



Published in final edited form as:

Chem Sci. 2017 January 1; 8(1): 507–514. doi:10.1039/C6SC03347D.

## Enantioselective, Convergent Synthesis of the Ineleganolide Core by a Tandem Annulation Cascade

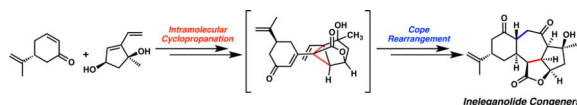
Robert A Craig II, Jennifer L. Roizen, Russell C. Smith, Amanda C. Jones, Scott C. Virgil, and Brian M. Stoltz

Warren and Katherine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

### Abstract

An enantioselective and diastereoselective approach toward the synthesis of the polycyclic norditerpenoid ineleganolide is disclosed. A palladium-catalyzed enantioselective allylic alkylation is employed to stereoselectively construct the requisite chiral tertiary ether and facilitate the synthesis of a 1,3-*cis*-cyclopentenediol building block. Careful substrate design enabled the convergent assembly of the ineleganolide [6,7,5,5]-tetracyclic scaffold by a diastereoselective cyclopropanation-Cope rearrangement cascade under unusually mild conditions. Computational evaluation of ground state energies of late-stage synthetic intermediates was used to guide synthetic development and aid in the investigation of the conformational rigidity of these highly constrained and compact polycyclic structures. This work represents the first successful synthesis of the core structure of any member of the polycyclic norcembranoid diterpene family of natural products. Advanced synthetic manipulations generated a series of natural product-like compounds that were shown to possess selective secretory antagonism of either interleukin-5 or interleukin-17. This bioactivity stands in contrast to the known antileukemic activity of ineleganolide and suggests the norcembranoid natural product core may serve as a useful scaffold for the development of diverse therapeutics.

### Graphical abstract



### Introduction

Target-directed synthesis provides an irreplaceable platform for the invention of approaches to not only the structures of interest, but also to previously unknown complex molecules of potential biological importance. Our group has been fascinated with the beautifully complex, highly oxygenated, and compact polycyclic norcembranoid ineleganolide (**1**) since its initial isolation in 1999 (Figure 1).<sup>1</sup> Over the following decades, the subsequent isolation of

sinulochmodin C (**2**)<sup>2</sup> and a series of closely related constitutional isomers (**3–7**)<sup>3</sup> as well as the disclosure of the biological activity of this family of norditerpenoids (e.g. antileukemic activity of ineleganolide)<sup>1,3a,d,4</sup> has fortified our interest in the synthesis of these molecules. Ineleganolide (**1**) poses a particularly formidable synthetic challenge. Characterized by a fused [6,7,5]-carbocyclic core, the natural product is constrained within a highly cupped configuration by a bridging dihydrofuranone ring. The periphery of this rigid polycyclic scaffold is decorated with a network of nine stereogenic centers, eight of which are contiguous.

Owing to intricate structural complexity found in these isomeric norditerpenoids, no de novo synthetic method exists that enables even the construction of the core scaffolding of any member of the family.<sup>5</sup> The only laboratory-furnished sample of ineleganolide (**1**) was produced by Pattenden in 2011 through biomimetic semisynthesis via transannular anionic cyclization cascade (Scheme 1).<sup>6</sup> Nicolaou,<sup>7</sup> Frontier,<sup>8</sup> and Romo<sup>9</sup> were unable to construct the carbocyclic core of ineleganolide through the synthetic application of similar cyclization cascades. Moeller sought to forge the ineleganolide skeleton (**10**) through electrochemical macrocyclization, but could not successfully construct the required cycloheptanone.<sup>10</sup> The Vanderwal group planned to construct the same C–C bond in the final stages of the synthetic route by intramolecular cyclization through a latent oxocarbenium (i.e. triflate **11**).<sup>11</sup> Representing the most advanced synthetic effort toward ineleganolide (**1**) to date, the prerequisite lactone epimerization could not be accomplished despite exhaustive efforts, thwarting the synthetic strategy.

## Results and Discussion

Exploring the retrosynthetic dissection of ineleganolide (**1**) with an eye toward the isomeric norcembranoids, the common 1,3-*cis*-cyclopentenediol moiety became an attractive synthon for the development of a convergent and modifiable synthetic strategy. In contrast to the unsuccessful previous synthetic strategies (cf. Scheme 1), which incorporate the dihydrofuranone ring at an early stage, we believed the late-stage introduction of this heterocycle would facilitate construction of the carbocyclic core. Thus, ineleganolide (**1**) was envisioned to arise from enone **12** after formation of the dihydrofuranone ring by oxa-Michael addition (Scheme 2). Enone **12** would be synthesized through selective olefin oxidation of cycloheptadiene **13**. Cope rearrangement of divinylcyclopropane **14** would forge tetracycle **13**.<sup>12</sup> Intramolecular cyclopropanation of  $\alpha$ -diazoester **15** would construct cyclopropane **14**. Cyclization precursor **15** would be assembled by the coupling of carboxylic acid **16** and 1,3-*cis*-cyclopentenediol **17**.

Starting with the preparation of diol **17**, we adapted a strategy based on our previously reported efficient and highly enantioselective synthesis of 1,3-*cis*-cyclopentenediol **22** (Scheme 3).<sup>13</sup> Using a palladium-catalyzed enantioselective allylic alkylation to form the chiral tertiary ether, silyl enol ether **18** was transformed into ketone **21** in 82% yield with 92% enantiomeric excess (*ee*). Judicious choice of the chiral ligand, the more readily available and cost-effective (*S*)-*t*-BuPHOX ((*S*)-**20**) provided chiral tertiary ether **21** in the (*S*)-configuration. A series of substrate-controlled diastereoselective transformations from ketone **21** then provided diol **22** in five steps, which serves as a building block for

norcembranoids in the non-natural enantiomeric series (cf. Figure 1).<sup>14</sup> Methylenation of diol **22** afforded diene **23** in near-quantitative yield. Ultimately, saponification of ester **23** furnished diol coupling partner *ent*-**17** in a combined 63% yield over 9 steps from enol ether **18**.

Construction of the complementary carboxylic acid fragment (*ent*-**16**) began with (*R*)-desmethylcarvone ((*R*)-**24**, Scheme 4).<sup>15</sup> The 1,2-addition of lithium enolate **25** under cerium-mediated reaction conditions followed by oxidative 1,3-allylic transposition of the intermediate allylic alcohol with oxoammonium salt TEMPO•BF<sub>4</sub><sup>16</sup> provided cyclohexenone **26**. Saponification of ethyl ester **26** followed by coupling with diol fragment *ent*-**17** and diazotransfer using *p*-ABSA (**27**) provided the pivotal tandem cyclization cascade precursor,  $\alpha$ -diazoester *ent*-**15** in 75% yield over three steps.

Pleasingly, initial attempts to accomplish the planned sequential intramolecular cyclopropanation-Cope rearrangement demonstrated that the transformation proceeded efficiently under mild conditions. Exposure of  $\alpha$ -diazoester *ent*-**15** to catalytic dirhodium tetraacetate (1 mol %) in dichloromethane at ambient temperature enabled the construction of cycloheptadiene **28**, containing the complete carbocyclic core of *ent*-ineleganolide (*ent*-**1**).<sup>17</sup> This cyclization cascade is notable given that it is completed under high dilution in less than 20 minutes at ambient temperature and employs an electronically deactivated olefin in the [3,3]-sigmatropic rearrangement. While examples of divinylcyclopropane rearrangements with electron-neutral and electron-rich olefins are abundant,<sup>12,18</sup> those employing conjugated olefins are limited and typically require forcing conditions.<sup>12c,19</sup>

We speculate that the deleterious effect of an electronically deactivated  $\pi$ -bond in the sequential Cope rearrangement is mitigated by substrate design. Cleavage of highly strained bridging cyclopropane *ent*-**14** upon isomerization to the cycloheptadiene product *ent*-**13** is associated with an increased enthalpic gain compared to a prototypical cyclopropane-fused Cope rearrangement that employs an isolated carbocycle.<sup>20</sup> Additionally, the unsubstituted vinyl group contributes minimal steric hindrance within the bis-*endo* configuration (cf. *ent*-**14**, Scheme 4) and highly organized boat-like transition state required for the *cis*-divinylcyclopropane rearrangement to proceed.<sup>12a,21</sup>

Although the construction of the carbocyclic core of *ent*-ineleganolide (*ent*-**1**) proceeds smoothly from  $\alpha$ -diazoester *ent*-**15**, no trace of the anticipated diene product (*ent*-**13**) was ever detected. Rather,  $\alpha,\beta$ -unsaturated enone **28** was isolated from the reaction mixture as the exclusive product. The 1,3-allylic isomerization is proposed to occur through a base-mediated olefin migration.  $\gamma$ -Deprotonation of  $\alpha,\beta$ -unsaturated ester *ent*-**13** by adventitious acetate and formation of an intermediate conjugated enolate facilitates this process. We hypothesize this isomerization is further aided by a relief of ring strain. These assertions are supported by the observation of an analogous olefin migration under similarly basic reaction conditions.<sup>22</sup>

Installation of the final requisite atom of *ent*-ineleganolide was accomplished by a hydroxyl-directed epoxidation of tetracycle **28** to provide epoxide **29** in 85% yield as a crystalline white solid, enabling the confirmation of the relative configuration by single crystal X-ray

diffraction (Scheme 5). Henceforth known as *ent*-isoinoleganolide A, epoxide **29** is the first known synthetic isomer of *ent*-ineleganolide (**ent-1**) that: (1) contains the full carbocyclic skeleton, (2) possesses all of the required atoms, and (3) has an identical overall oxidation state.

The direct transformation of *ent*-isoinoleganolide A (**29**) into enone **ent-12** was planned via *syn*-facial 1,2-hydride migration, but this approach proved unsuccessful despite exhaustive investigation.<sup>23</sup> Instead, alternative access to tetracycle **ent-12** was developed through the nucleophilic opening of the epoxide moiety within *ent*-isoinoleganolide A (**29**). This ring opening proceeded with concomitant transannular oxa-Michael addition to furnish bromide **30** in near-quantitative yield. Gratifyingly, direct oxidation of the secondary alkyl bromide could be affected through a Kornblum oxidation manifold,<sup>24</sup> affording diketone **31** in 96% yield.

This efficient transformation stands in stark contrast against canonical examples of oxidation under Kornblum conditions. Substrates are usually limited to primary or benzylic halides; only rare and uniformly low yielding examples of the successful Kornblum oxidation of an unactivated secondary halide are found.<sup>24b,25</sup> We hypothesize that the bridging furyl oxygen is critical for this transformation, aiding in the abstraction of the secondary bromide and stabilization of the intermediate carbocation (cf. **33**, Scheme 5). Indeed, the analog lacking the furyl tether fails to produce any trace of oxidation product under similar conditions.<sup>26</sup>

Pleased to have achieved access to ketopyran **31**, we refocused our attention on advancement toward *ent*-ineleganolide (**ent-1**). Chemoselective reduction of ketopyran **31** was observed by the tuning the reduction potential of samarium(II) iodide using lithium chloride as an additive.<sup>27</sup> Under these conditions, in situ generated SmCl<sub>2</sub> cleaves the  $\alpha$ -alkoxyketone bond to provide tetracyclic diol **32**. Installation of the hydrogen from the  $\alpha$ -face upon protonation of the intermediate Sm-enolate was confirmed by single crystal X-ray diffraction. This stereochemical outcome provides the C(7) configuration found within *ent*-ineleganolide. Selective dehydration of diol **32** under acidic conditions provided the desired enone (**ent-12**), another non-natural isomer of *ent*-ineleganolide (*ent*-isoinoleganolide B).

Although we were optimistic this isomer would proceed to *ent*-ineleganolide (**ent-1**) spontaneously by tandem olefin isomerization-oxa-Michael addition, this outcome was not observed. Therefore, with enone **ent-12** in hand, this transformation was investigated in a stepwise manner. Despite intensive efforts to accomplish the isomerization of tetrasubstituted enone **ent-12** to vinylogous diketone **34** (Scheme 6), no trace of either intermediate **34** or *ent*-ineleganolide (**ent-1**) was ever detected.<sup>28</sup> Surprised by the lack of productive reactivity, density functional theory (DFT) was used to explore the thermodynamics of the desired transformation.<sup>29</sup> *ent*-Isoinoleganolide B (**ent-12**) likely exists in the conformation as shown in Scheme 6 (left).<sup>30</sup> In this configuration, the isopropenyl group prefers the pseudoequatorial position and the central cycloheptenone is creased, bisecting the molecule. Relative to the ground state energy of this intermediate, the ground state energy of vinylogous diketone **34** is 13.4 kcal/mol higher in its lowest energy product-like conformation, which posits a pseudoaxial isopropenyl moiety and isomerized cycloheptenone. However, the ground state energy of the natural product (**ent-1**) in its

known configuration<sup>1</sup> is 14.2 kcal/mol lower than vinylogous diketone **34** and overall 0.8 kcal/mol lower in energy than *ent*-isoneleganolide B (*ent*-**12**).

The large ground state energy difference between tetra-substituted enone *ent*-**12** and vinylogous diketone **34** in addition to the empirical evidence for the inability to accomplish the desired olefin isomerization in the laboratory suggest the energy barrier for the conversion from enone *ent*-**12** to diketone **34** is experimentally insurmountable. This is likely due to the large conformational shift required for the isomerization event and the reduced enthalpic stability of the conjugated system. The necessary contortion of the central cycloheptenone renders production of the fully conjugated vinylogous diketone moiety unfeasible. The comparative minimum ground state energy of the natural product (*ent*-**1**) and the large exergonic difference compared to vinylogous diketone **34** reinforced the use of this intermediate in continued synthetic efforts.

Toward this end, the oxidation state manipulation of carbocyclic diene core **28** was explored (Scheme 7). Although conjugate reduction of enone **28** could not be accomplished using nucleophilic hydride sources, development of samarium(II) iodide-mediated reaction conditions, including careful control of reaction temperature and sensible selection of additive, enabled diastereoselective conjugate reduction to provide allylic alcohol **35**.<sup>27</sup> Subsequent hydroxyl-directed epoxidation afforded saturated ketone **36** as a crystalline white solid. The relative configuration of epoxide **36** was established by single crystal X-ray diffraction analysis, confirming the installation of the [6,7]-ring junction in the thermodynamically preferred *trans* configuration identical to that found within *ent*-ineleganolide (*ent*-**1**). As anticipated, application of the previously developed three step Kornblum oxidation procedure for the conversion of epoxide **36** to ketone **37** failed in the absence of the transannular furyl bridge (vide supra), forcing a strategic reevaluation.<sup>26</sup>

In place of a nucleophilic epoxide opening, methods for a radical-mediated reductive epoxide cleavage were investigated. Employing in situ generated titanocene(III) chloride using zinc metal as the optimal reductant, epoxide **36** was opened in regioselective fashion to give the 1,3-diol product.<sup>31</sup> Elaboration to the cycloheptanone was accomplished by oxidation of the newly revealed secondary alcohol to provide *2H-ent*-ineleganolide (**37**) in 33% yield in only two steps from epoxide **36**.

The intermediacy of a tertiary radical at C(7) after the C–O bond scission, in analogous fashion to the reductive opening of ketopyran **31** (see Scheme 5), enabled the installation of the hydrogen on the  $\alpha$ -face as desired. Single crystal X-ray diffraction served not only to confirm the assignment of this relative configuration, but also revealed the conformational similarities between *2H-ent*-ineleganolide (**37**) and *ent*-ineleganolide (cf. *ent*-**1**, Scheme 6). *2H-ent*-Ineleganolide (**37**) contains the *trans*-[6,7]-ring junction, with the isopropenyl substituent in the axial position, and all required stereocenters and functional moieties except the dihydrofuranone bridge. Unfortunately, the conversion of *2H-ent*-ineleganolide (**37**) to *ent*-ineleganolide (*ent*-**1**) proved nontrivial. Formation of the final requisite bond through Suárez reaction,<sup>32</sup> selenoxide elimination, palladium-mediated oxidative desaturation<sup>33</sup> or by employing either lead(IV) acetate or hypervalent iodine reagents<sup>34</sup> failed to produce any traces oxidation at the apical cycloheptanone methylene.

Surprised by the difficulty of functionalizing the central cycloheptanone within *2H-ent*-ineleganolide (**37**), we again turned to computational chemistry. The solid-state conformation of *2H-ent*-ineleganolide (**37A<sup>Ax</sup>**, Figure 2), determined by single crystal X-ray diffraction, revealed the prototypical conformation encountered throughout our synthetic endeavors (e.g. **29**, Scheme 5 and *ent*-**12**, Scheme 6). Conformational isomerization of the isopropenyl moiety into the equatorial position (**37A<sup>Ax</sup>**→**37A<sup>equ</sup>**) increases the ground state energy by 1.0 kcal/mol. Comparatively, the energy minimized conformations **37B<sup>Ax</sup>** and **37B<sup>equ</sup>**, in which *2H-ent*-ineleganolide has adopted the natural product-like configuration within the central cycloheptanone (cf. *ent*-**1**, Scheme 6),<sup>1</sup> are slightly lower. Although the lowest energy conformations of each state (**37A<sup>Ax</sup>** vs. **37B<sup>Ax</sup>**) are equivalent within the error of the computational method, empirical evidence for the difficulty of functionalizing the apical cycloheptanone methylene suggests that there is a large energy barrier that hinders the interconversion between these conformational isomers. Further computational studies are being pursued in order to more completely understand the energetics of the desired transformation.

Throughout the course of these studies, a reasonably large collection of natural-product like compounds was generated. Owing to the known antileukemic properties of ineleganolide, these “ineleganoloids,” in the non-natural enantiomeric series, were evaluated for their activity in DU145 (human prostate cancer) and A2038 (human melanoma) cell viability assays<sup>35</sup> as well as against other oncological targets (EZH2<sup>36</sup> and CD73<sup>37</sup>). Although no notable activity toward any oncological target was discovered, the concurrent screening of this library for activity against targets in other therapeutic areas (i.e., neurological, cardiological, autoimmune, and endocrine function) revealed activity of various ineleganoloids.<sup>38</sup> Diene **28**, bromide **30**, ketopyran **31**, and epoxide **36** were identified as selective interleukin-5 or -17 (IL-5 and IL-17, respectively) secretory inhibitors without significant cytotoxicity (Figure 3).<sup>39</sup> Both IL-5 and IL-17 represent attractive pharmaceutical targets considering their pivotal role in autoimmune response and autoimmune disease (e.g., rheumatoid arthritis).<sup>40</sup> The activity of the ineleganoloids stands in stark contrast with the inability of ineleganolide (**1**) to inhibit cytokine release.<sup>3a</sup> Further investigation of these preliminary results is ongoing and assessment of the biological activity of the ineleganoloids in the natural enantiomeric series will follow in due course.

## Conclusions

In conclusion, an efficient enantioselective and diastereoselective synthetic route to the tetracyclic core of ineleganolide has been disclosed. Convergent assembly of the core scaffold was accomplished by the coupling of two enantioenriched fragments, including a 1,3-*cis*-cyclopentenediol building block common to the polycyclic norcembranoid diterpenes. Tandem intramolecular cyclopropanation-Cope cyclization cascade enabled the diastereoselective construction of the tetracyclic [6,7,5,5]-scaffold of ineleganolide in a single step, providing synthetic access to the core of the polycyclic norcembranoid diterpenes for the first time. Guided by computational data, synthetic advancement facilitated the construction of the first synthetic isomers and analogs of ineleganolide. These natural product-like ineleganoloids advanced the understanding of the conformational

restraints influencing chemistry of the highly compact norcembranoid diterpene scaffold and have led to the identification of biologically active ineleganolide analogs.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

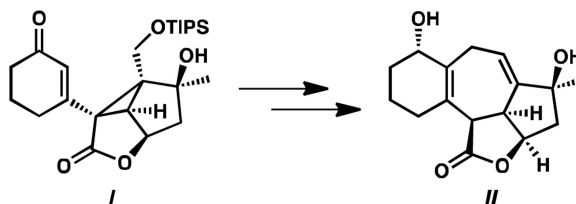
## Acknowledgments

The authors wish to thank the NIH-NIGMS (R01GM080269), Amgen, the Gordon and Betty Moore Foundation, and Caltech for financial support and Eli Lilly & Co. for assistance with biological activity screening. Additionally, the authors gratefully acknowledge Larry Henling and Dr. Michael Takase (Caltech) for X-ray crystallographic structural determination, Dr. Mona Shahgholi and Naseem Torian (Caltech) for mass spectrometry assistance, and Dr. David VanderVelde (Caltech) for NMR experimental assistance and helpful discussion. Additionally, Dr. Jeffrey C. Holder, Dr. Corey M. Reeves, Prof. Hosea M. Nelson, Dr. Jonny R. Gordon, Dr. Pamela M. Tadross, and Beau P. Pritchett (Caltech) and Dr. Ryan Deluca and Dr. Nick Cox (Stanford) are thanked helpful discussion. R.A.C. gratefully acknowledges the support of this work provided by a fellowship from the National Cancer Institute of the National Institutes of Health (NIH) under Award Number F31A17435. J.L.R. thanks the California Tobacco-Related Disease Research Program of the University of California, Grant Number 14DT-0004 for a predoctoral fellowship. A.C.J. thanks the NIH for the support of this work provided by a postdoctoral fellowship (Award Number F32GM082000).

## Notes and references

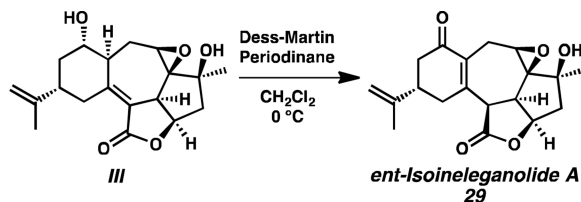
1. Duh C-Y, Wang S-K, Chia M-C, Chiang MY. *Tetrahedron Lett.* 1999; 40:6033.
2. Tseng Y-J, Ahmed AF, Dai C-F, Chiang MY, Sheu J-H. *Org. Lett.* 2005; 7:3813. [PubMed: 16092882]
3. (a) Lillsunde K-E, Festa C, Adel H, de Marino S, Lombardi V, Tilvi S, Nawrot D, Zampella A, D'Souza L, D'Auria M, Tammela P. *Mar. Drugs.* 2014; 12:4045. [PubMed: 25056629] (b) Radhika P, Subba Rao PV, Anjaneyulu V, Asolkar RN, Laatsch H. *J Nat. Prod.* 2002; 65:737. [PubMed: 12027754] (c) Sheu J-H, Ahmed AF, Shiue R-T, Dai C-F, Kuo Y-H. *J Nat. Prod.* 2002; 65:1904. [PubMed: 12502336] (d) Iguchi K, Kajiyama K, Yamada Y. *Tetrahedron Lett.* 1995; 36:8807.
4. (a) Huang C-Y, Tseng Y-J, Chokkalingam U, Hwang T-L, Hsu C-H, Dai C-F, Sung P-J, Sheu J-H. *J Nat. Prod.* 2016; 79:1339. [PubMed: 27142697] (b) Tseng Y-J, Wang S-K, Duh C-Y. *Mar. Drugs.* 2013; 11:3288. [PubMed: 23985899] (c) Huang K-J, Chen Y-C, El-Shazly M, Du Y-C, Su J-H, Tsao C-W, Yen W-H, Chang W-B, Su Y-D, Yeh Y-T, Lu M-C. *Molecules.* 2013; 18:2924. [PubMed: 23459302] (d) Kamel HN, Slattery M. *Pharm. Biol.* 2005; 43:253.
5. While most synthetic efforts toward the polycyclic norcembranoids have been focused on ineleganolide (**1**), one attempt was made to synthesize the core of yonanolide (**5**), see: Ueda Y, Abe H, Iguchi K, Ito H. *Tetrahedron Lett.* 2011; 52:3379.
6. (a) Li Y, Pattenden G. *Tetrahedron.* 2011; 67:10045. (b) Li Y, Pattenden G. *Nat. Prod. Rep.* 2011; 28:1269. [PubMed: 21637894] (c) Li Y, Pattenden G. *Nat. Prod. Rep.* 2011; 28:429. [PubMed: 21212904]
7. Pratt, BA. Ph.D. dissertation. La Jolla, California: Scripps Research Institute; 2008.
8. (a) O'Connell, C. Ph.D. dissertation. Belfast, Northern Ireland, U.K.: Queen's University of Belfast; 2006. O'Connell, CE., *Frontier, AJ. Abstracts of Papers, 32nd Northeast Regional Meeting of the American Chemical Society; Oct 31–Nov 3, 2004; Rochester, NY. American Chemical Society; 2004. GEN-088*
9. (a) Liu, G. Ph.D. dissertation. College Station, Texas: Texas A&M University; 2011. Liu, G., Romo, D. *Abstracts of Papers, 237th American Chemical Society National Meeting; Mar 22–26, 2009; Salt Lake City, UT. American Chemical Society; 2009. ORGN-083*
10. (a) Tang, F. Ph.D. dissertation. St. Louis, Missouri: Washington University in St. Louis; 2009. (b) Tang F, Moeller KD. *Tetrahedron.* 2009; 65:10863. (c) Tang F, Moeller KD. *J Am. Chem. Soc.* 2007; 129:12414. [PubMed: 17894501]

11. (a) Horn EJ, Silverston JS, Vanderwal CD. *J Org. Chem.* 2016; 81:1819. [PubMed: 26863401] (b) Horn, EJ. Ph.D. dissertation. Irvine, CA: University of California at Irvine; 2014.
12. (a) Krüger S, Gaich T, Beilstein J. *Org. Chem.* 2014; 10:183.(b) Davies HML, Stafford DG, Doan BD, Houser JH. *J Am. Chem. Soc.* 1998; 120:3326.(c) Davies HML. *Tetrahedron.* 1993; 49:5203. (d) Vogel E. *Angew. Chem., Int. Ed.* 1963; 2:1.
13. Craig RA II, Roizen JL, Smith RC, Jones AC, Stoltz BM. *Org. Lett.* 2012; 14:5716. [PubMed: 23101616]
14. The naturally occurring enantiomers of inelegranolide (**1**) and the related norcembranoid diterpenes (**2–7**) were originally established by analogy to the known absolute stereochemistry of sinulochmodin C (**2**, see reference 2). The natural enantiomers of norditerpenoids **1–7** could be accessed using (*R*)-*t*-BuPHOX ((*R*)-**20**), which has been synthesized and used by our group in the enantioselective total synthesis of (+)-Liphagal, see: Day JJ, McFadden RM, Virgil SC, Kolding H, Alleva JL, Stoltz BM. *Angew. Chem., Int. Ed.* 2011; 50:6814. Alternatively, more cost-effective PHOX ligands derived (*R*)-valine have been shown to be comparably effective to (*R*)-*t*-BuPHOX for the enantioselective formation of ketone **21** from enol ether **18**, see: Craig RA II, Stoltz BM. *Tetrahedron Lett.* 2015; 56:4670. [PubMed: 26257445]
15. (*R*)-Desmethylocarvone ((*R*)-**24**) is available in 6 steps from (*R*)-carvone, see: González MA, Ghosh S, Rivas F, Fischer D, Theodorakis EA. *Tetrahedron Lett.* 2004; 45:5039. Chen J, Marx JN. *Tetrahedron Lett.* 1997; 38:1889. Lavallée J-F, Spino C, Ruel R, Hogan KT, Deslongchamps P. *Can. J. Chem.* 1991; 70:1406.
16. Shibuya M, Tomizawa M, Iwabuchi Y. *J Org. Chem.* 2008; 73:4750. [PubMed: 18500838]
17. Although no trace of cyclopropane *ent*-**14** has been detected during the conversion of  $\alpha$ -diazoester *ent*-**15** to cycloheptadiene **28**, the isolation of cyclopropane **I** and the subsequent step-wise advancement to cycloheptadiene **II** supports the assertion that a tandem cyclopropanation-Cope rearrangement cascade is operative. Without isolated intermediates, however, we are unable to conclusively rule out the formation of cycloheptadiene product **28** through a direct (4 + 3) cycloaddition from  $\alpha$ -diazoester *ent*-**15**, see: Guzmán PE, Lian Y, Davies HML. *Angew. Chem. Int. Ed.* 2014; 53:13083.

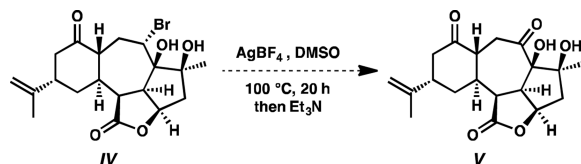


18. (a) Gaydou M, Miller RE, Delpont N, Ceccon J, Echavarren AM. *Angew. Chem. Int. Ed.* 2013; 52:6396.(b) Vaswani RG, Day JJ, Wood JL. *Org. Lett.* 2009; 11:4532. [PubMed: 19810762] (c) Davies HML, Calvo RL, Townsend RJ, Ren P, Churchill RM. *J Org. Chem.* 2000; 65:4261. [PubMed: 10891124] (d) Kende AS, Smalley TL Jr, Huang H. *J Am. Chem. Soc.* 1999; 121:7431.
19. (a) Osler JD, Unsworth WP, Taylor RJK. *Org. Biomol. Chem.* 2013; 11:7587. [PubMed: 24097156] (b) Ito H, Takeguchi S, Kawagishi T, Iguchi K. *Org. Lett.* 2006; 8:4883. [PubMed: 17020327] (c) Fukuyama T, Liu G. *J Am. Chem. Soc.* 1996; 118:7426.(d) Wender PA, Eissenstat MA, Filosa MP. *J Am. Chem. Soc.* 1979; 101:2196.
20. For comparisons of the strain energy of isolated cyclopropanes with fused cyclopropane ring systems, see: Borst MLG, Ehlers AW, Lammertsma K. *J Org. Chem.* 2005; 70:8110. [PubMed: 16277336] Wiberg KB, Kass SR, de Meijere A, Bishop KC III. *J Am. Chem. Soc.* 1985; 107:1003.
21. (a) Zora M. *J Mol. Struct.: THEOCHEM.* 2004; 681:113.(b) Zora M. *J Org. Chem.* 2003; 68:9635. [PubMed: 14656088] (c) Zora M, Özkan I, Dani man MF. *J Mol. Struct.: THEOCHEM.* 2003; 636:9.(d) Doering WVE, Roth WR. *Angew. Chem. Int. Ed.* 1963; 2:115.
22. Oxidation of diol **III** resulted in reformation of isoinlegranolide A (**29**) after olefin migration in the presence of the adventitious acetate byproduct derived from Dess-Martin periodinane.



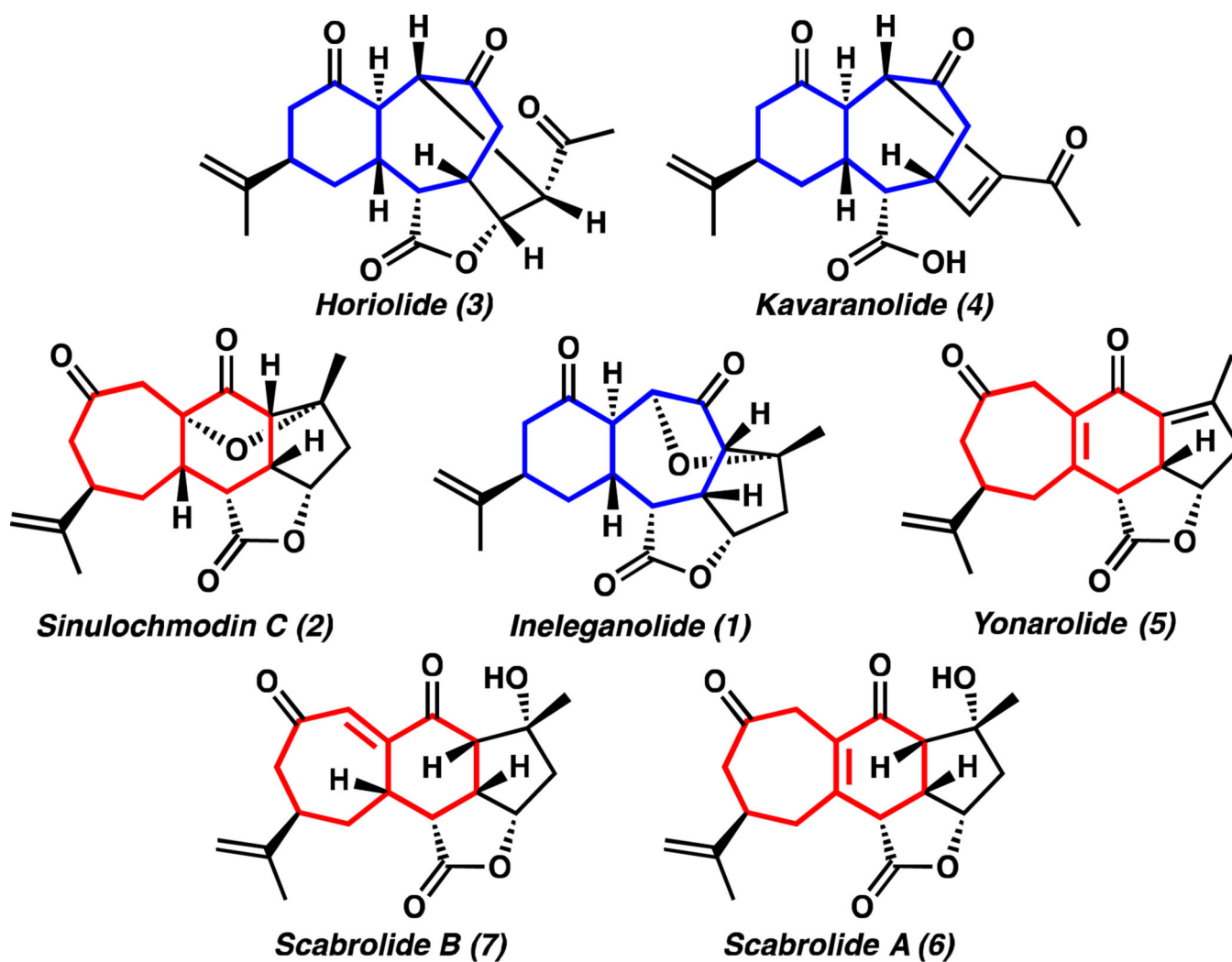


23. A characteristic list of the conditions attempted to induce the desired epoxide isomerization:  $\text{H}_2\text{SO}_4/\text{CHCl}_3$ ,  $\text{SiO}_2/\text{CHCl}_3$ ,  $\text{DBU}/\text{CHCl}_3$ ,  $\text{KO}t\text{-Bu}/\text{THF}$ ,  $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2/\text{benzene}$ ,  $\text{BF}_3\cdot\text{Et}_2\text{O}/\text{CHCl}_3$ ,  $\text{In}(\text{OTf})_3/\text{CHCl}_3$ ,  $\text{Al}(\text{O}i\text{-Pr})_3/\text{CHCl}_3$ ,  $\text{Ti}(\text{O}i\text{-Pr})_4/\text{THF}$ ,  $\text{Zn}(\text{OTf})_2/\text{toluene}$ ,  $\text{Mg}(\text{OTf})_2/\text{toluene}$ ,  $\text{MgCl}_2/\text{toluene}$ .
24. (a) Ly TW, Liao J-H, Shia K-S, Liu H-J. *Synthesis*. 2004:271. (b) Ganem B, Boeckman RK Jr. *Tetrahedron Lett.* 1974; 15:917. (c) Kornblum N, Jones WJ, Anderson GJ. *J Am. Chem. Soc.* 1959; 81:4113.
25. (a) Liu H-J, Sun D. *Tetrahedron Lett.* 1997; 38:6159. (b) Dave P, Byun H-S, Engel R. *Synth. Commun.* 1986; 16:1343.
26. Under analogous Kornblum oxidation conditions, bromide **IV** fails to undergo any oxidative transformation. In fact, bromide **IV** does not react until heated above 120 °C, at which point only dehydration of the substrate is observed.

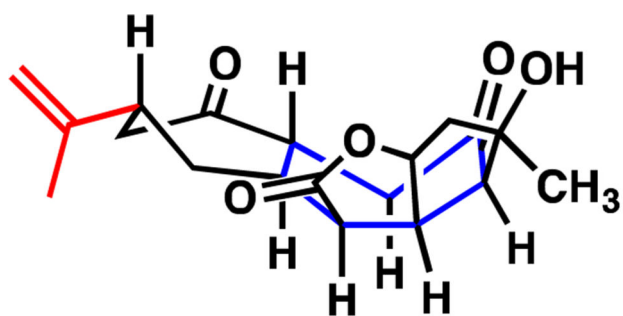


27. (a) Szostak M, Spain M, Procter DJ. *J Org. Chem.* 2014; 79:2522. [PubMed: 24517639] (b) Reisman SE, Ready JM, Weiss MM, Hasuoka A, Hirata M, Tamaki K, Ovaska TV, Smith CJ, Wood JL. *J Am. Chem. Soc.* 2006; 128:1448. [PubMed: 16448105] (c) Miller RS, Sealy JM, Shabangi M, Kuhlman ML, Fuchs JR, Flowers RA. *J Am. Chem. Soc.* 2000; 122:7718.
28. A characteristic list of the conditions attempted to induce the desired olefin isomerization:  $\text{DBU}/\text{CH}_2\text{Cl}_2$ ,  $\text{PdCl}_2(\text{CH}_3\text{CN})_2/\text{CH}_2\text{Cl}_2$ , Grubbs Gen. II/MeOH,  $\text{RhCl}_3\cdot\text{H}_2\text{O}/\text{EtOH}$ , LHMDS/THF.
29. Calculations were performed with Spartan '10 (Wavefunction, Inc., Irvine, CA). The in vacuo equilibrium geometry for each structure was calculated by a series of sequential calculations as follows: Hartree–Fock computation (equilibrium geometry, 3-21G basis set), DFT (equilibrium geometry, B3LYP/6-31G basis set), DFT (energy, B3LYP/6-311+G\*\* basis set), DFT (equilibrium geometry, B3LYP/6-311+G\*\* basis set). The error from these calculations is  $\pm 0.23$  kcal/mol, thus all energy differences larger than 0.46 kcal/mol were considered significant. Except for molecular mechanics and semi-empirical models, the calculation methods used in Spartan have been documented in: Shao Y, Molnar LF, Jung Y, Kussmann J, Ochsenfeld C, Brown ST, Gilbert ATB, Slipchenko LV, Levchenko SV, O'Neill DP, DiStasio RA Jr, Lochan RC, Wang T, Beran GJO, Besley NA, Herbert JM, Lin CY, Van Voorhis T, Chien SH, Sodt A, Steele RP, Rassolov VA, Maslen PE, Korambath PP, Adamson RD, Austin B, Baker J, Byrd EFC, Dachsel H, Doerksen RJ, Dreuw A, Dunietz BD, Dutoi AD, Furlani TR, Gwaltney SR, Heyden A, Hirata S, Hsu C-P, Kedziora G, Khalliulin RZ, Klunzinger P, Lee AM, Lee MS, Liang WZ, Lotan I, Nair N, Peters B, Proynov EI, Pieniazek PA, Rhee YM, Ritchie J, Rosta E, Sherrill CD, Simmonett AC, Subotnik JE, Woodcock HL III, Zhang W, Bell AT, Chakraborty AK, Chipman DM, Keil FJ, Warshel A, Hehre WJ, Schaefer HF III, Kong J, Krylov AI, Gill PMW, Head-Gordon M. *Phys. Chem. Chem. Phys.* 2006; 8:3172. [PubMed: 16902710]
30. The conformation of *ent*-isoinleganolide B (**ent-12**) was established by two-dimensional NOE studies and by analogy to the conformation of precursors **28–32**, as established by single crystal X-ray diffraction. The ground state energies of the other conformations of *ent*-isoinleganolide B (**ent-12**) were additionally assessed by our computational method and are all within  $\pm 1.8$  kcal/mol of one another. For full details, see Supporting Information.
31. (a) Jiménez T, Campaña AG, Bazdi B, Paradas M, Arráez-Román D, Segura-Carretero A, Fernández-Gutiérrez A, Oltra JE, Robles R, Justicia J, Cuerva JM. *Eur. J. Org. Chem.* 2010:4288.

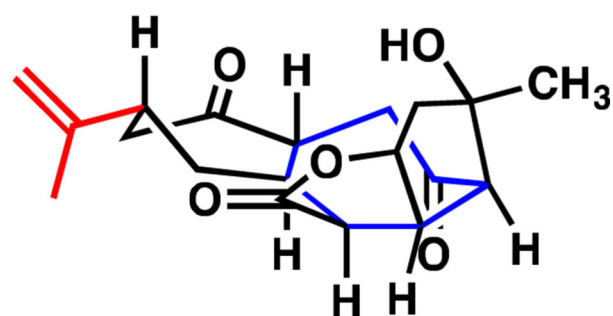
- (b) Gansäuer A, Pierobon M, Bluhm H. *Angew. Chem., Int. Ed.* 1998; 37:101.(c) RajanBabu TV, Nugent WA. *J Am. Chem. Soc.* 1994; 116:986.(d) RajanBabu TV, Nugent WA, Beattie MS. *J Am. Chem. Soc.* 1990; 112:6408.
32. (a) Betancor C, Freire R, Pérez-Martín I, Prangé T, Suárez E. *Tetrahedron.* 2005; 61:2803.(b) de Armas P, Concepción JI, Francisco CG, Hernández R, Salazar JA, Suárez E. *J Chem. Soc., Perkin Trans. 1.* 1989:405.(c) Concepción JI, Francisco CG, Hernández R, Salazar JA, Suárez E. *Tetrahedron Lett.* 1984; 25:1953.
33. A wide variety of conditions were screened for palladium-mediated oxidative desaturation both directly from ketone **37** as well as stepwise through the intermediate silyl enol ether without success. For select examples, see: Diao T, Stahl SS. *J Am. Chem. Soc.* 2011; 133:14566. [PubMed: 21851123] Ohmori N. *J Chem. Soc., Perkin Trans. 1.* 2002:755. Degrado SJ, Mizutani H, Hoveyda AH. *J Am. Chem. Soc.* 2001; 123:755. [PubMed: 11456598]
34. Efforts were focused on the application of 2-iodoxybenzoic acid (IBX) and PhI(OH)(OTs), see: Nicolaou KC, Montagnon T, Baran PS, Zhong YL. *J Am. Chem. Soc.* 2002; 124:2245. [PubMed: 11878978] Moriarty RM, Vaid RK, Hopkins TE, Vaid BK, Prakash O. *Tetrahedron Lett.* 1990; 31:201.
35. Compounds **28**, **29**, **30**, **31**, and **32** were screened against DU145 and A2038 cell viability assays in triplicate, revealing no significant activity. Special, personal thanks to Prof. David Horne and Prof. Sangkil Nam (City of Hope, Duarte, CA) for their assistance in performing these cell viability assays.
36. Chase A, Cross NCP. *Clin. Cancer Res.* 2011; 17:2613. [PubMed: 21367748]
37. Young A, Mittal D, Stagg J, Smyth MJ. *Cancer Discov.* 2014; 4:879. [PubMed: 25035124]
38. Biological activity data generated through the Open Innovation Drug Discovery Program (OIDD) and screening data were supplied courtesy of Eli Lilly and Company—used with Lilly's permission. To learn more about the Lilly Open Innovation Drug Discovery program, please visit the program website at <https://openinnovation.lilly.com> (last accessed on 06-15-2016).
39. Biological activity data was generated employing a high throughput screen based on primary blood mononuclear cells (PMBCs) and using 10  $\mu$ M of compound. The results are reported as follows: compound number (% secretory inhibition IL-5, % secretory inhibition IL-17, % PMBC cell death). Diene **28** (7.8, 38.1, 3.9), bromide **30** (47.2, 3.8, 4.9), ketopyran **31** (40.2, < 2, 6.7), epoxide **36** (40.2, < 2, 5.9). See Supporting Information and Table S1 for full details.
40. (a) Chang SH, Dong C. *Cell. Signalling.* 2011; 23:1069. [PubMed: 21130872] (b) Kouro T, Takatsu K. *Int. Immunol.* 2009; 21:1303. [PubMed: 19819937] (c) Simmons DL. *Drug Discovery Today.* 2006; 11:210. [PubMed: 16580598]



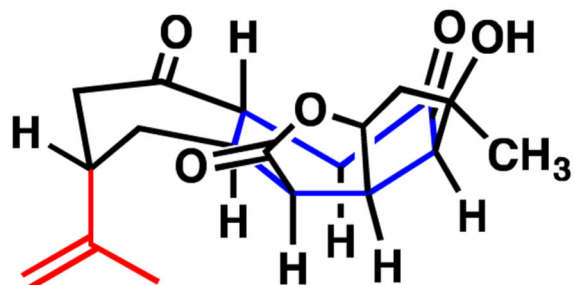
**Figure 1.** Isomeric [6,7]- and [7,6]-Norcembranoid Diterpene Natural Products (blue and red, respectively).



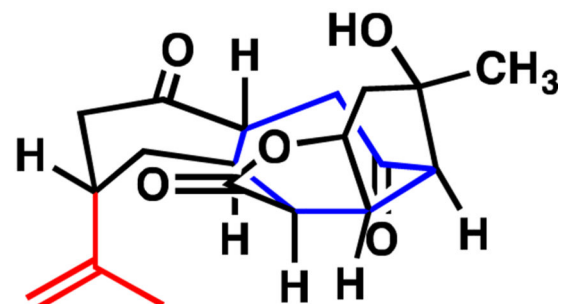
**37A<sup>equ</sup> : 1.0 kcal/mol**



**37B<sup>equ</sup> : 0.6 kcal/mol**

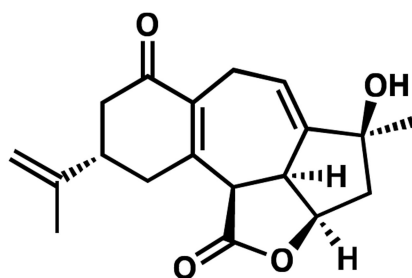
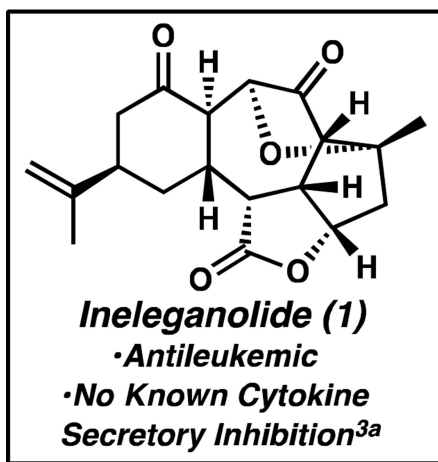


**37A<sup>ax</sup> : 0.0 kcal/mol**

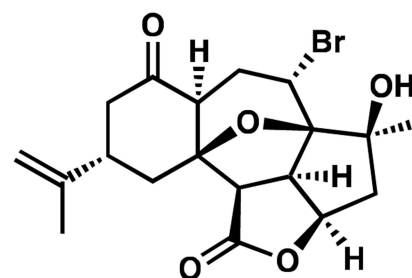


**37B<sup>ax</sup> : -0.1 kcal/mol**

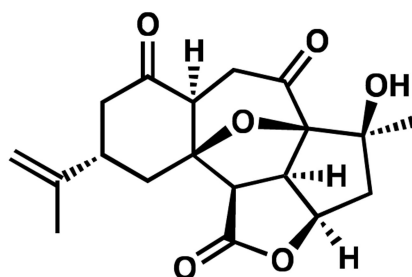
**Figure 2.**  
Conformational Isomers of 2H-ent-Ineleganolide.



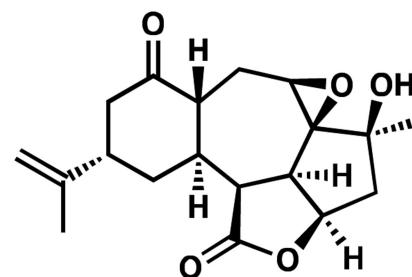
**28**  
*Selective IL-17  
Secretory Antagonist*



**30**  
*Selective IL-5  
Secretory Antagonist*

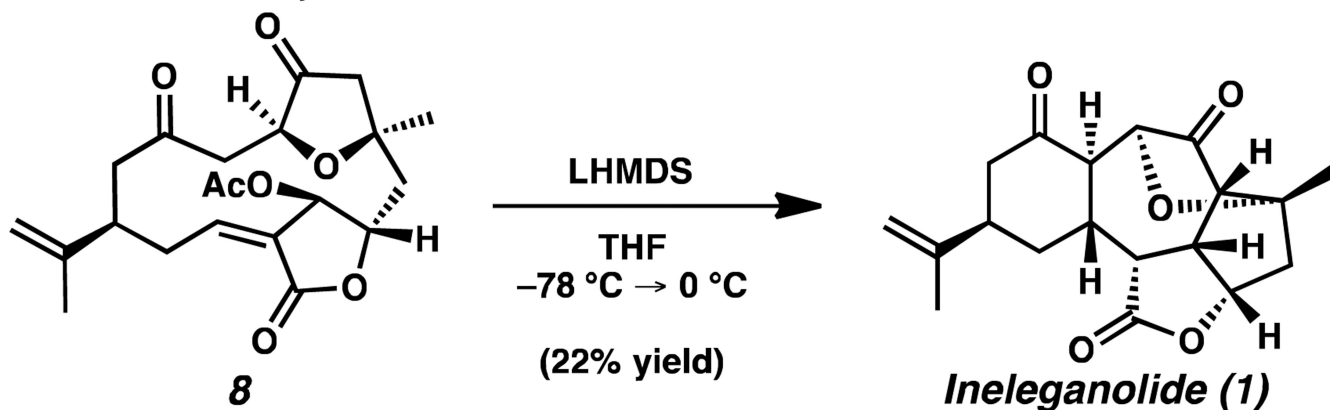
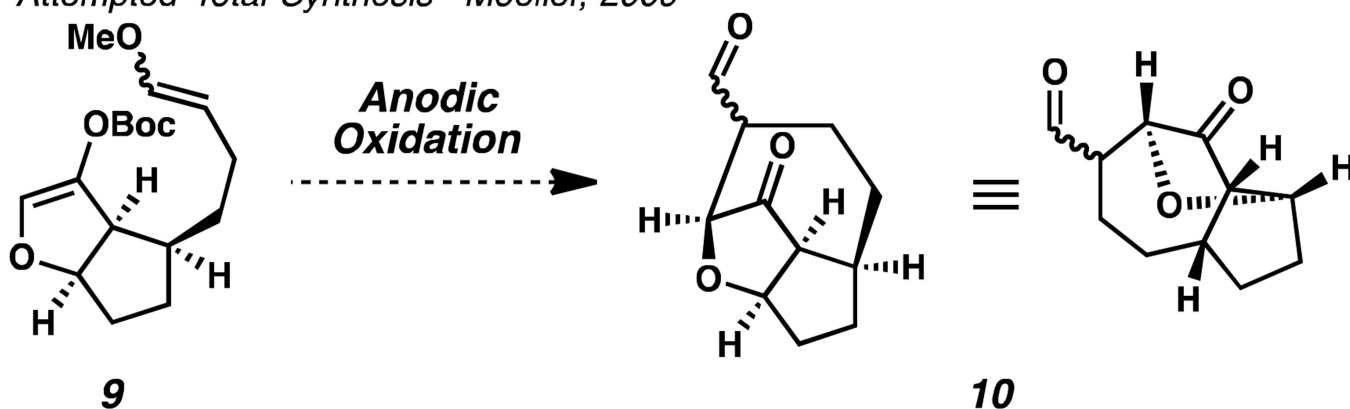
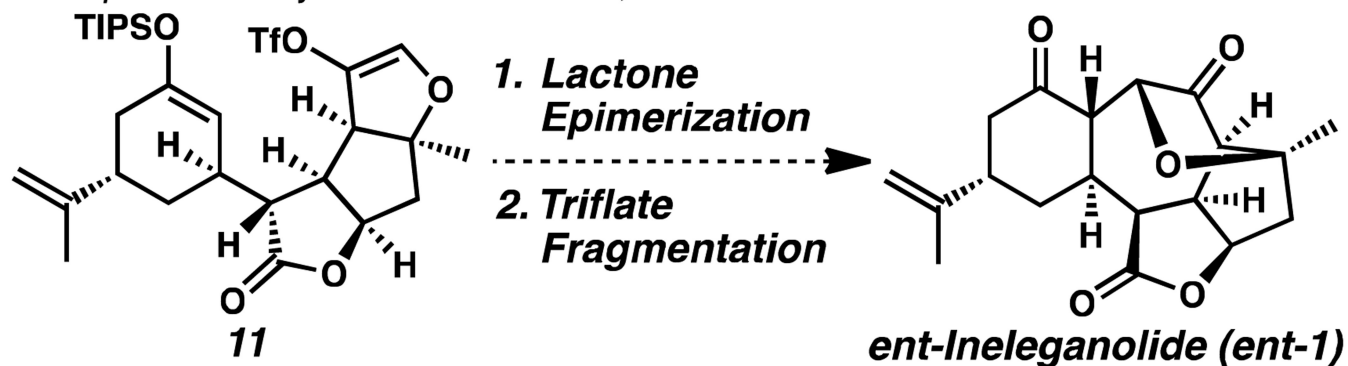


**31**  
*Selective IL-5  
Secretory Antagonist*



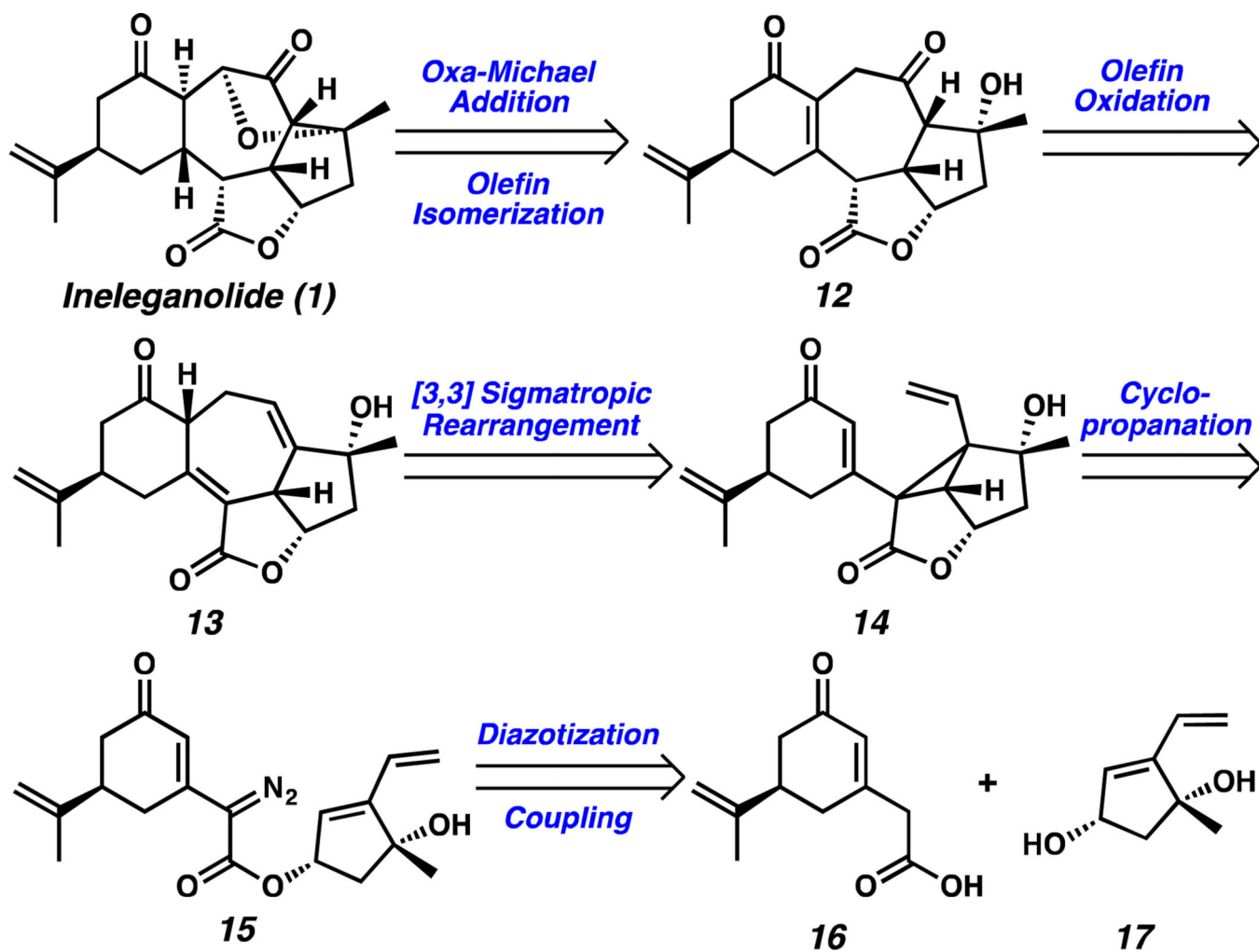
**36**  
*Selective IL-5  
Secretory Antagonist*

**Figure 3.**  
Biological Activity of Select Ineleganoloids.

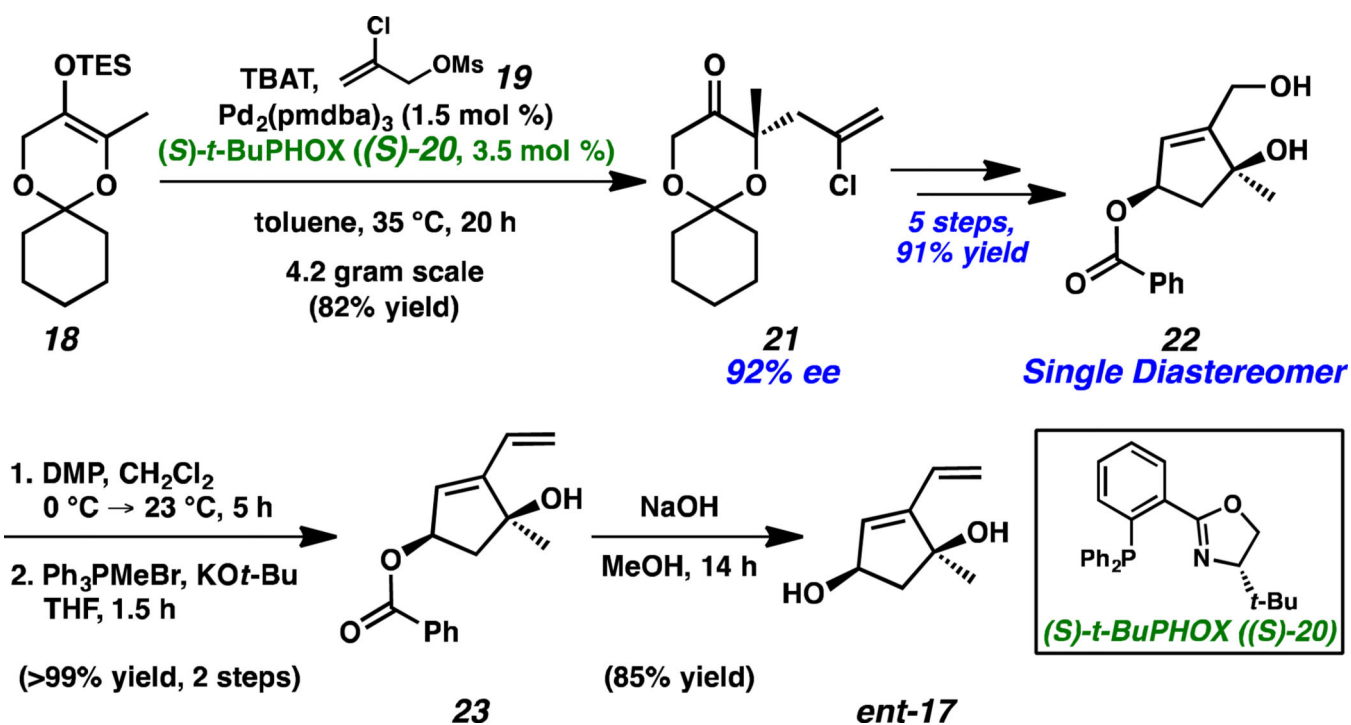
*Biomimetic Semisynthesis - Pattenden, 2011**Attempted Total Synthesis - Moeller, 2009**Attempted Total Synthesis - Vanderwal, 2016*

Scheme 1.

Biomimetic Semisynthesis and Previous Synthetic Attempts Toward Ineleganolide (1).

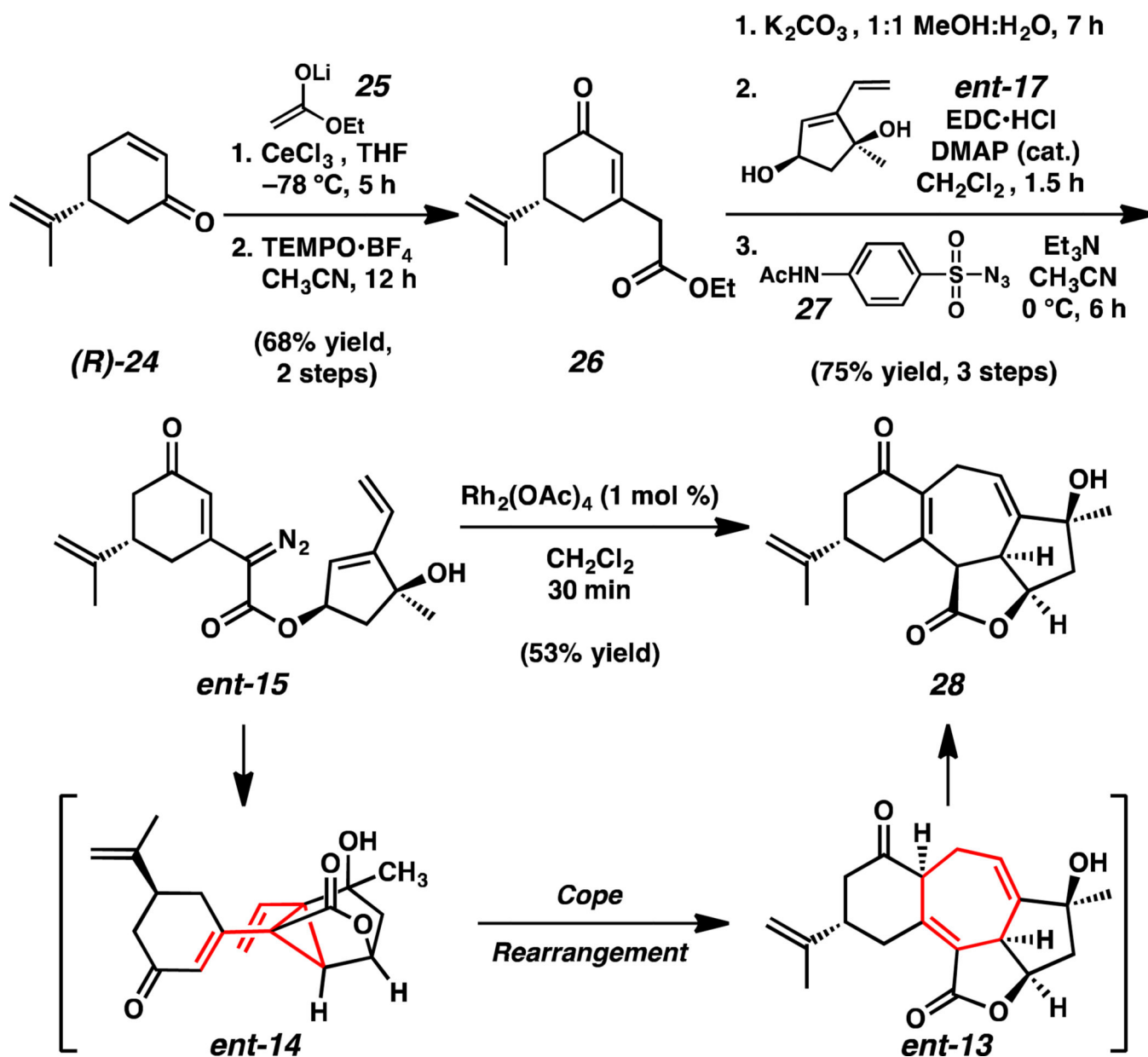


**Scheme 2.**  
Retrosynthetic Analysis of Ineleganolide (1).

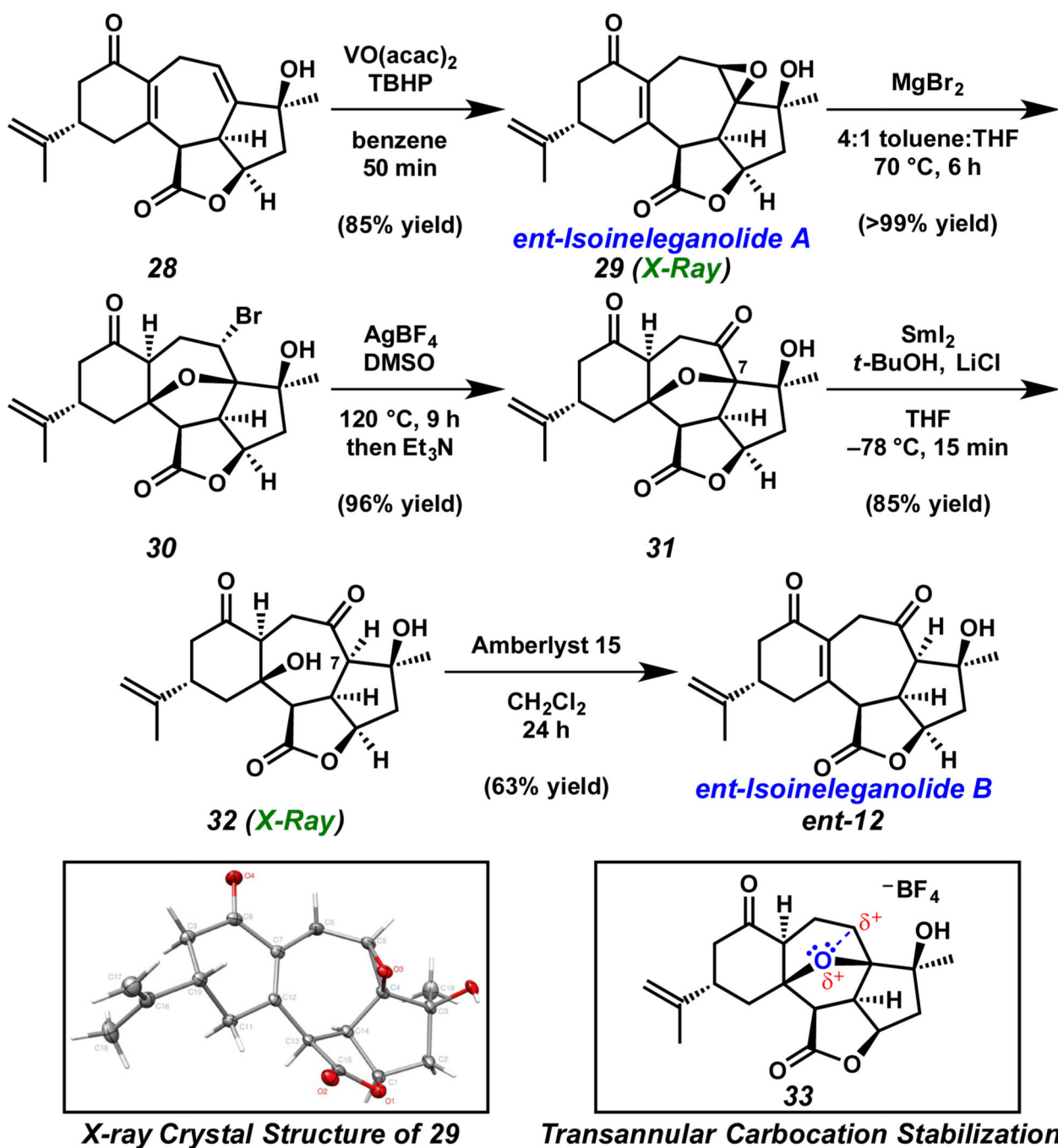


Scheme 3.  
Enantioselective Synthesis of 1,3-*cis*-Cyclopentenediol Coupling Partner *ent-17*.

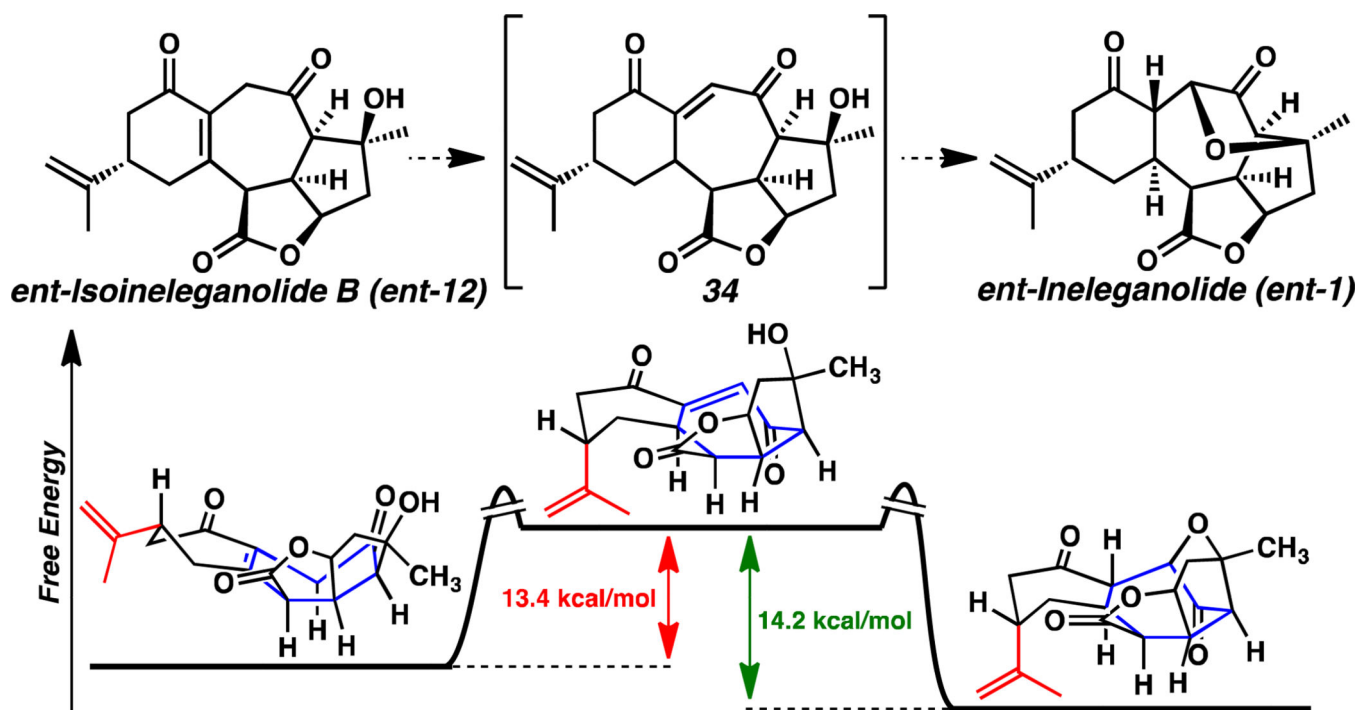




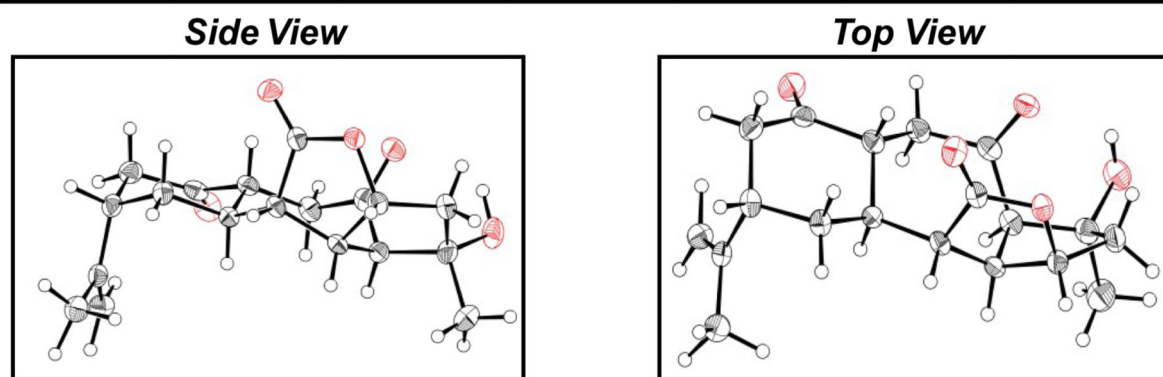
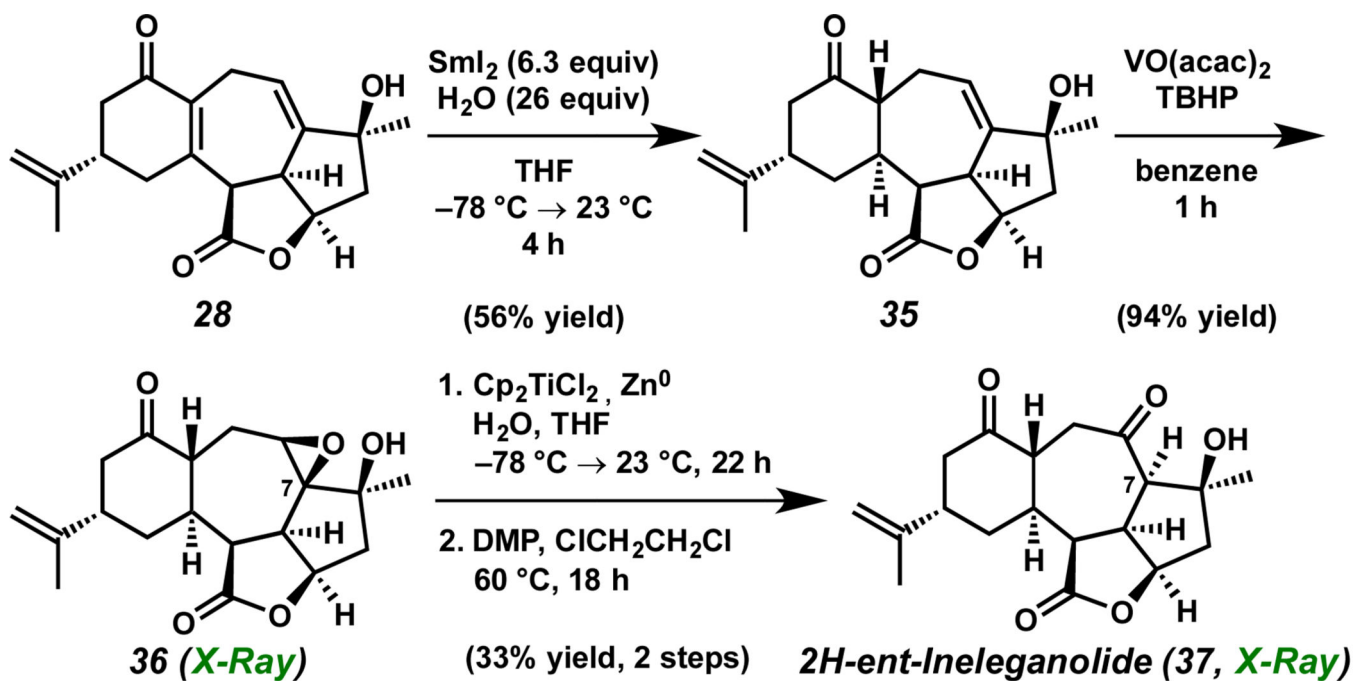
Scheme 4.  
Convergent Assembly of the Ineleganolide [6,7,5,5]-Tetracyclic Core.



Scheme 5.  
Synthesis of *ent*-Isoineleganolides A and B.



**Scheme 6.**  
Conformational Assessment and Relative Ground State Energies.



**X-ray Crystal Structure of 2H-ent-ineleganolide (37)**

**Scheme 7.**  
 Redox Manipulation of Diene 28.