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Traversing Biosynthetic Carbocation Landscapes in the Total Synthesis of Andrastin and Terretonin Meroterpenes

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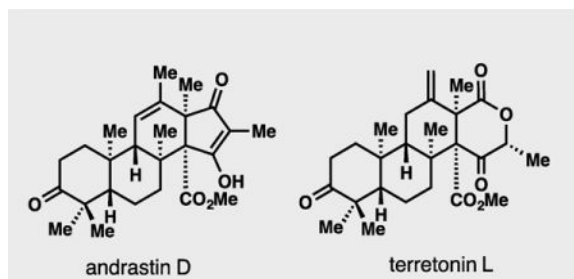
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Abstract

Meroterpenes derived from dimethylorsellinic acid (DMOA) and farnesyl pyrophosphate have attracted much biosynthetic attention, yet only recently have synthetic solutions to any family members appeared. A key point of divergence in DMOA-derived meroterpene biosynthesis is the protoaustinoide A carbocation which can be diverted to either the berkeleyone, andrastin, or terretonin structural classes via cyclase-controlled rearrangement pathways. Herein we show that the protoaustinoide bicyclo[3.3.1]nonane nucleus can be reverted to either andrastin or terretonin ring systems under abiotic reaction conditions. The first total syntheses of members of these natural product families are reported as their racemates.

Graphical abstract

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Keywords

total synthesis; meroterpene; biosynthesis; natural product

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Supporting information for this article is given via a link at the end of the document.

Over 100 structurally fascinating, fungal-derived natural products are assembled from 3,5-dimethylorsellinic acid (DMOA) and farnesyl pyrophosphate (FPP).^[1] These meroterpenes, while historically the subject of intense biosynthetic interest,^[1,2] have only very recently seen members succumb to total synthesis efforts.^[3] The andrastins (see **1–6**),^[2,4] terretonins (see **10–15**),^[2,5,6] and their downstream congeners in particular, represent a large subset of DMOA-derived members with interesting biological profiles and unique carbocyclic frameworks (Figure 1).^[1] To date these compounds have evaded successful chemical synthesis attempts.^[7] Herein we report the first total synthesis of members of these families using a strategy that is inspired by nature's pathway, but uses completely abiotic chemistry. Density functional theory (DFT) calculations have also shed light on the specific molecular interactions responsible for shaping the energetic landscape in the early stages of DMOA-derived meroterpene biosynthesis.^[8]

A key point of divergence in DMOA-derived meroterpene synthesis is the protoaustinoid carbocation (**17**), which is derived from FPP/DMOA-conjugate **16** via a cyclase-mediated polyene cyclization (Figure 2).^[1b] We estimate that over 80% of all DMOA-derived meroterpenes traverse **17** or a related intermediate. Proton loss of H_a affords protoaustinoid A (**18**) which serves as a precursor to the berkeleyone, austin, and related families.^[1b] In *Aspergillus nidulans*, this process is mediated by the cyclase AusL.^[2e] The biosynthesis of the terretonin and andrastin families is generally believed to involve a 1,2-shift pathway prior to proton loss (see **17**→**19**) thus converting the bicyclo[3.3.1]nonane skeleton into a 5,6-fused ring system. In *Aspergillus terreus*, the Trt1 cyclase mediates selective proton abstraction of H_b forming a trisubstituted alkene,^[2i,2j,2m] while in *Penicillium chrysogenum*, a methyl proton (H_c) is selectively abstracted by AdrI.^[2l] Two of our groups (T.R.N and T.J.M.) recently prepared protoaustinoid A (**18**) *en route* to distinct total syntheses of berkeleyone A.^[3] While these pathways did not directly proceed through carbocation **17**, we wondered if **18** (or a suitable synthetic surrogate) could be “reverted” to the andrastin and terretonin ring systems directly in the absence of enzymes, possibly driven by a thermodynamic preference for **5** and/or **8**. If feasible, this could potentially open up synthetic access to nearly half of the remaining DMOA-derived members believed to proceed through carbocation **17**.

Although the synthetic strategy described above was computationally predicted to be favorable for the conversion of protoaustinoid A (**18**) to andrastin E (**5**) ($G = -2.0$ kcal/mol, see SI for details),^[9,10] DFT calculations indicate that formation of the less stable 1,1-disubstituted alkene-containing preterretonin A (**8**) is unfavorable by 5.9 kcal/mol. Analysis of the carbocation intermediates believed to be involved in these conversions (i.e. **17** and **19**), revealed that the tautomeric form of the vinylogous acid functionality determines whether the protoaustinoid or andrastin framework is energetically favored. For one pair of regioisomers (**17-enol1** and **19-enol1**), the two different ring systems are comparable in energy ($G = +0.4$ kcal/mol) and kinetically accessible ($G^\ddagger = +9.1$ kcal/mol). However, the regioisomeric vinylogous acid **17-enol2** presents an exergonic pathway to the andrastin 5,6-fused bicyclic framework, and **19-enol2** ($G = -8.4$ kcal/mol), by a nearly barrierless pathway ($G^\ddagger = +0.8$ kcal/mol for **TS-enol2**). The basis for the disparate stability of these isomers is derived from greater stabilization of the carbocation by the neighboring carbonyl

oxygen lone-pair in **19-enol2** than the more distal carbonyl in **19-enol1** (see SI for details). Intriguingly, these theoretical findings suggest that controlling tautomeric state may be an effective molecular approach by which biosynthetic machinery can influence the chemical fate of the proposed cationic intermediates.

While these calculations indicate the facility of the rearrangement, surprisingly we have had difficulty in forming *either* preterretinin (**8**) or andrastin E (**5**) via treatment of protoaustinoide A (**18**) (or its corresponding A-ring ketone) with acid, wherein tautomerization between enol isomers is expected to occur. Under a variety of acidic conditions, only decomposition or complex, unidentified product mixtures have resulted. We initially attributed these failures to the difficulty in protonating the exocyclic olefin over several more basic functional groups combined with the sensitivity of the 1,3-diketone. Seeking alternative chemoselective methods for carbocation generation, we were drawn to recent work by Shigehisa and co-workers who reported an exceedingly mild, Co-catalyzed hydroalkoxylation reaction via an oxidative variant of the classic Mukaiyama hydration process.^[11,12] Substrate **21** was prepared in one-step from tetracyclic building block **20**, an intermediate we have prepared in gram quantities *en route* to the synthesis of berkeleyone A (Scheme 1).^[3a] Subjecting **21** to modified Shigehisa conditions (cat. Co(II), PhSiH₃, *N*-fluoropyridinium salt (F⁺) oxidant) yet omitting the alcohol trapping agent cleanly promoted the desired rearrangement.^[13] Notably, we have been unable to elicit this bond rearrangement on **21** using a variety of Brønsted acids, although the corresponding regioisomeric vinylogous ester of **21** gives detectable quantities of rearranged product.^[14] When one equivalent of phenylsilane and *N*-fluoropyridinium salt were employed, the andrastin framework was favored over the exocyclic, terretinin-type alkene system (~3:1 ratio of **22:23** along with recovered **21**). Increasing the equivalents of F⁺ oxidant and phenylsilane to 2.5 allowed for very clean formation of **22** as essentially a single olefin isomer in 90% isolated yield. The structure of the newly minted 5,6-fused ring system was confirmed by single crystal X-ray diffraction and following Krapcho-type demethylation (LiCl, DMSO,), (±)-andrastin D (**4**) was furnished in 77% yield thus completing the first total synthesis of a member of this meroterpenoid class.

While this strategy offers high yielding, selective entry into the andrastins, it presents a challenge for the synthesis of terretinins as the thermodynamic product is obtained. Cognizant of the disparate alkene patterns produced by titanocene-mediated epoxide opening cascades, as compared to their acid-mediated counterparts,^[15] we wondered if a purely radical-based homoallyl-type rearrangement/HAT process could be used to forge **23** preferentially (Figure 3).^[16] After significant exploration, we discovered that when **21** was subjected to conditions developed by Carreira for radical olefin hydrochlorination (cat. Co(II), PhSiH₃, TsCl, MeOH),^[17] we observed formation of **23** in 43% isolated yield with only trace amounts of **22** (<5%). The remaining mass balance was largely recovered starting material and we did not observe the expected tertiary chloride product.^[18] We suspect that the steric encumbrance surrounding radical intermediates **24–26** precludes efficient trapping with TsCl and a final hydrogen atom transfer (HAT) from the less-hindered methyl position ensues preferentially forming **23**.^[15,19,20] We also assume that under the more powerfully

oxidizing Co(II)/F⁺ conditions, radical **26** is converted into carbocation **27** which is ultimately funneled into **22** via loss of a proton.^[11]

Demethylation of **23** (LiCl,) afforded preterrenoid (**7**), thus allowing us to explore late-stage oxidative chemistry potentially leading to the hallmark terretonin lactone ring systems which are found in several permutations (see colored rings, Figure 1).^[2i] Stereoselective oxidation of **7** with magnesium monoperoxyphthalate (MMPP) afforded terretonin (**9**) as a single diastereomer whose structure was confirmed by single crystal X-ray diffraction. Treating this key biosynthetic precursor with catalytic quantities of NaOMe in MeOH afforded (±)-terretonin L (**10**) as the major product (46%), thus formally accomplishing the same retro-Claisen/esterification cascade as the putative hydrolase Trt14 in *Aspergillus oryzae*.^[2i] Notably a single diastereomer was obtained, likely due to a preference for the newly-formed methyl stereocenter to reside in the pseudoequatorial position away from the top face of the congested polycyclic ring system. Interestingly, a ring-opened ester assigned as **28** was also isolated in 32% yield; this structure would correspond to 6,7-deoxyterretonin G (see **15**, Figure 1). Abe and co-workers did not observe a product of this type when reacting terretonin (**9**) with Trt14, indicating the chemoselectivity of this enzyme.

In summary, we have examined early, fundamental steps in DMOA-derived meroterpene synthesis both experimentally and computationally. By initially analyzing the energetic landscape of the system, we realized that a biomimetic 1,2-shift should be feasible in the absence biosynthetic machinery and by investigating abiotic reaction conditions, we demonstrate that selective formation of either andrastin or terretonin scaffolds are possible from protoaustinoid bicyclo[3.3.1]nonane skeletons. With a better understanding of the key skeletal forming chemistry in DMOA-derived meroterpene biosynthesis, efforts can now focus on exploring the synthesis of more highly oxidized congeners. Finally, in-depth studies on how the aforementioned cyclase enzymes manipulate these cationic intermediates, particularly how they prevent energetically favorable rearrangements, may lead to new insights in meroterpene enzymology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. a) Geris R, Simpson TJ. Nat Prod Rep. 2009; 26:1063. [PubMed: 19636450] b) Matsuda Y, Abe I. Nat Prod Rep. 2016; 33:26. [PubMed: 26497360] c) Matsuda Y, Awakawa T, Mori T, Abe I. Curr Opin Chem Biol. 2016; 31:1. [PubMed: 26610189]

2. a) Cox R. *Nat Prod Rep.* 2014; 31:1045. b) Simpson TJ, Stenzel DJ. *J Chem Soc Chem Commun.* 1981:1042. c) Scott FE, Simpson TJ, Trimble LA, Vederas JC. *J Chem Soc Chem Commun.* 1986; 214d) Matsuda Y, Awakawa T, Wakimoto T, Abe I. *J Am Chem Soc.* 2013; 135:10962. [PubMed: 23865690] e) Lo HC, Entwistle R, Guo CJ, Ahuja M, Szewczyk E, Hung JH, Chiang YM, Oakley BR, Wang CCC. *J Am Chem Soc.* 2012; 134:4709. [PubMed: 22329759] f) Matsuda Y, Iwabuchi T, Fujimoto T, Awakawa T, Nakashima Y, Mori T, Zhang H, Hayashi F, Abe I. *J Am Chem Soc.* 2016; 138:12671. [PubMed: 27602587] g) Uchida R. *J Antibiot.* 1996; 49:418. [PubMed: 8682717] h) McIntyre CR, Simpson TJ. *J Chem Soc Chem Commun.* 1981; 1043i) Matsuda Y, Iwabuchi T, Wakimoto T, Awakawa T, Abe I. *J Am Chem Soc.* 2015; 137:3393. [PubMed: 25671343] j) Matsuda Y, Awakawa T, Itoh T, Wakimoto T, Kushiro T, Fujii I, Ibizuka Y, Abe I. *ChemBioChem.* 2012; 13:1738. [PubMed: 22782788] k) Matsuda Y, Quan Z, Mitsuhashi T, Li C, Abe I. *Org Lett.* 2016; 18:296. [PubMed: 26731665] l) Matsuda Y, Awakawa T, Abe I. *Tetrahedron.* 2013; 69:8199. m) Guo CJ, Knox BP, Chiang Y-M, Lo HC, Sanchez JF, Lee KH, Oakley BR, Bruno KS, Wang CCC. *Org Lett.* 2012; 14:5684. [PubMed: 23116177] n) Matsuda Y, Wakimoto T, Mori T, Awakawa T, Abe I. *J Am Chem Soc.* 2014; 135:15326. o) Valiante V, Mattern DJ, Schüffler A, Horn F, Walther G, Scherlach K, Petzke L, Dickhaut J, Guthke R, Hertweck C, Nett M, Thines E, Brakhage AA. *ACS Chem Biol.* 2017; article ASAPdoi: 10.1021/acscchembio.7b00003
3. a) Ting CP, Xu G, Zeng X, Maimone TJ. *J Am Chem Soc.* 2016; 138:14868. [PubMed: 27809506] b) Elkin M, Szewczyk SM, Scruse AC, Newhouse TR. *J Am Chem Soc.* 2017; 139:1790. [PubMed: 28102673]
4. Uchida R, Shiomi K, Inokoshi J, Sunazuka T, Tanaka H, Iwai Y, Takayanagi H, Mura S. *J Antibiot.* 1996; 49:418. [PubMed: 8682717]
5. a) Springer JP, Dorner JW, Cole RJ, Cox RH. *J Org Chem.* 1979; 44:4852. b) Li GY, Li BG, Yang T, Yin JH, Qi HY, Liu GY, Zhang GL. *J Nat Prod.* 2005; 68:1243. [PubMed: 16124769] c) Liu XH, Miao FP, Qiao MF, Cichewicz RH, Ji NY. *RSC Advances.* 2013; 3:588. d) Fukuda T, Kurihara Y, Kanamoto A, Tomoda H. *J Antibiot.* 2014; 67:593. [PubMed: 24802208]
6. For a complete list of terretinin structures isolated to date, see the Supporting Information.
7. Okamoto R, Takeda K, Tokuyama H, Ihara M, Toyota M. *J Org Chem.* 2013; 78:93. [PubMed: 23106671]
8. For a review of DFT calculations on terpene-forming carbocation rearrangements, see: Tantillo DJ. *Nat Prod Rep.* 2011; 28:1035. [PubMed: 21541432]
9. Frisch, MJ., et al. *Gaussian '09*, revision D.01. Gaussian, Inc; Wallingford, CT: 2013.
10. For systematic evaluation and recommendation of using B3LYP geometries and mPW1PW91 single point energies, see: Matsuda SPT, Wilson WK, Xiong Q. *Org Biomol Chem.* 2006; 4:530. [PubMed: 16446812]
11. Shigehisa H, Aoki T, Yamaguchi S, Shimizu N, Hiroya K. *J Am Chem Soc.* 2013; 135:10306. [PubMed: 23819774]
12. For a recent review on metal-mediated radical olefin hydrofunctionalization, see: Crossley SWM, Obradors C, Martinez RM, Shenvi RA. *Chem Rev.* 2016; 116:8912. [PubMed: 27461578]
13. The corresponding free vinylogous acid of **21** was not compatible with the reaction conditions of this transformation as the *N*-fluoropyridinium salt led to significant byproduct formation even in the absence of the Co(II) catalyst.
14. Demethylation and remethylation of **21** yielded an inseparable ~1:1 mixture of **21** and its corresponding vinylogous ester regioisomer (iso-**21**). When this mixture was heated with *p*-TsOH in PhH we detected small amounts of the ring-shifted product, but only from iso-**21**. The published synthetic pathway to **20** however, cannot be used to make iso-**21** selectively since this regioisomer does not undergo a key bridgehead deprotonation reaction (see ref. 3a). Thus this was not considered to be a viable option for the synthesis of andrastins.
15. Justicia J, Álvarez de Cienfuegos L, Campaña AG, Miguel D, Jakoby V, Gansäuer A, Cuerva JM. *Chem Soc Rev.* 2011; 40:3525. [PubMed: 21487573]
16. For recent examples of 3-exo radical cyclizations initiated by a metal-catalyzed HAT process, see: Lo JC, et al. *J Am Chem Soc.* 2017; 139:2484. [PubMed: 28094980]
17. Gaspar B, Carreira EM. *Angew Chem Int Ed.* 2008; 47:5758. *Angew Chem.* 2008; 120:5842.

18. Similar results are obtained by replacing TsCl with *tert*-Butyl hydroperoxide (TBHP). Presumably these reagents oxidize the Co(II) precatalyst to Co(III) which is required for the initial HAT.
19. Crosley SWM, Barabé F, Shenvi RA. J Am Chem Soc. 2014; 136:16788. [PubMed: 25398144]
20. DFT studies on a simplified model system indicate that the radical rearrangement is both facile and significantly exergonic. The conversion of model radical **24** to **26** is downhill by 8 kcal/mol with activation barriers of 11.6 kcal/mol for **24** → **25** and 4.9 kcal/mol for **25** → **26** (see Supporting Information).

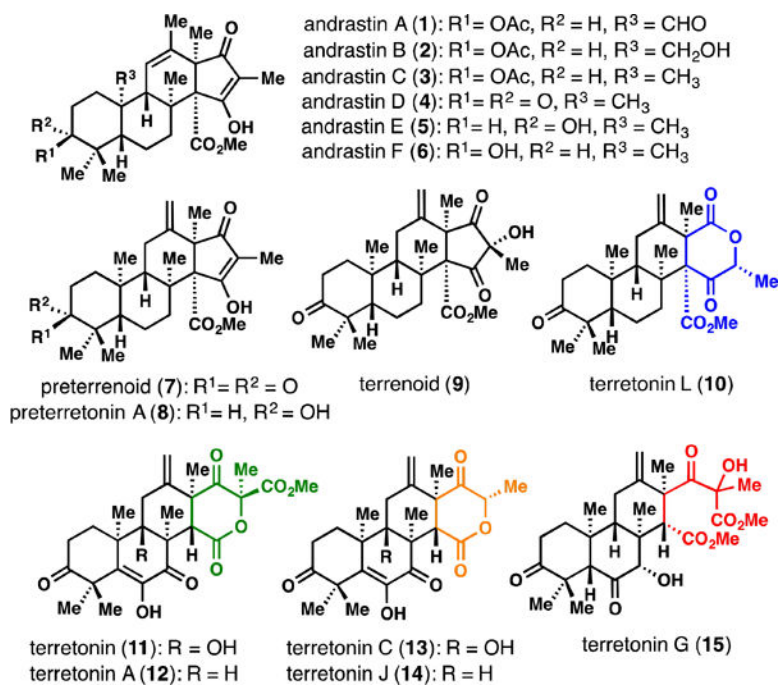


Figure 1. Representative andrastin and terretonin-type meroterpenes.^[6]

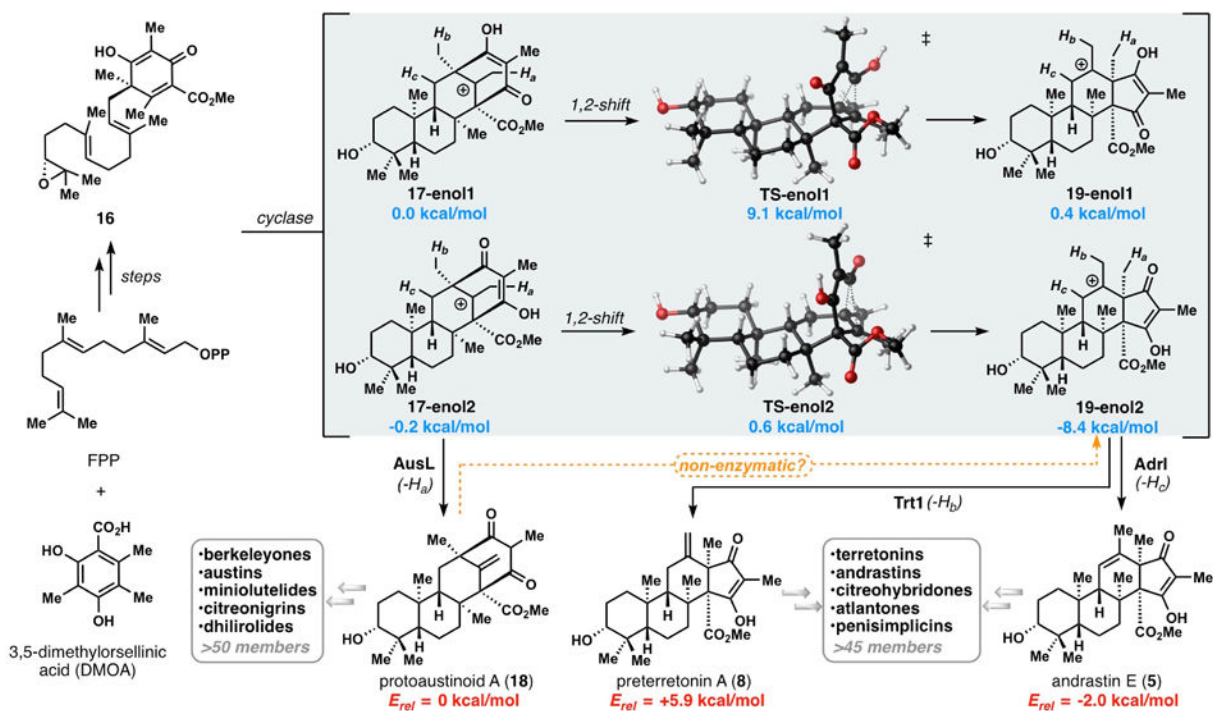


Figure 2.

Key steps in the early stages of DMOA-derived meroterpenoid biosynthesis showing the divergence of cationic vinyllogous acid tautomers (17-enol1 and 17-enol2) to form protoaustinoide A (18), preterretonin A (8), and andrastin E (5). Energy values shown are in kcal/mol and were obtained using Gaussian '09 at the mPW1PW91/6-31+G(d,p)//B3LYP/6-31+G(d,p) level of theory.^[9,10]

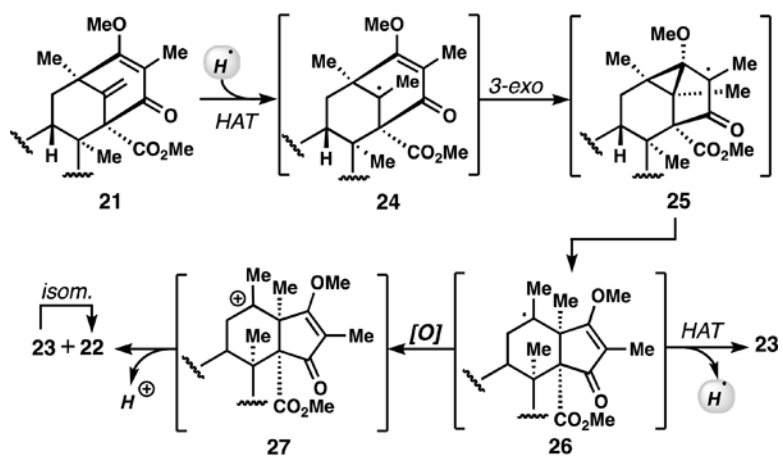
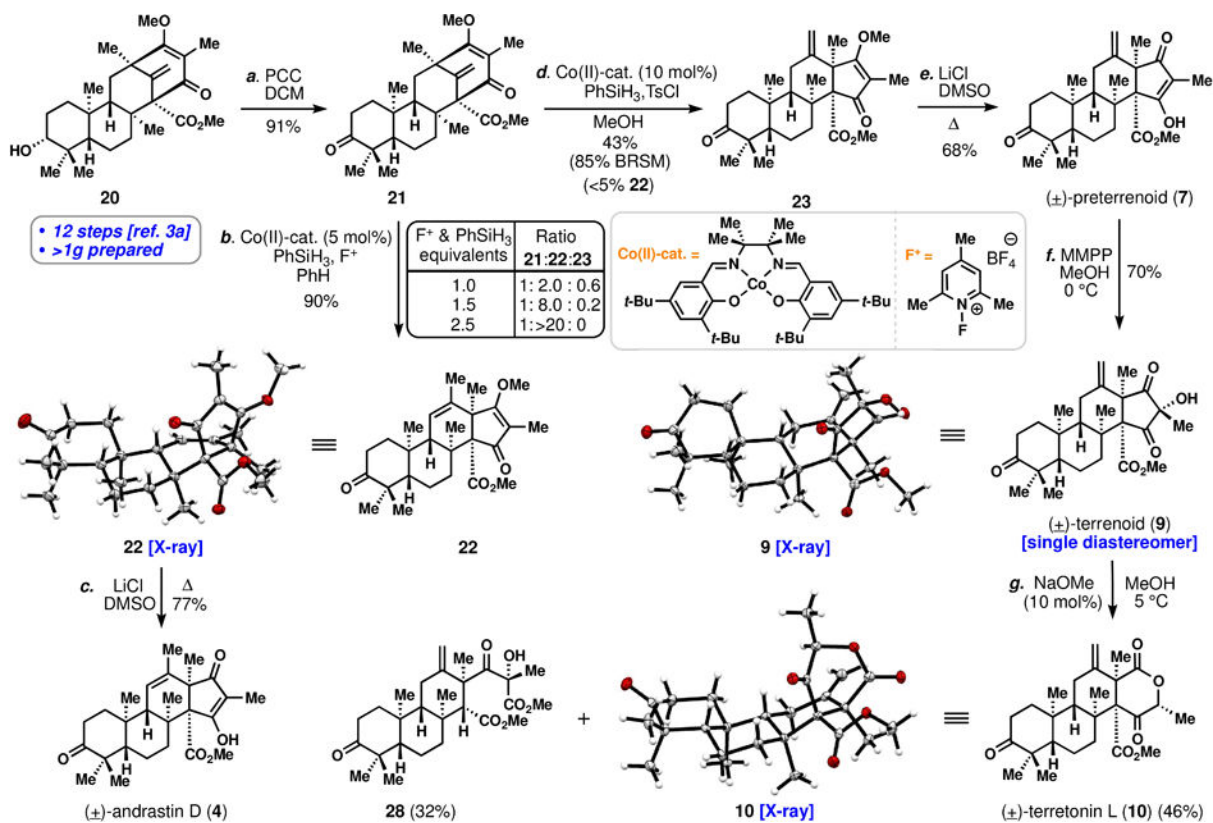


Figure 3.
Abiotic radical-based HAT isomerization process

**Scheme 1.**

Total syntheses of andrastin D (**4**), preterrenoid (**7**), terrenoid (**9**), and terretonin L (**10**).

Reagents and conditions: a) PCC (4 equiv), DCM, 25 °C, 2 h, 91%; b) Co(II)-cat. (5 mol %), PhSiH₃ (2.5 equiv), F⁺ (2.5 equiv), PhH, rt, 2 h, 90%; c) LiCl (40 equiv), DMSO, 120 °C, 2 h, 77%; d) Co(II)-cat. (10 mol %), PhSiH₃ (2.5 equiv), TsCl (1.5 equiv), MeOH, rt, 3 h, 43% (85% BRSM); e) LiCl (40 equiv), DMSO, 120 °C, 1.5 h, 68%; f) MMPP (2 equiv), MeOH, 0 °C, 2 h, 70%; g) NaOMe (0.1 equiv), MeOH, 5 °C, 24 h, 46% + 32% of **24**; PCC = pyridinium chlorochromate, MMPP = magnesium monoperoxyphthalate.