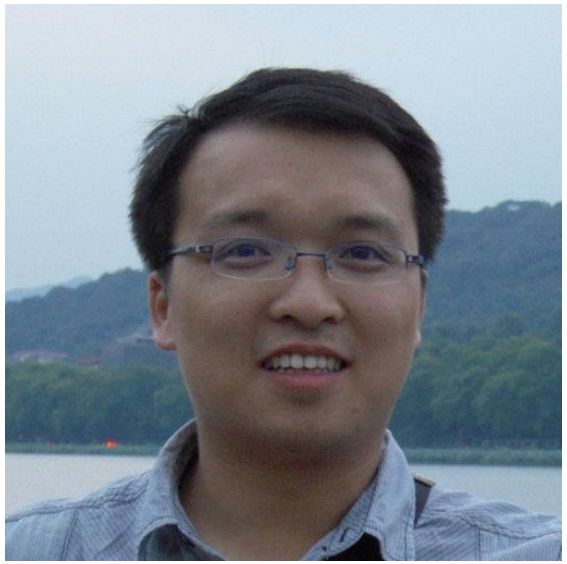
16 (-)-berkelic acid **1**

Salomon, C. J., Mata, E. G., & Mascaretti, O. A., *J. Org. Chem.*, **1994**, 59(24), 7259-7266v

Rodriguez route : 7 steps, gram scale (1.2 g - methyl ester, 25 mg - acid)



Reagents and conditions: a) AgOTf (5 mol%), THF and then H2, Pd/C (5 mol%), MeOH (83%); b) I2, PPh3, imidazole, Et2O/CH3CN (3:1) (52%); c) LDA, DMPU, THF and then TBAF·3H2O, MeOH (88%); d) (Bu3Sn)2O, toluene.



Qianghui Zhou
Doctor , Professor
Wuhan University (China)
2015 -present

Angewandte Chemie
GDCh Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Zuschrift | Full Access

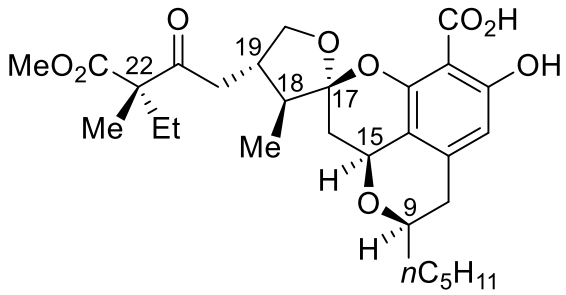
A Concise Total Synthesis of (−)-Berkelic Acid

Prof. Dr. Hong-Gang Cheng, Zhenjie Yang, Ruiming Chen, Liming Cao, Wen-Yan Tong, Qiang Wei, Qingqing Wang, Chenggui Wu, Prof. Dr. Shuanglin Qu, Prof. Dr. Qianghui Zhou

First published: 30 November 2020 | https://doi.org/10.1002/ange.202014660

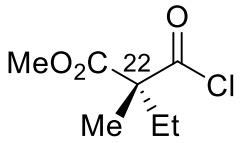
1. *Angew. Chem. Int. Ed.*, **2020**, 10.1002/anie.202014660

Zho Recent route – Retrosynthetic approach



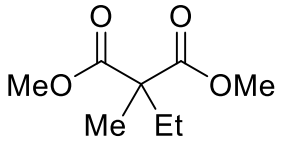
(-)-berkelic acid **1**

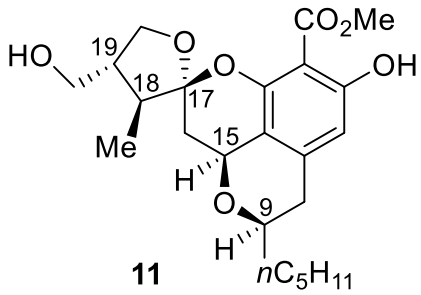
Ni-catalysed reductive coupling



17

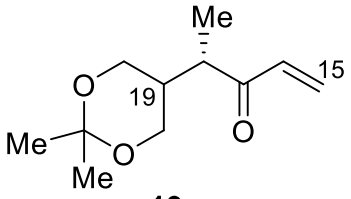
enzyme catalysed desymetrization



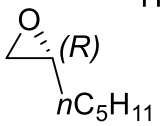


11

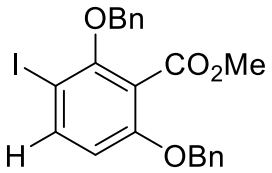
deprotection/ spiroacetalization/ desymmetrization



19

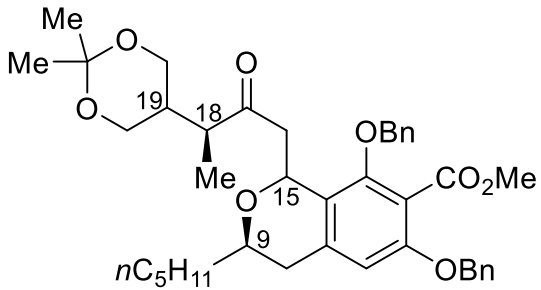


21



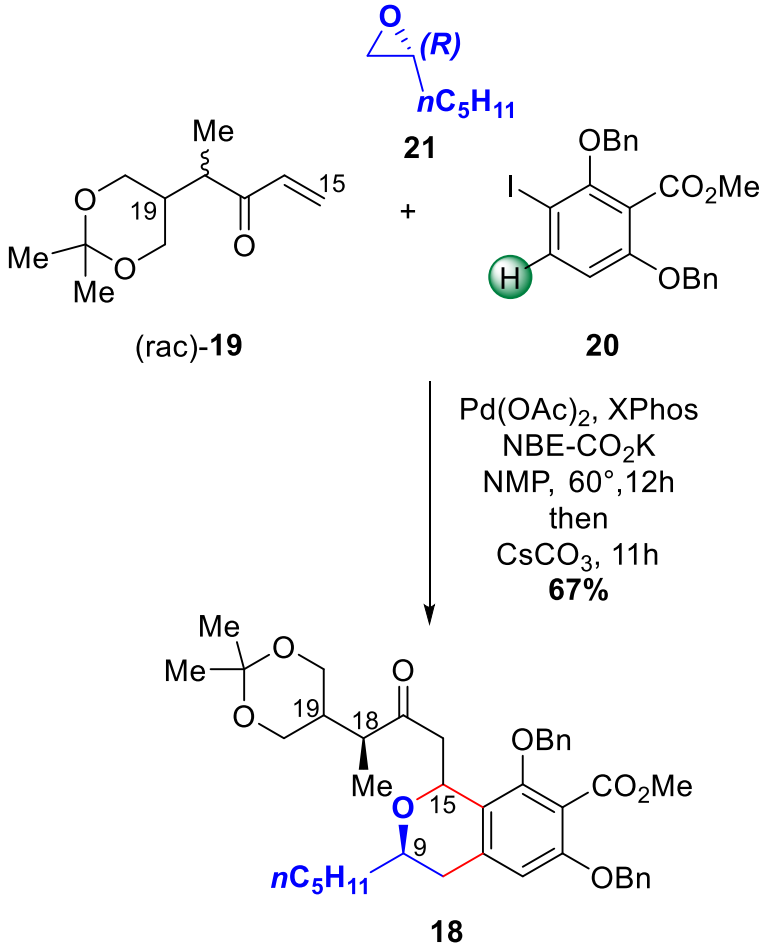
20

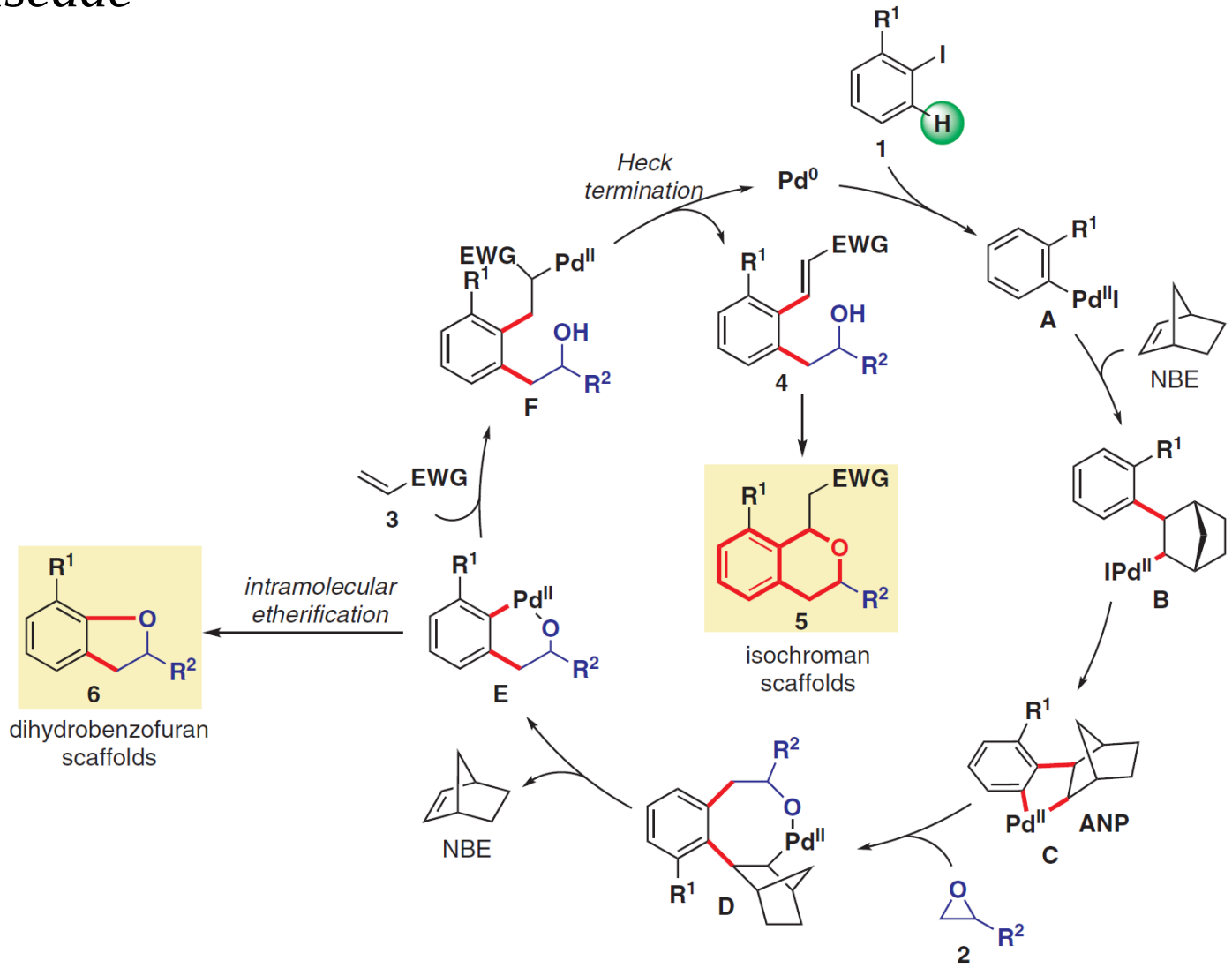
Catellani/ oxa-Michael



18

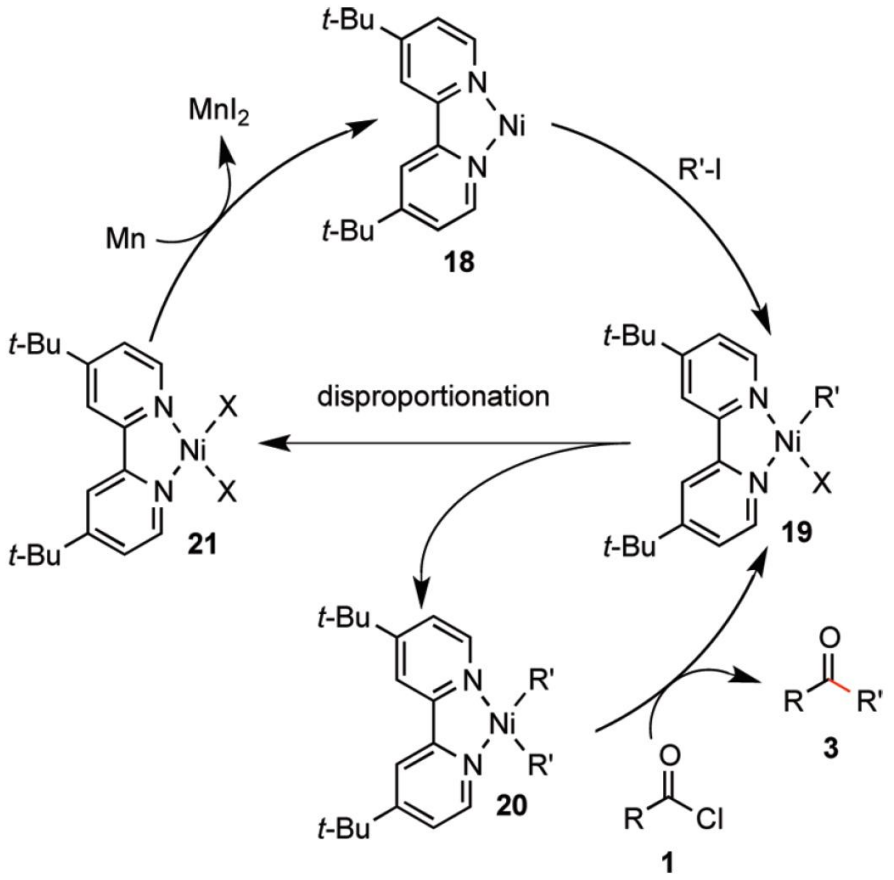
Catellani reaction/oxa-Michael cascade

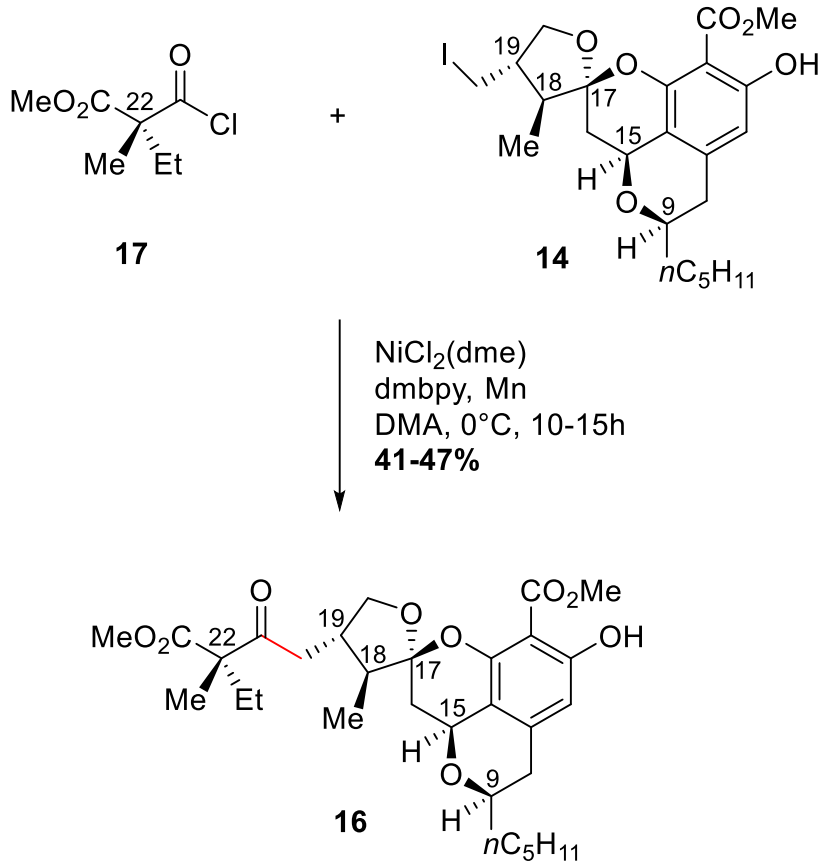




From epoxides : C. Wu, H.-G. Cheng, Q. Zhou, *Synlett* **2020**, 31, 829-837.

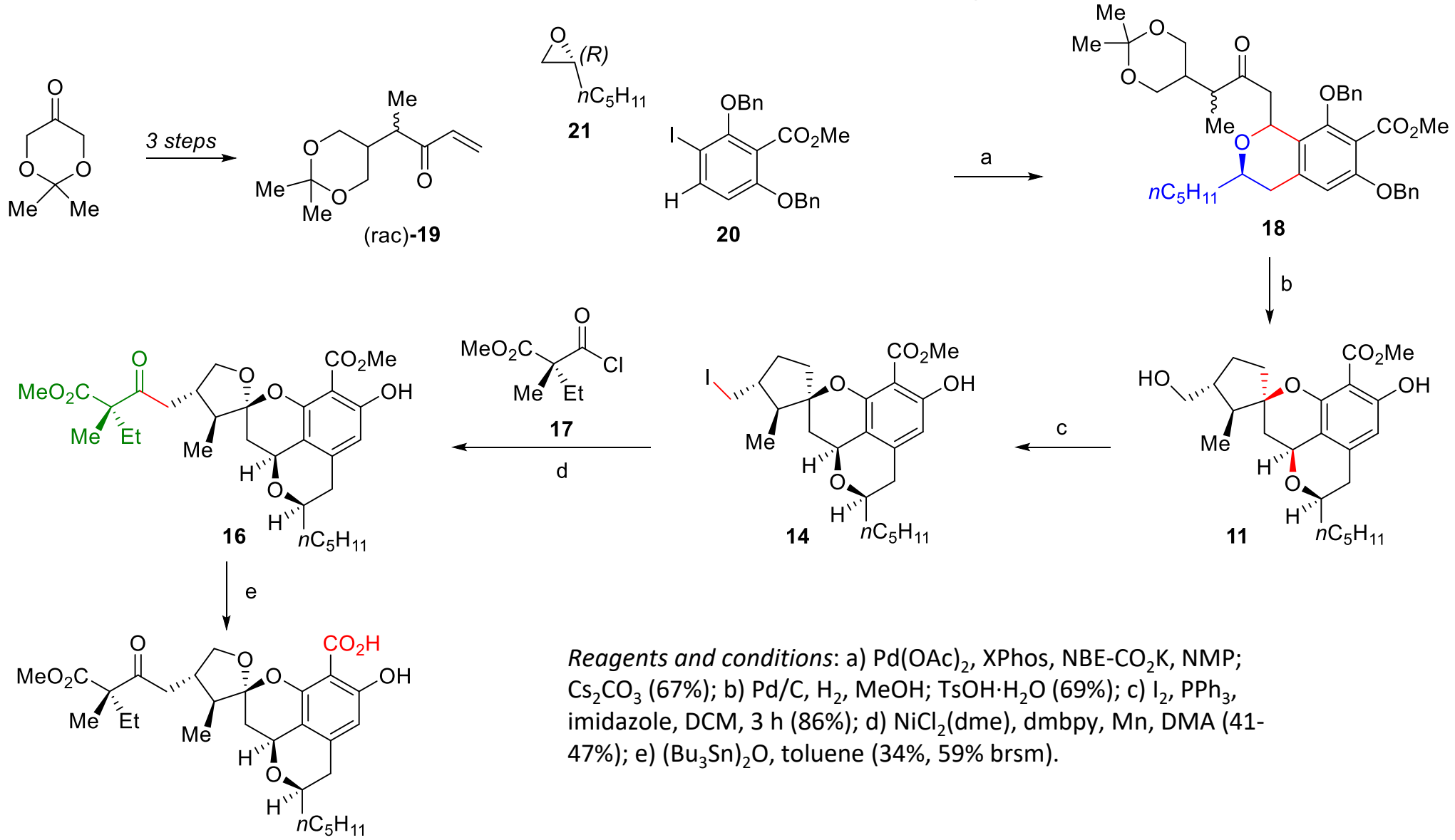
Ni-catalyzed reductive coupling





A. C. Wotal, D. J. Weix, *Org. Lett*. **2012**, 14, 1476-1479

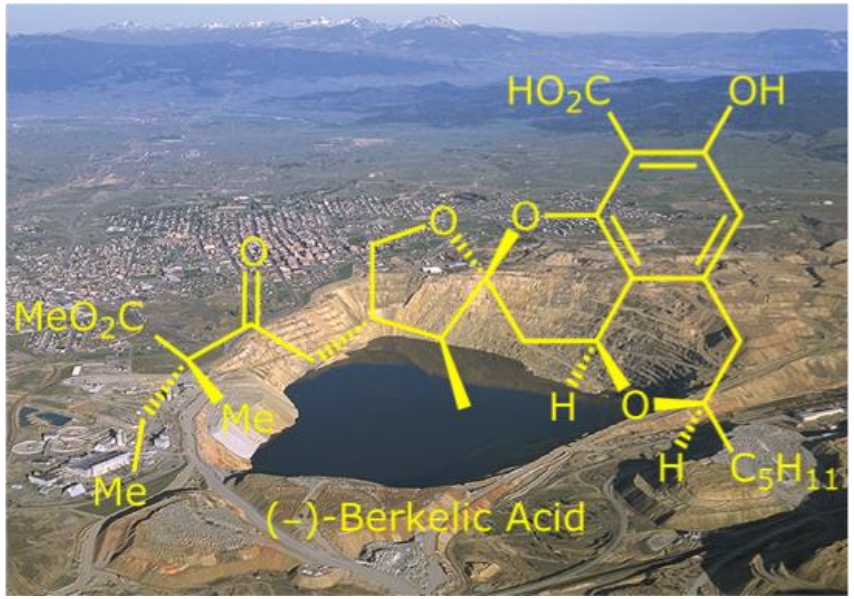
Zhou recent route : 8 steps linear sequence, 4% overall yield



Reagents and conditions: a) $Pd(OAc)_2$, XPhos, NBE-CO_2K, NMP; Cs_2CO_3 (67%); b) Pd/C, H_2, MeOH; $TsOH{\cdot}H_2O$ (69%); c) I_2, PPh_3, imidazole, DCM, 3 h (86%); d) $NiCl_2$(dme), dmbpy, Mn, DMA (41-47%); e) $(Bu_3Sn)_2O$, toluene (34%, 59% brsm).

Conclusion :

- The synthesis of (-)-berkelic acid was realized with success applying different retrosynthetic routes.
- 3 methods in the formation of the spirocycle chromane core motif were shown
- High amount of synthetic acid were obtained, allowing the revision of biological activity testing.



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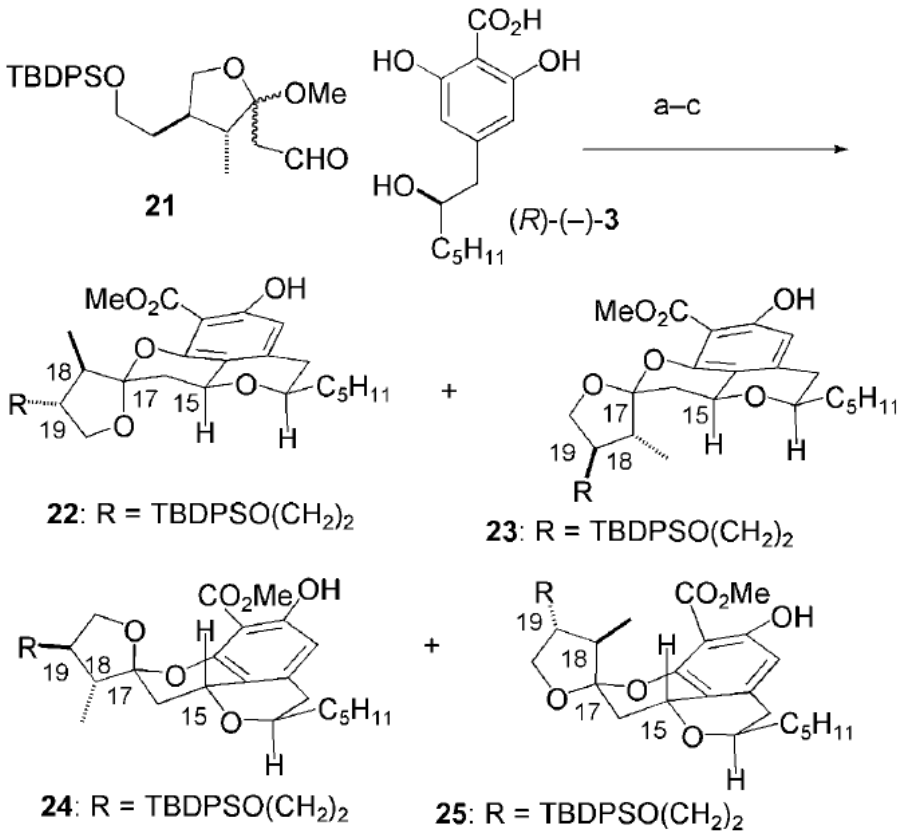
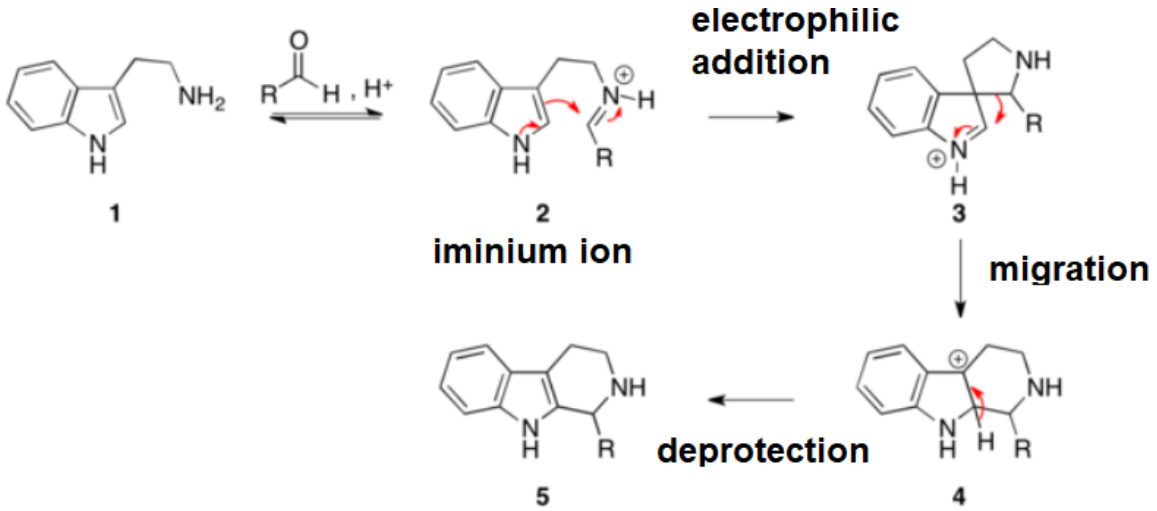
A Concise Total Synthesis of (–)-Berkelic Acid

Thank you for your attention!

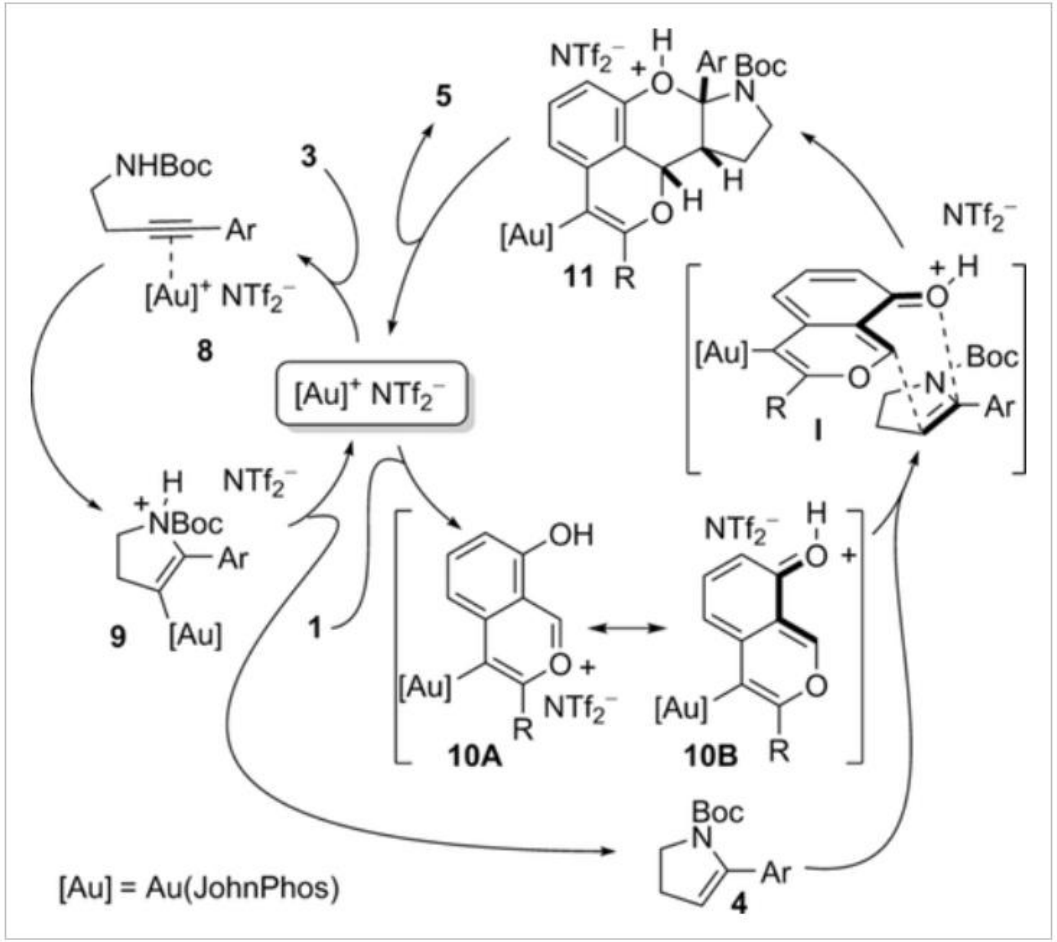
Pictet-Spengler Reaction



Scheme 5. Reactions and conditions: a) Dowex 50WX8-400-H^+, MeOH, 25 °C, 12 h; b) CH_2N_2, ether; c) 0.2% TFA in $CDCl_3$, 25 °C, 12 h. TFA = trifluoroacetic acid.



Au catalysed polycyclisation

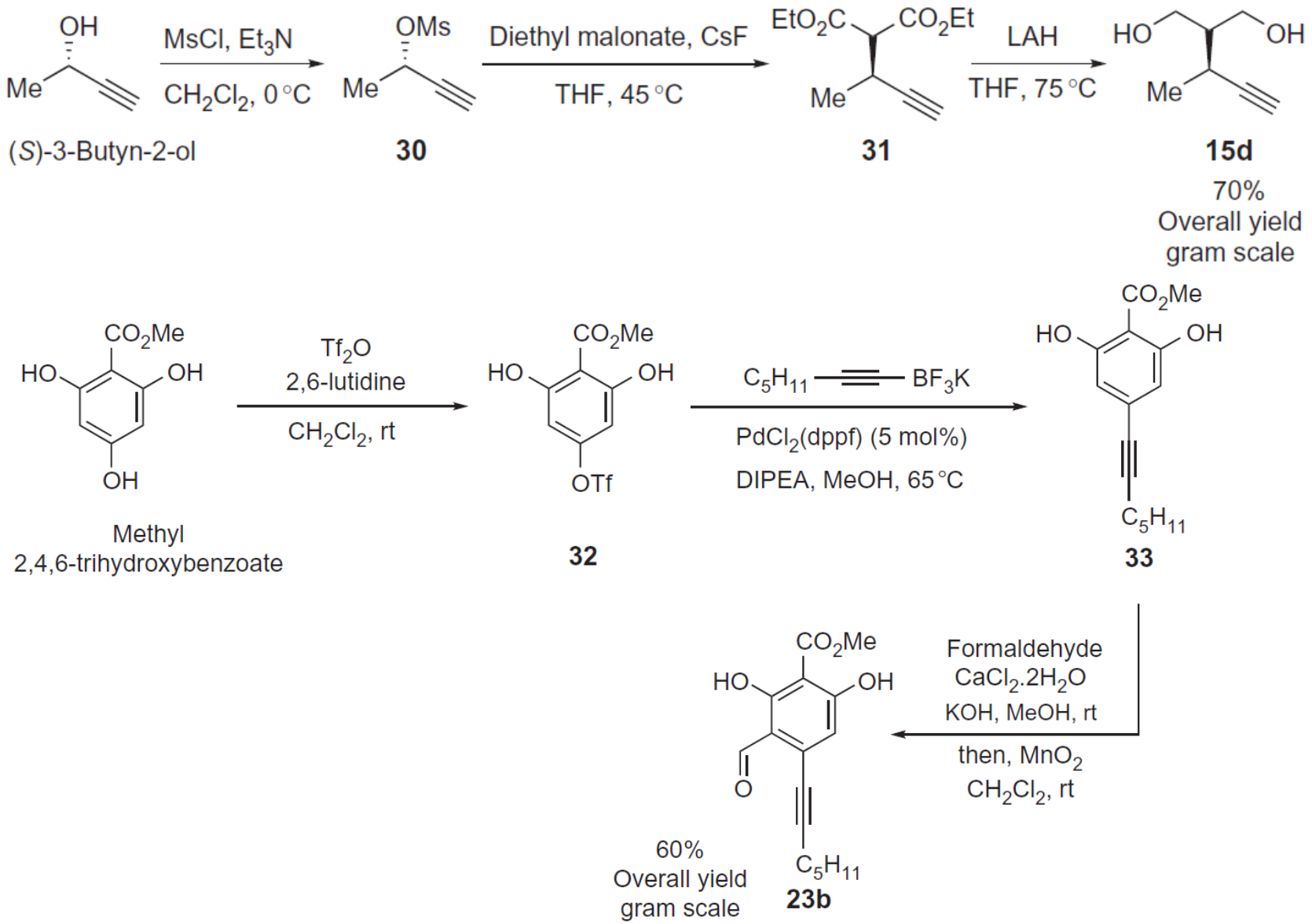


Scheme 4 Open in figure viewer | PowerPoint

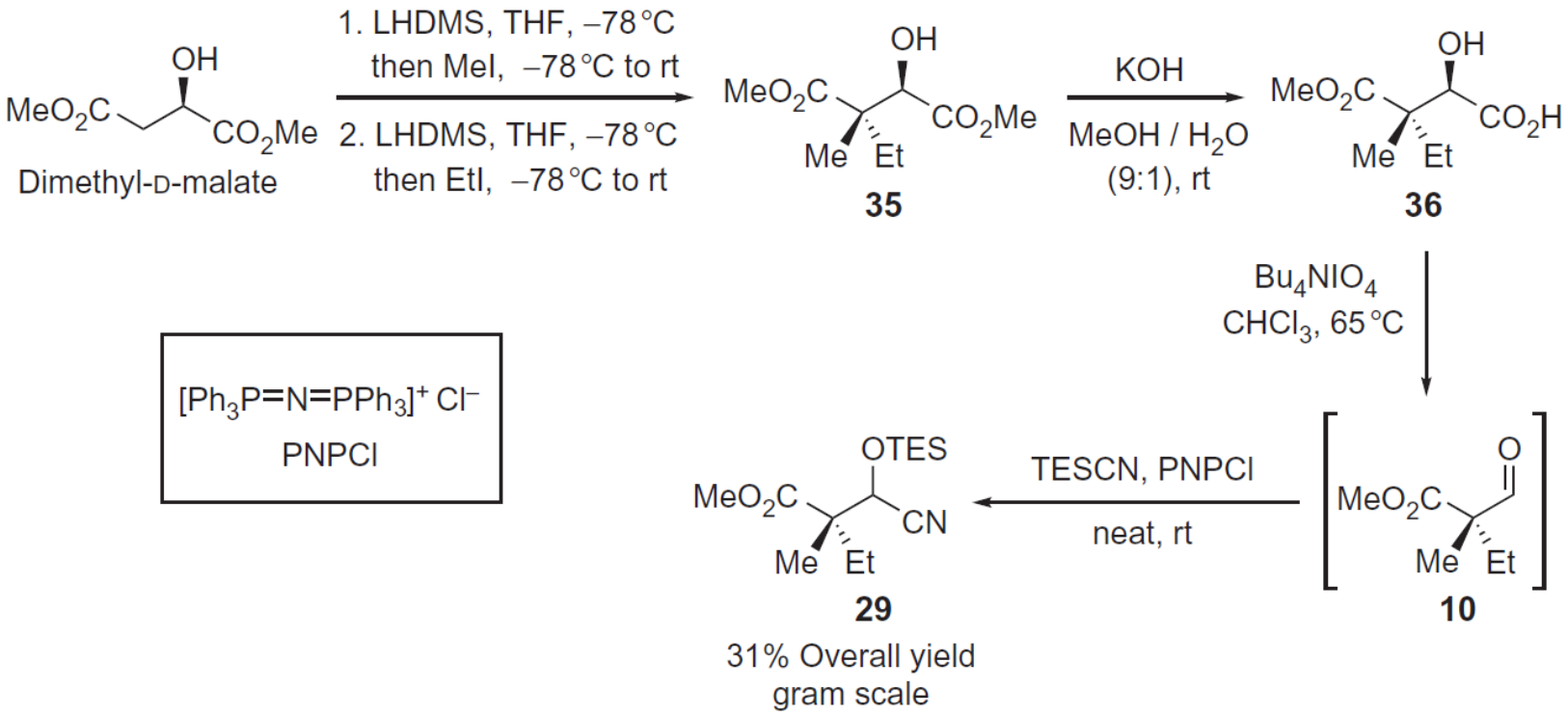
Proposed mechanism for the formation of compounds **5**.

- following an *endo* trajectory

Scalable route – Synthesis of precursors

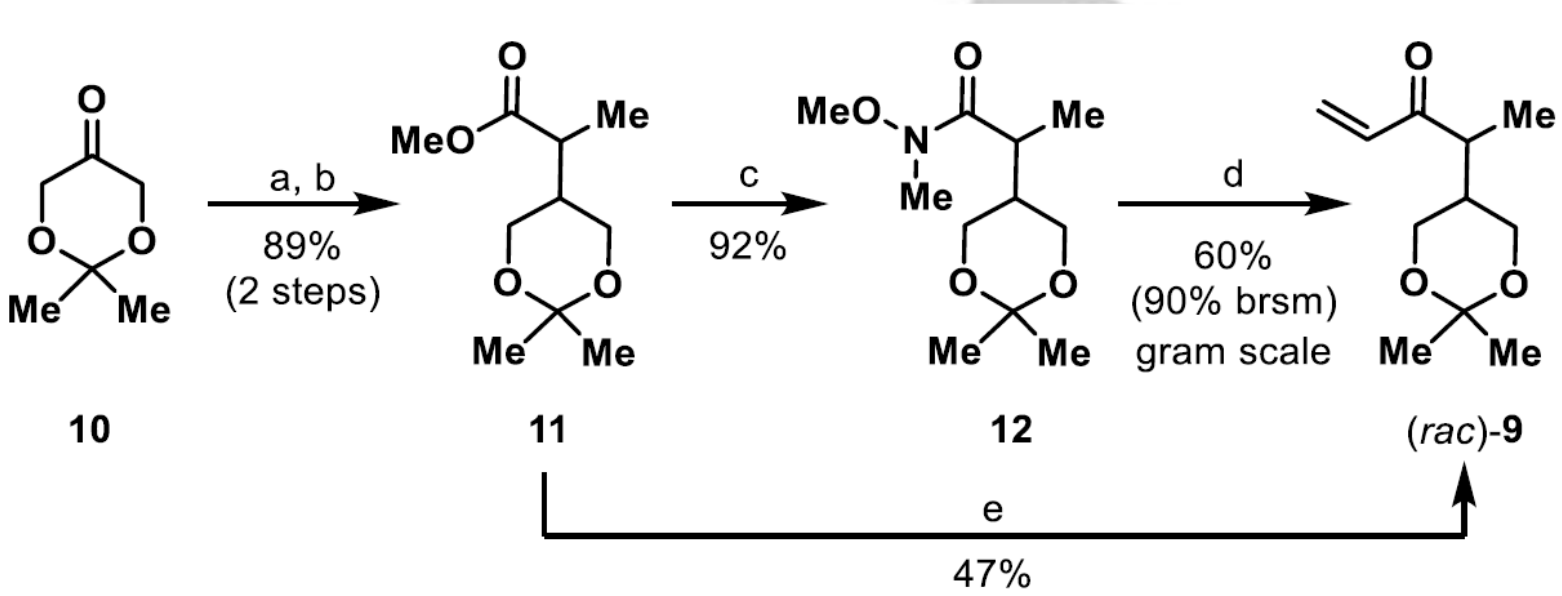


Scalable route – Synthesis of the cyanohydrin fragment



SCHEME 16 Scalable synthesis of the cyanohydrin fragment.

Recent route – Synthesis of precursor ***9***



Scheme 2. Retrosynthetic analysis of (–)-berkelic acid (**1**). Reagents and conditions: a) methyl 2-(diethoxyphosphoryl)propanoate, *n*BuLi, THF, -78 °C to 0 °C; b) H_2, Pd/C, MeOH, RT; c) *i*PrMgCl, *N*-methoxymethylamine hydrochloride, THF, RT; d) vinyl-magnesium bromide, THF, 0 °C; e) LDA, $MePO(OMe)_2$, $(CH_2O)_n$, THF, 0 °C. brsm: based on recovered starting material. THF = tetrahydrofuran. RT = room temperature. LDA = lithium diisopropylamide.