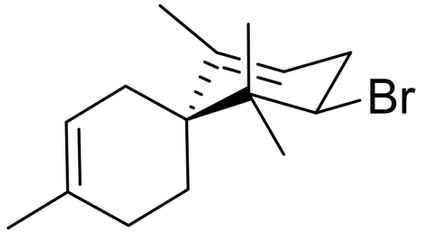
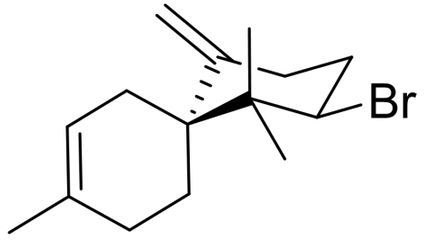
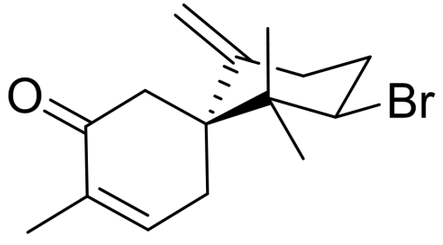
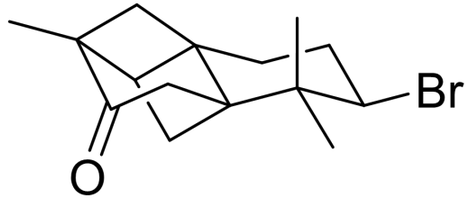
A Unified Approach for the Enantioselective Synthesis of the Brominated Chamigrene Sesquiterpenes

Burckle, A. J.; Vasilev, V. H.; Burns, N. Z. *Angew. Chem. Int. Ed.* **2016,** *55,* 11476–11479.







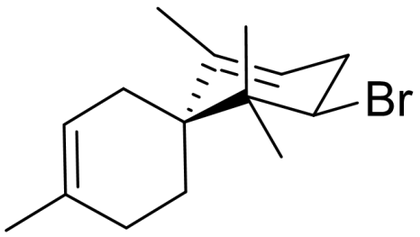


Zachary X. Giustra

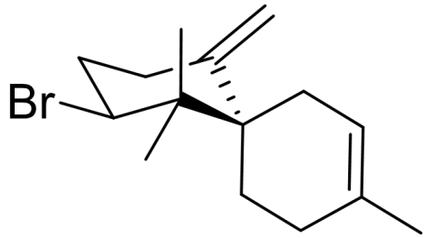
Liu Group

January 1, 2017

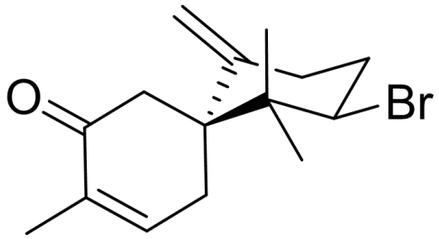
Previous Isolation and Biological Activity



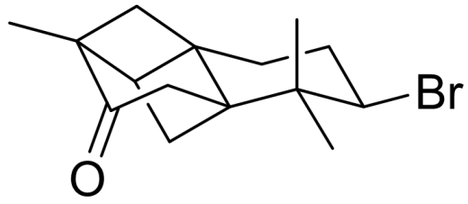
(–)-α-bromochamigrene (**1**)



(+)-β-bromochamigrene (**2**)



(–)-dactylone (**3**)



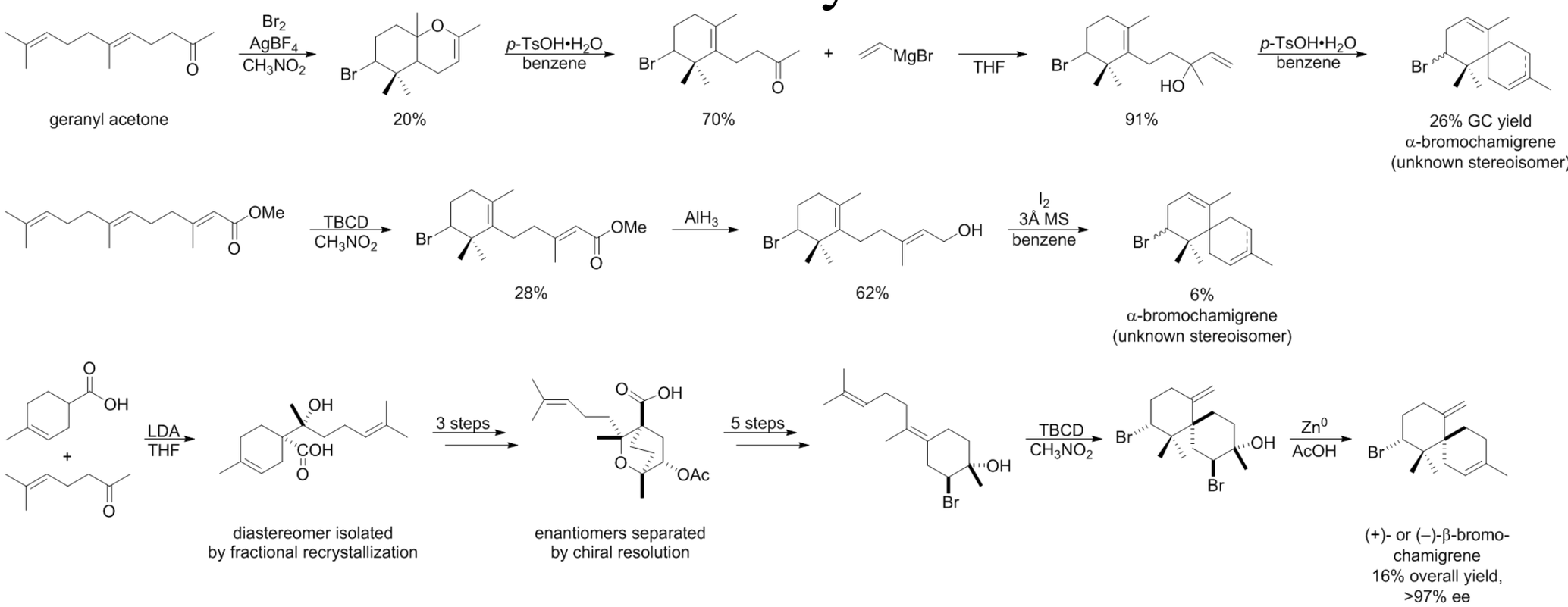
(+)-aplydactone (**4**)

- (–)-α- and (+)-β-bromochamigrene (**1** and **2**) isolated from seaweeds of the genus *Laurencia.*

- Dactylone (**3**) and aplydactone (**4**) isolated from the sea hare *Aplyia dactylomela*; dactylone exhibited activity against human lung, colon, and skin cancer cell lines.

Howard, B. M.; Fenical, W. *Tetrahedron Lett.* **1976,** *17,* 2519–2520.
Guella, G.; Öztunç, A.; Mancini, I.; Pietra, F. *Tetrahedron Lett.* **1997,** *38,* 8261–8264.
Fedorov, S. N.; Reshetnyak, M. V.; Schedrin, A. P.; Ilyin, S. G.; Struchkov, Y. T.; Stonik, V. A.; Elyakov, G. B. *Dokl. Akad. Nauk. SSSR* **1989,** *305,* 877–879.
Fedorov, S. N.; Radchenko, O. S.; Shubina, L. K.; Kalinovsky, A. I.; Gerasimenko, A. V.; Popov, D. Y.; Stonik, V. A. *J. Am. Chem. Soc.* **2001,** *123,* 504–505.
Fedorov, S. N.; Shubina, L. K.; Bode, A. M.; Stonik, V. A. *Cancer Res.* **2007,** *67,* 5914–5920.

Previous Syntheses



- Only racemic syntheses of α-bromochamigrene have been reported (Faulkner, 1976 and Kato, 1978); the stereochemistry of the final products obtained by these approaches was not determined.

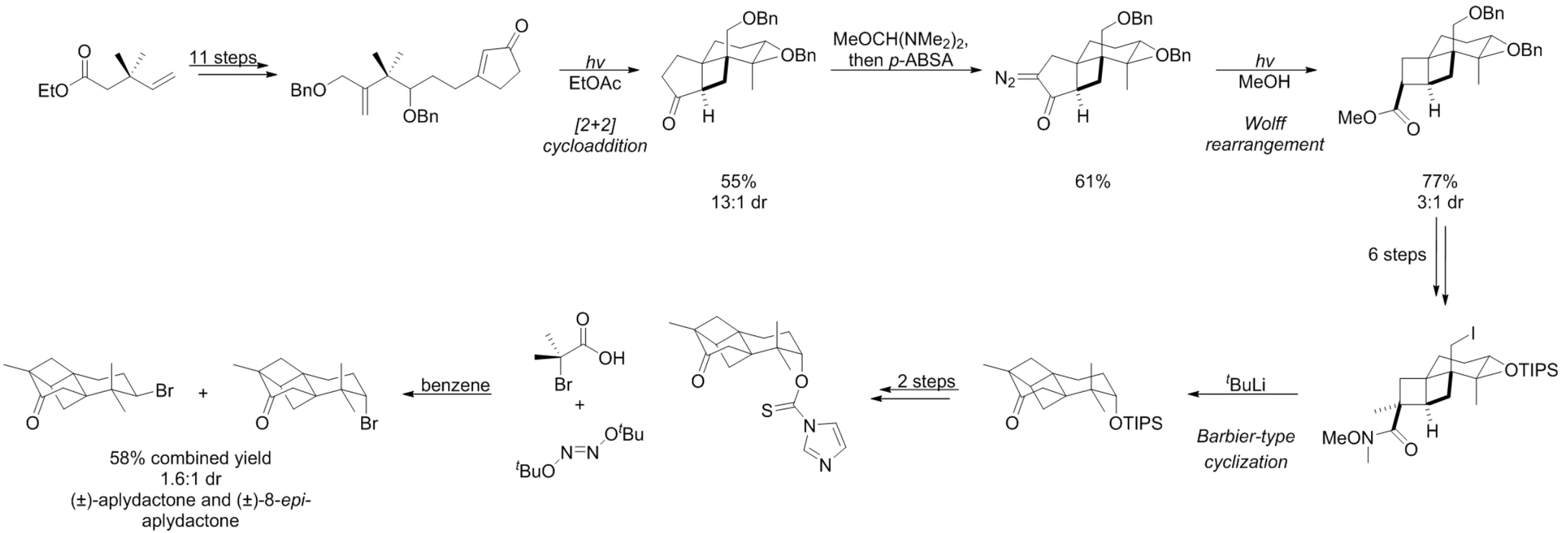
- Both enantiomers of β-bromochamigrene ((+)-**2** and (–)-*ent*-**2**) have been synthesized by a route involving fractional recrystallization and classical resolution (Martin, 1986).

- All syntheses feature a bromonium-induced cyclization of terpenoid precursors to construct the C–Br bond present in the final products.

LDA = lithium diisopropyl amide; TBCD = 2,4,4,6-tetrabromocyclohexane-2,5-dienone

Wolinsky, L. E.; Faulkner, D. J. *J. Org. Chem.* **1976,** *41,* 597–600.
Ichinose, I.; Kato, T. *Chem. Lett.* **1978,** 61–62.
Martín, J. D.; Pérez, C.; Ravelo, J. L. *J. Am. Chem. Soc.* **1986,** *108,* 7801–7811.

Previous Syntheses

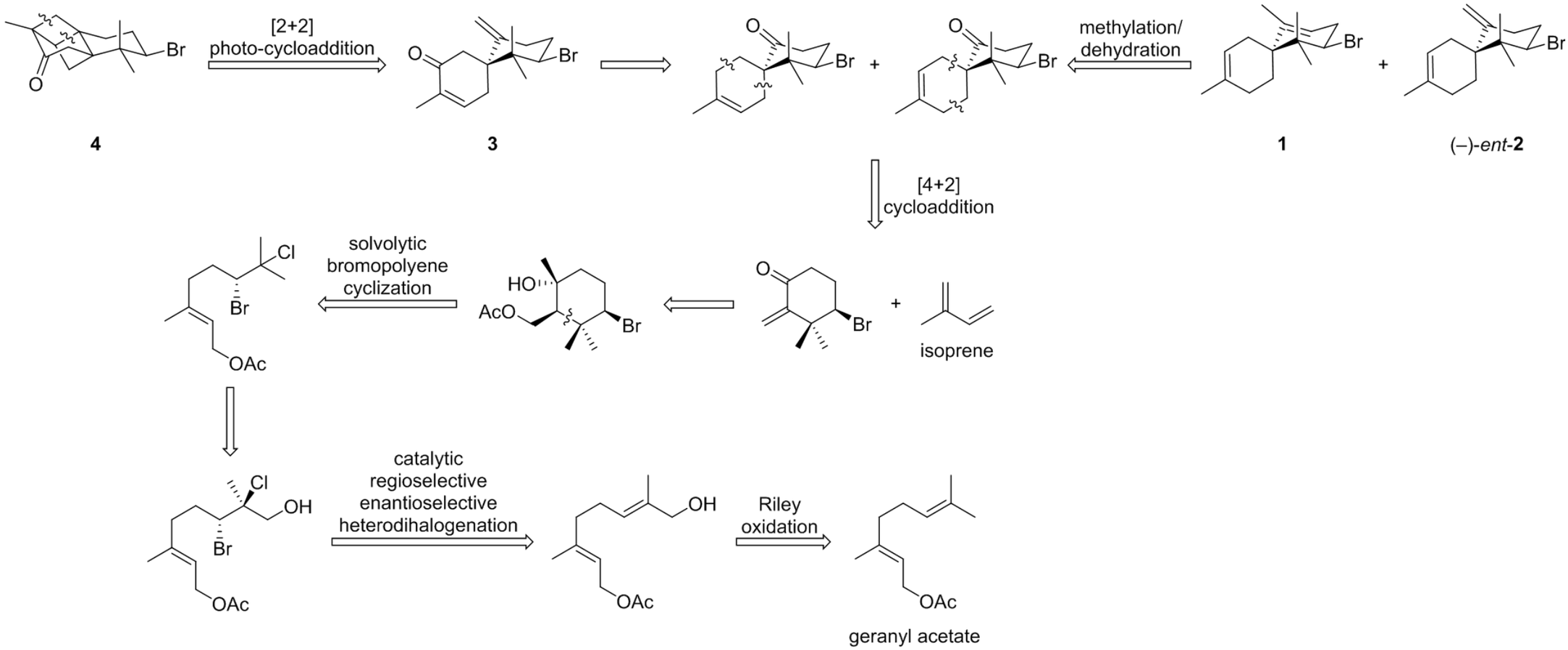


- No previously reported syntheses of **3**.
- First racemic synthesis of aplydactone reported in the very previous issue of *Angew. Chem. Int. Ed.*
- C–Br bond formed via late-stage radical bromination.

p-ABSA = 4-acetamidobenzenesulfonyl azide

Meier, R.; Trauner, D. *Angew. Chem. Int. Ed.* **2016,** *55,* 11251–1255.

Retrosynthesis



- Catalytic, enantioselective heterodihalogention of allylic alcohol to form C–Br bond, and set up solvolysis-assisted cyclization through non-racemizing bromonium intermediate.

- Form spirocycle through Diels-Alder [4+2] cycloaddition.

- Derive **1** and (–)-*ent*-**2** from one Diels-Alder diastereomer, and **3** from the other.

- Convert **3** directly to **4** via [2+2] photocycloaddition.

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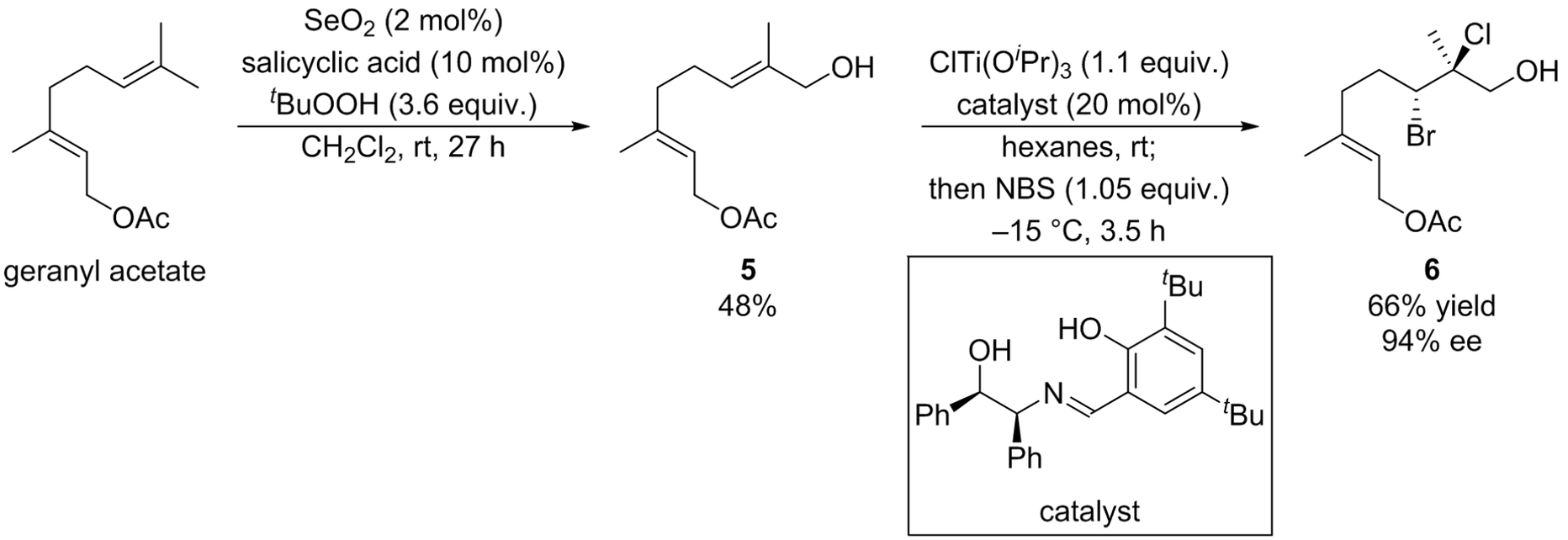
Forward Synthesis



- SeO_2 allylic oxidation selective for more electron-rich alkenes, more substituted terminus of tri-substituted alkenes; rendered catalytic in SeO_2 with excess ^{t}BuOOH.

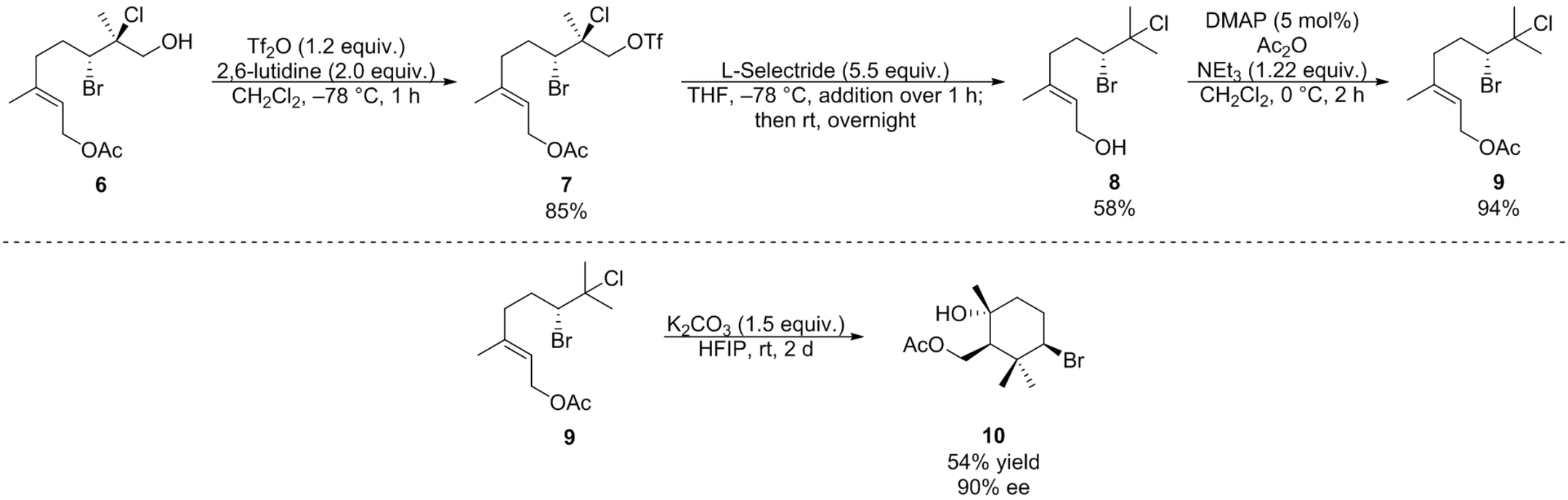
- Catalyzed heterodihalogenation is chemoselective for allylic alcohols over trisubstituted alkenes.

- OH group controls regioselectivity by directing chloride addition to the proximal carbon of the alkene.

NBS = *N*-bromosuccinimide

Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977,** *99,* 5526–55528.
Hu, D. X.; Seidl, F. J.; Bucher, C.; Burns, N. Z. *J. Am. Chem. Soc.* **2015,** *137,* 3795–3798.
Burckle, A. J.; Vasilev, V. H.; Burns, N. Z. *Angew. Chem. Int. Ed.* **2016,** *55,* 11476–11479.

Forward Synthesis



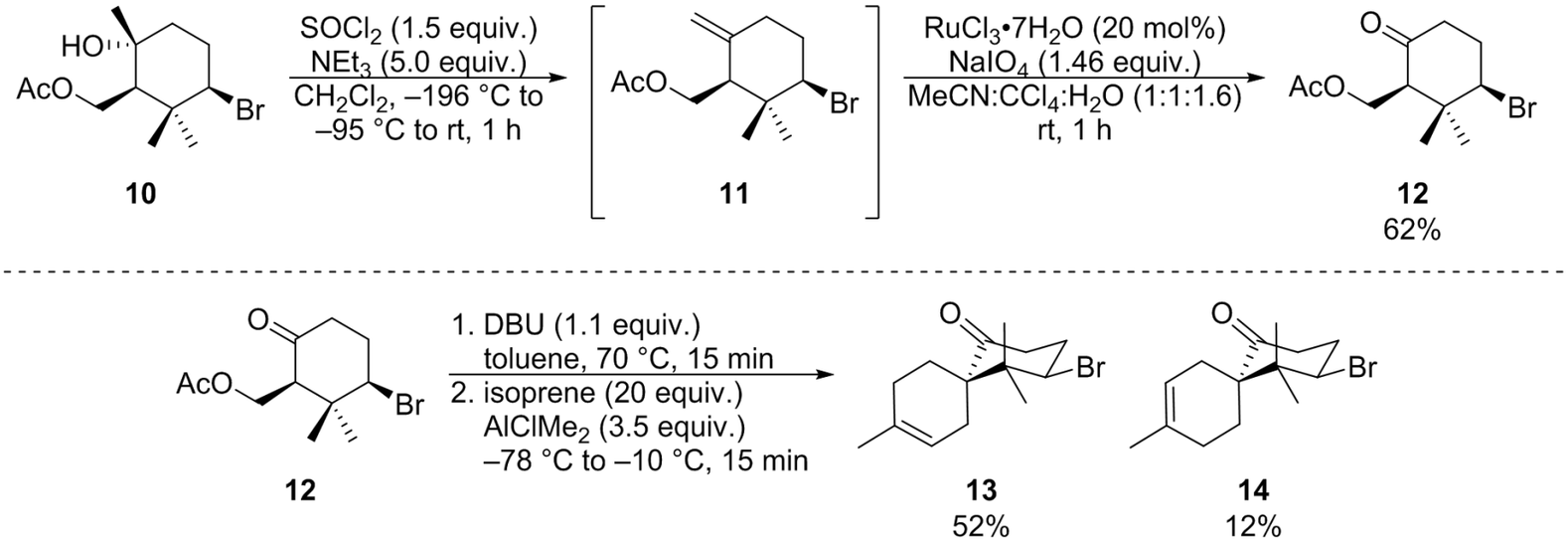
- HFIP serves as a non-nucleophilic, ionizing solvent.

- Enantiomerically pure bromonium ions have been generated previously from bromohydrins, but not from dihalides.

Tf_2O = trifluoromethanesulfonic anhydride; L-Selectride = lithium tri(*sec*-butyl)borohydride;
HFIP = 1,1,1,3,3,3-hexafluoroisopropanol

Schadt, F. L.; Bentley, T. W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1976,** *98,* 7667–7674.
Denmark, S. E.; Burk, M. T.; Hoover, A. J. *J. Am. Chem. Soc.* **2010,** *132,* 1232–1233.
Braddock, D. C.; Marklew, J. S.; Thomas, A. J. F. *Chem. Commun.* **2011,** *47,* 9051–9053.
Burckle, A. J.; Vasilev, V. H.; Burns, N. Z. *Angew. Chem. Int. Ed.* **2016,** *55,* 11476–11479.

Forward Synthesis



- Dehydration of **10** had to be run under N_2 (rather than argon) to avoid possible condensation of the reaction atmosphere at –196 °C.

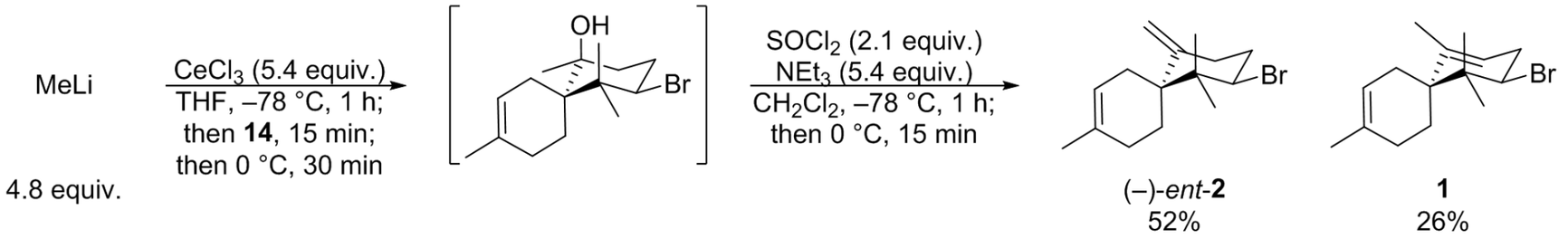
- Addition of MeCN to the solvent system for RuO_4 oxidation was originally found by Sharpless to improve overall reaction performance.

- The initial elimination product from the addition of DBU to **12** underwent spontaneous hetero-Diels-Alder dimerization upon attempts to isolate it, so a two-step procedure was devised to obtain **13** and **14** directly.

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981,** *46,* 3936–3938.
Burckle, A. J.; Vasilev, V. H.; Burns, N. Z. *Angew. Chem. Int. Ed.* **2016,** *55,* 11476–11479.

Forward Synthesis

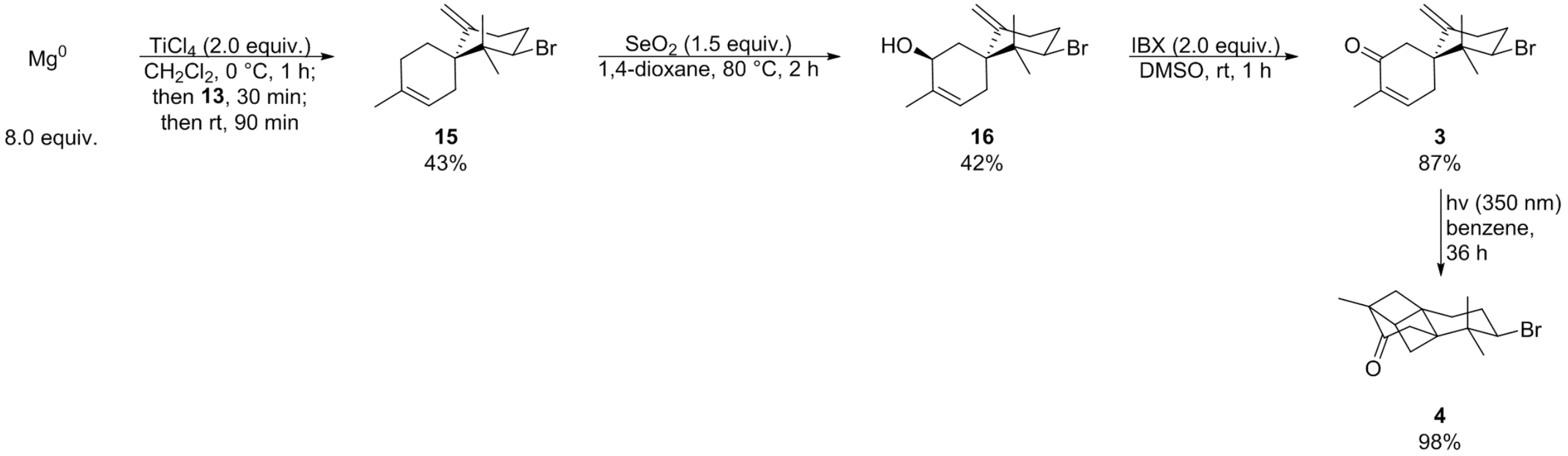


- Methylation with $MeCeCl_2$ generated *in situ* had previously been used by Stoltz in the synthesis of the related halogenated chamigrene (+)-elatol.

- **1** and (–)-*ent*-**2** were isolated as a mixture from column chromatography and were only separated for analysis by preparative TLC.

White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008,** *130,* 810–811.
Burckle, A. J.; Vasilev, V. H.; Burns, N. Z. *Angew. Chem. Int. Ed.* **2016,** *55,* 11476–11479.

Forward Synthesis



- Only the $Mg^0/TiCl_4/CH_2Cl_2$ system afforded effective methylenation of **13**, probably due to steric congestion.

- Successful conversion of **3** to **4** by [2+2] photocyclization was surprising given the 2001 isolation report's conclusion that this reaction was ineffective.

- Significant decomposition was observed when 254 nm light was used; minor but significant conversion (~15%) was observed when **3** was exposed to regular sunlight for 8 days.

IBX = 2-iodoxybenzoic acid

Yan, T.-H.; Tsai, C.-C.; Chien, C.-T.; Cho, C.-C.; Huang, P.-C. *Org. Lett.* **2004,** *6,* 4961–4963.

Fedorov, S. N.; Radchenko, O. S.; Shubina, L. K.; Kalinovsky, A. I.; Gerasimenko, A. V.; Popov, D. Y.; Stonik, V. A. *J. Am. Chem. Soc.* **2001,** *123,* 504–505.

Burckle, A. J.; Vasilev, V. H.; Burns, N. Z. *Angew. Chem. Int. Ed.* **2016,** *55,* 11476–11479.

Summary

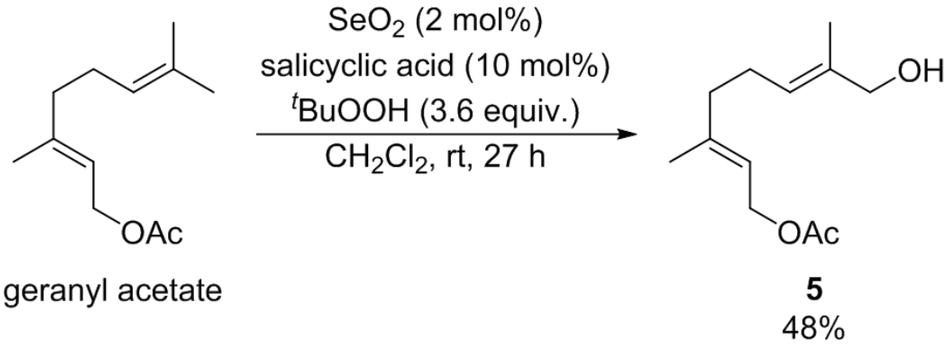
- Syntheses of (–)-α-bromochamigrene, (–)-*ent*-β-bromochamigrene, (–)-dactylone, and (+)-aplydactone all from a common precursor ultimately derived from geranyl acetate.

- Early catalytic, enantioselective heterodihalogenation sets Br-containing stereocenter found in the final products.

- Formation of non-racemizing bromonium intermediate under solvolytic conditions leads to stereoselective cyclization.

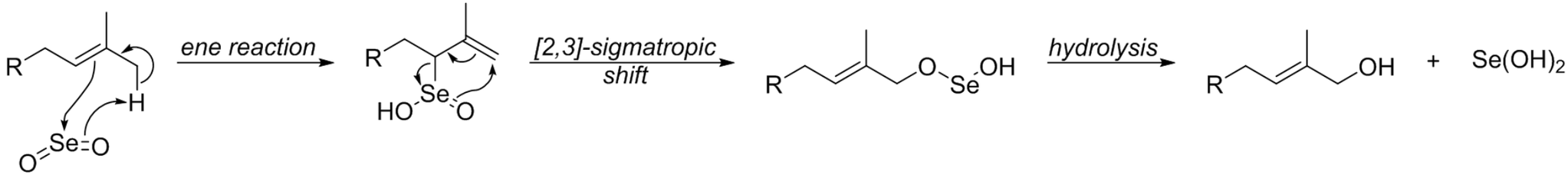
- Direct, possibly biomimetic, conversion of (–)-dactylone to (+)-aplydactone with UV irradiation was successful, contrary to negative results reported in prior literature.

Mechanisms:
Riley SeO_2 Oxidation

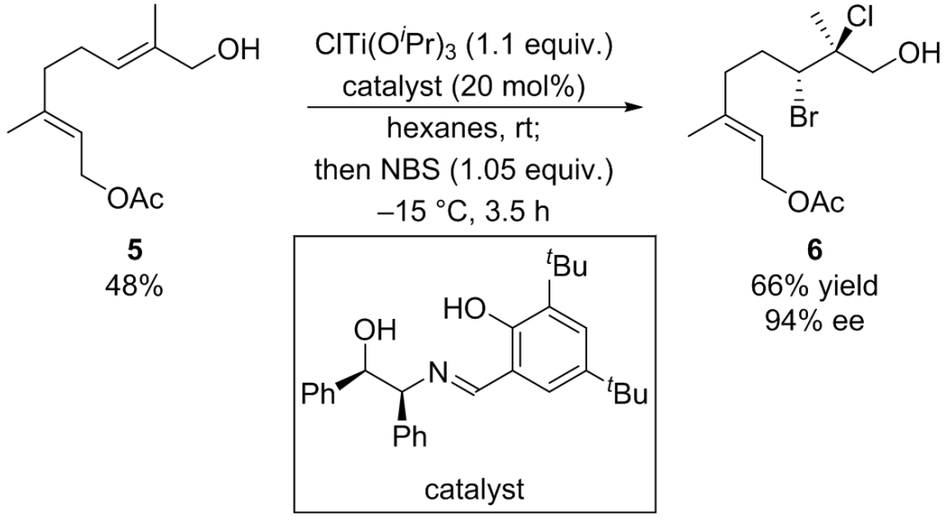


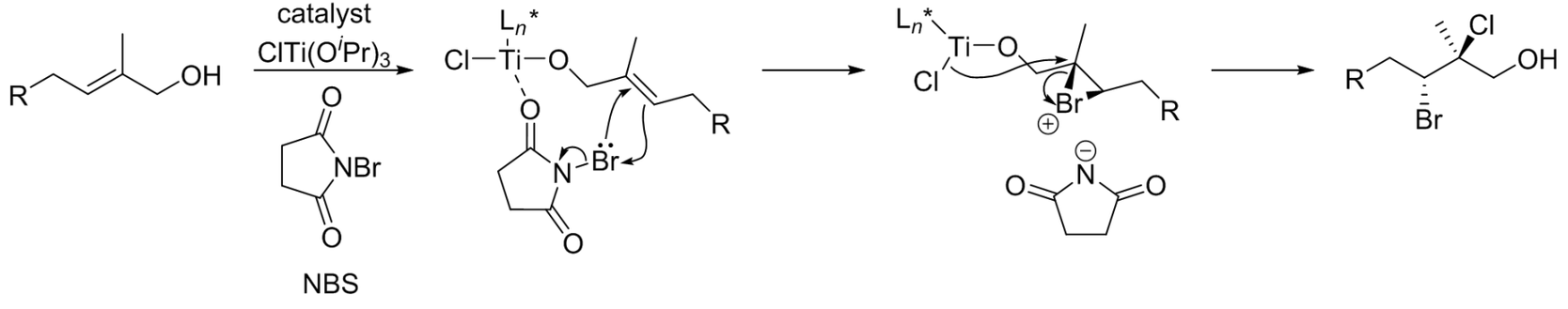
geranyl acetate

5
48%

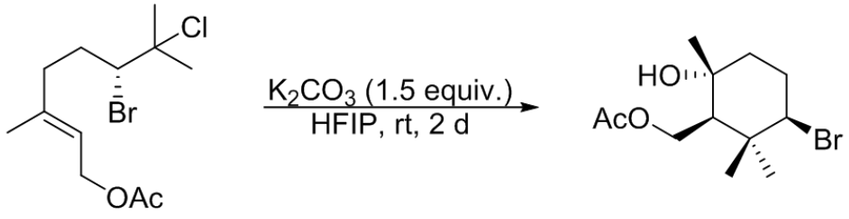


Mechanisms: Heterodihalogenation

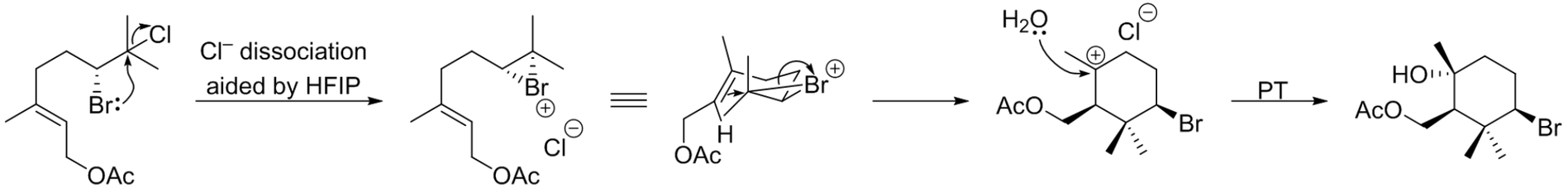




Mechanisms:
Solvolysis-Assisted Cyclization

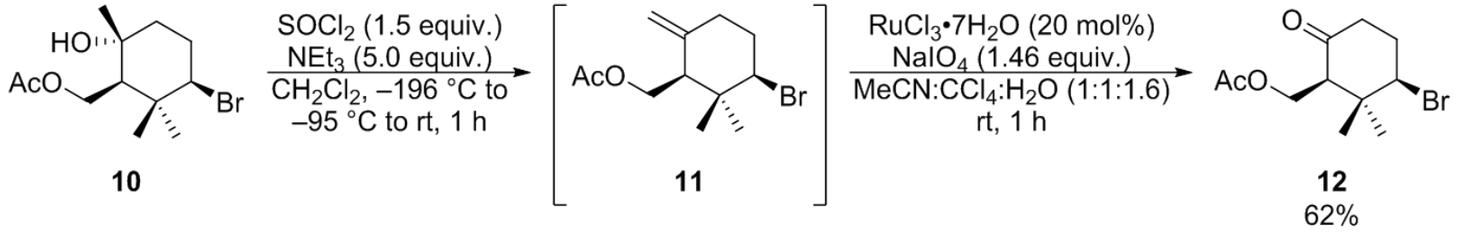


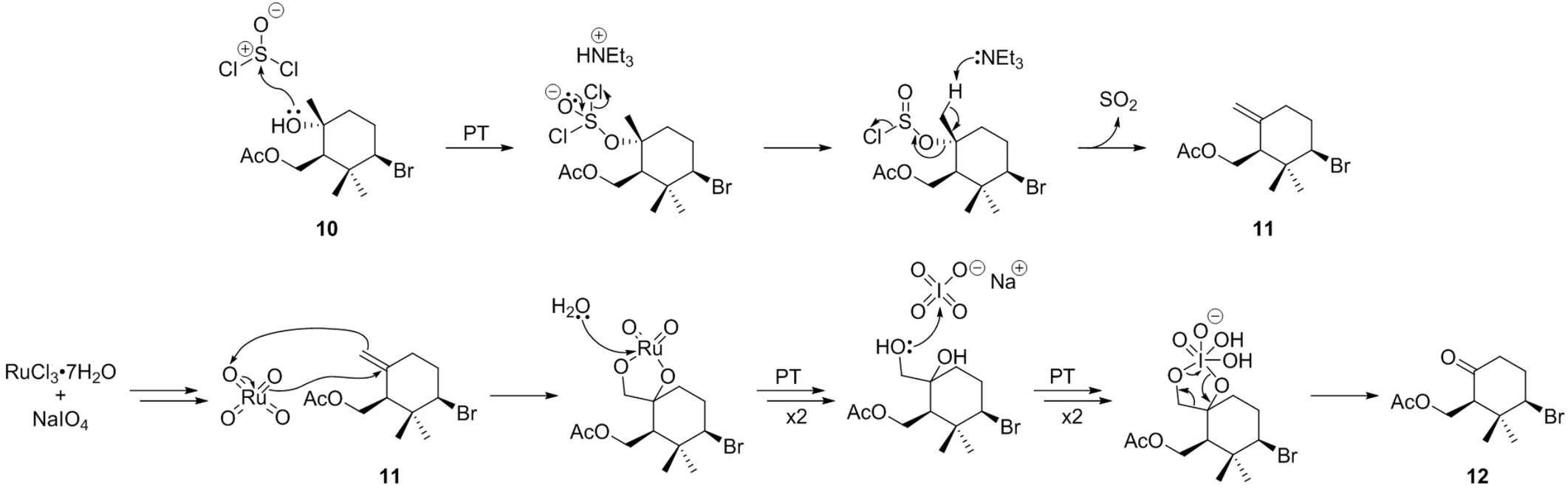
9 **10**
54% yield
90% ee



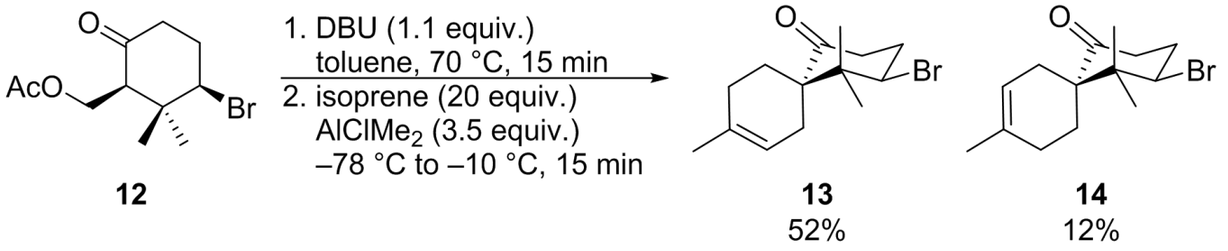
9 **10**

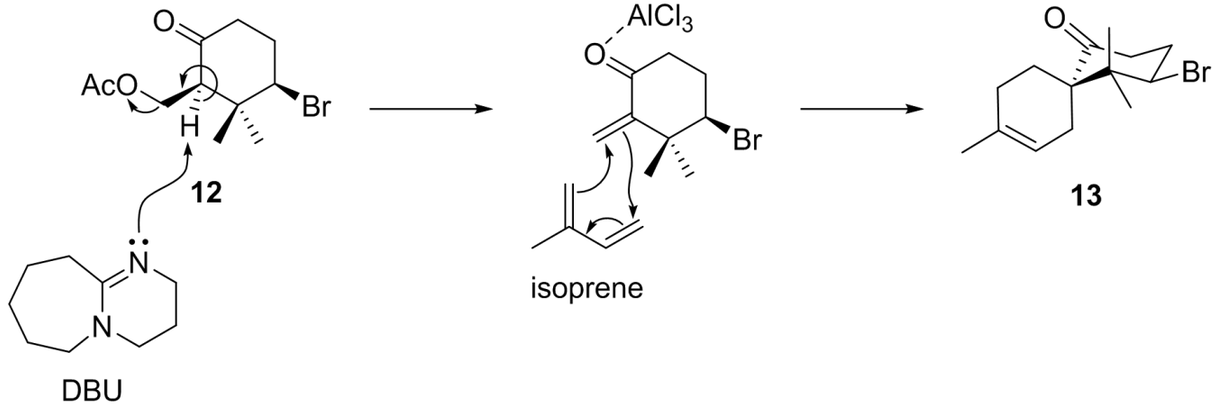
Mechanisms:
Dehydration and Oxidation



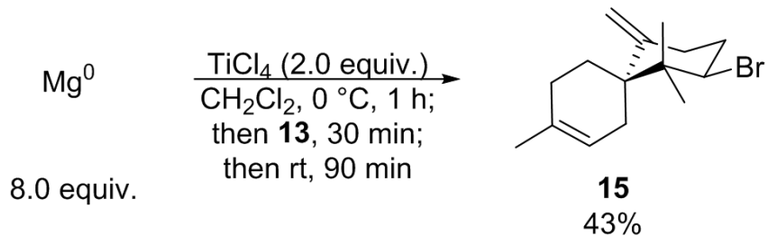


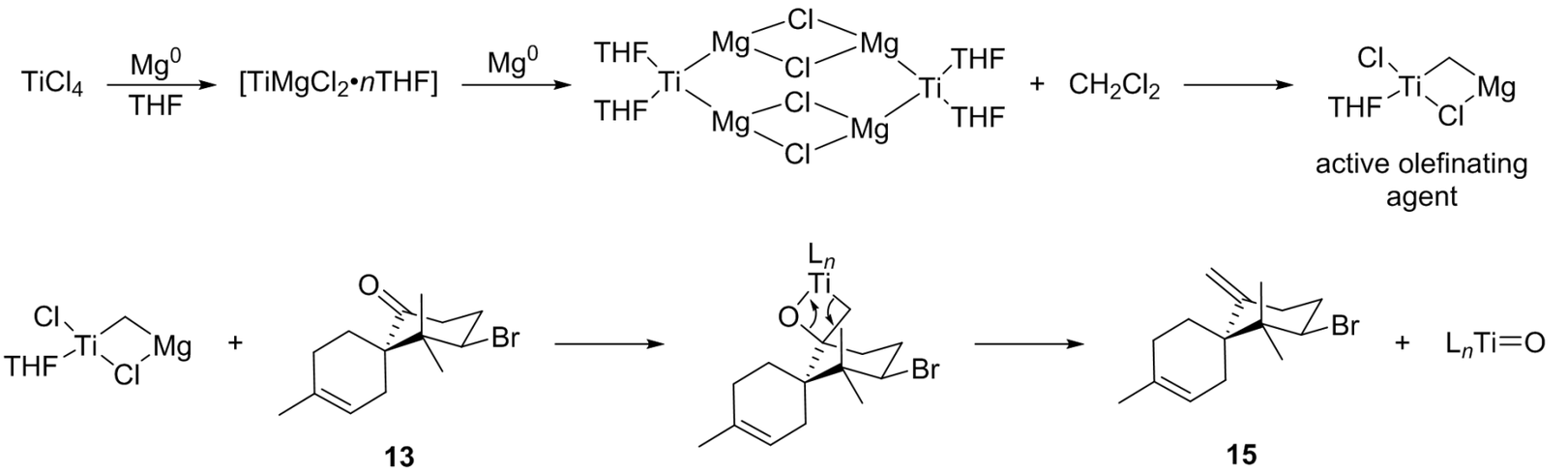
Mechanisms:
Spirocycle Formation





Mechanisms: $Mg^0/TiCl_4/CH_2Cl_2$ Methenylation

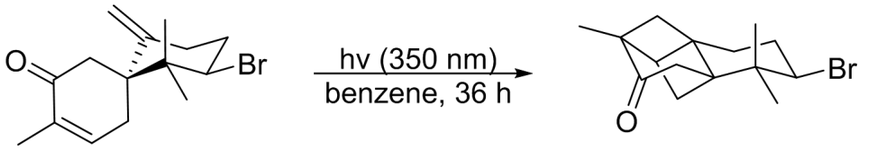




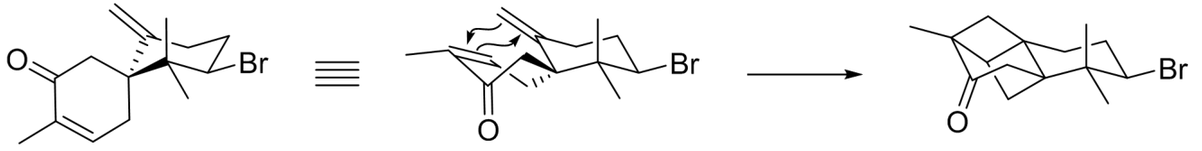
Aleandri, L. E.; Bogdanović, B.; Gaidies, A.; Jones, D. J.; Liao, S.; Michalowicz, A.; Rozière, J.; Schott, A. *J. Organomet. Chem.* **1993,** *459,* 87–93.

Yan, T.-H.; Tsai, C.-C.; Chien, C.-T.; Cho, C.-C.; Huang, P.-C. *Org. Lett.* **2004,** *6,* 4961–4963.

Mechanisms:
[2+2] Photocycloaddition



3 **4**
98%



3 **4**