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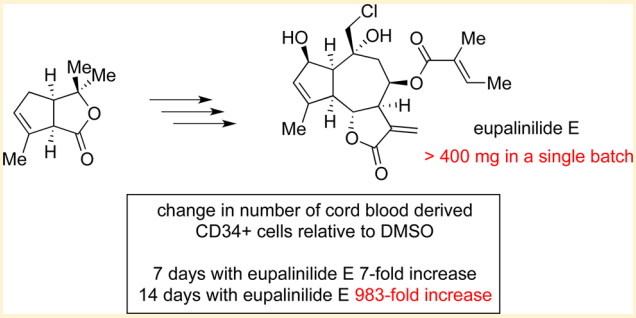
# Synthesis of Eupalinilide E, a Promoter of Human Hematopoietic Stem and Progenitor Cell Expansion

Trevor C. Johnson,[†] Matthew R. Chin,[‡] Tianxu Han,[§] John Paul Shen,[∥] Tariq Rana,[§] and Dionicio Siegel*[,⊥]

[†]Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, California 92093, United States
[‡]Gilead Sciences, Inc., Foster City, California 94404 United States
[§]Department of Pediatrics, University of California, San Diego, La Jolla, California 92093, United States
[∥]School of Medicine, University of California, San Diego, La Jolla, California 92093, United States
[⊥]Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, La Jolla, California 92093, United States

Supporting Information

**ABSTRACT:** Improving the ex vivo and in vivo production of hematopoietic stem and progenitor cells (HSPCs) has the potential to address the short supply of these cells that are used in the treatment of various blood diseases and disorders. Eupalinilide E promotes the expansion of human HSPCs and inhibits subsequent differentiation, leading to increased numbers of clinically useful cells. This natural product represents an important tool to uncover new methods to drive expansion while inhibiting differentiation. However, in the process of examining these effects, which occur through a novel mechanism, the natural product was consumed, which limited additional investigation. To provide renewed and improved access to eupalinilide E, a laboratory synthesis has been developed and is reported herein. The synthetic route can access >400 mg in a single batch, employing reactions conducted on useful scales in a single vessel. Key transformations enabling the approach include a diastereoselective borylative enyne cyclization and a late-stage double allylic C−H oxidation as well as adapted Luche reduction and aluminum-mediated epoxidation reactions to maximize the synthetic efficiency. Retesting of the synthetic eupalinilide E confirmed the compound's ability to expand HSPCs and inhibit differentiation.




There has been a focused effort to discover compounds that direct stem cell fate by controlling the cell's ability to undergo duplication, thereby increasing the population of stem cells, a process termed expansion. The use of stem cells derived from cord blood (CB) has developed into an effective alternative to the use of stem cells collected from adults when suitable donors are not available.[1,2] However, stem cells derived from CB have limitations due to increased graft failure, delayed hematopoietic recovery, and poor immune reconstitution. The use of 2 units of CB for transplantation has reduced the rate of graft failure in adult recipients by providing higher numbers of CD34+ cells from different sources.[3] However, the development of a cost-effective, cryopreserved product that can be used to circumvent human leukocyte antigen (HLA) complications has yet to be realized. To date, multiple approaches for chemically expanding hematopoietic stem and progenitor cells (HSPCs) have reached clinical trials, providing hope for the development of universal, scalable methods for expansion, with molecules of note including StemRegenin 1 (SR1)[4] and UM171[5] as well as the synthetic prostaglandin derivative 16,16-dimethyl-PGE2 (FT1050),[6,7] which enhances engraftment (Figure 1).[8] Unfortunately, at this time there is no defined solution, and additional methods for expansion are needed to ensure that the world will have access to a large-scale, accessible resource of HSPCs for future human health.

A series of sesquiterpene lactones, including eupalinilide E, were isolated from *Eupatorium lindleyanum*, a plant investigated as a result of its ethnobotanical use as an antibacterial or antihistamine agent. Eupalinilide E was differentiated from the isolated guaianolide-based compounds because it possesses selective cytotoxic activity against A549 cells (lung cancer harboring KRAS mutation) with an $IC_{50}$ of 28 nM and no effect on P388 cells (leukemia).[9] Although it was found to possess selective cytotoxicity against a difficult cancer cell line, further evaluation of eupalinilide E did not occur beyond the initial isolation until the discovery of its ability to promote HSPC expansion. In an effort to discover new agents to control stem cell fate, the Schultz laboratory screened Norvartis' natural product collection. From their assay of 704 pure natural products of variable origin, eupalinilide E was shown to remarkably promote

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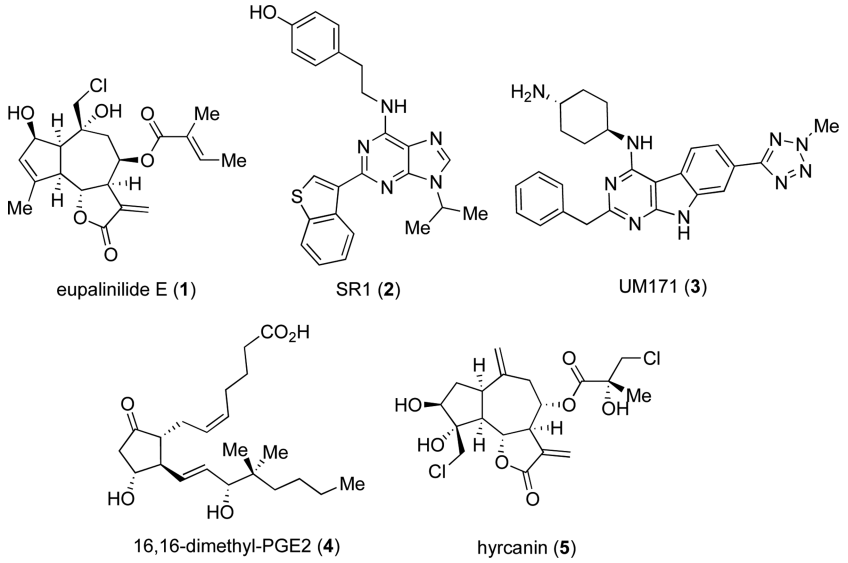


**Figure 1.** Structures of eupalinilide E (**1**), SR1 (**2**), UM171 (**3**), 16,16-dimethyl-PGE2 (**4**), and hyrcanin (**5**).

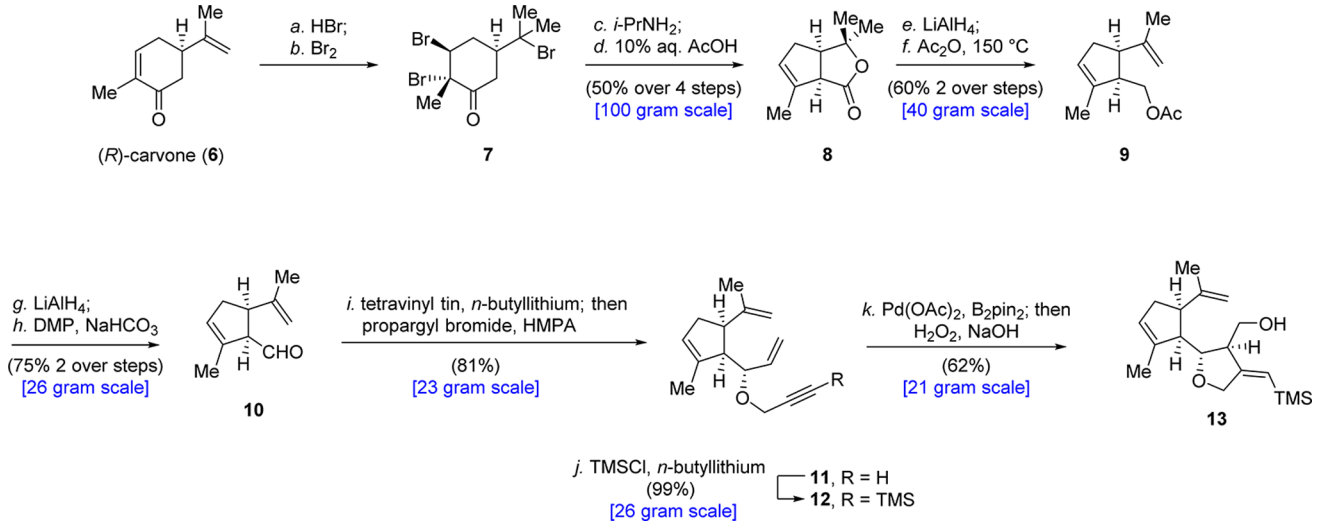


**Figure 2.** Scaled synthesis of enyne cyclization product **13**. Conditions: (*a*) (*R*)-carvone (**6**), HBr, AcOH, 0 °C, 1 h; (*b*) $Br_2$, AcOH, 23 °C, 2.5 h; (*c*) **7**, *i*-$PrNH_2$, $Et_2O$, 0 °C, 12 h; (*d*) 10% aq. AcOH, THF, 50 °C, 3 h (50% over four steps); (*e*) **8**, $LiAlH_4$, $Et_2O$, 0 °C, 1 h (99%); (*f*) **9**, $Ac_2O$, 150 °C, 16 h; (*g*) $LiAlH_4$, $Et_2O$, 0 °C, 1 h (49% over two steps); (*h*) DMP, $NaHCO_3$, $H_2O$, $CH_2Cl_2$, 23 °C, 45 min (87%); (*i*) tetravinyltin, *n*-butyllithium, −78 to 23 °C, 15 min, then **10**, −78 °C, 15 min, then HMPA, propargyl bromide, −78 to 23 °C, 3 h (one pot, 81%); (*j*) **11**, *n*-butyllithium, −78 °C, 20 min, then TMSCl, −78 to 23 °C, 30 min (99%); (*k*) **12**, $Pd(OAc)_2$ (5 mol %), $B_2pin_2$, PhMe, MeOH, 50 °C, 15 h, then $H_2O_2$, NaOH, THF, 0 °C, 1 h (>20:1 d.r., 62% over two steps). DMP, Dess−Martin periodinane; HMPA, hexamethylphosphoramide; TMSCl, trimethylsilyl chloride; $Pd(OAc)_2$, palladium(II) acetate; $B_2pin_2$, bis(pinacolato)diboron.

the expansion of human HSPCs.[10] Importantly, this activity was achieved using mobilized peripheral blood and cord blood. This effect was demonstrated at different concentrations, and the majority of the experiments used solutions with eupalinilide E at 600 nM, approximately 20-fold the concentration reported to kill A549 lung cancer cells. This modulation was found to proceed through a novel mechanism relative to other compounds that promote expansion. In the first 7 days after treatment with eupalinilide E, there was a 50% increase in the percentage of CD34+ cells and a 2-fold increase in the number of THY1+ cells (cells bearing CD34+ and THY1+ immunophenotypes on the surface of undifferentiated cells identify them as hematopoietic stem and progenitor cells, respectively). After prolonged incubation (18 days), there was a 4.5-fold increase in the number of cells as a result of incubation with eupalinilide E. Finally, after 45 days there was a 45-fold increase in the number of cells compared with controls using dimethyl sulfoxide (DMSO) vehicle. The increase in the number of CD34+ and THY1+ cells was found to be the result of eupalinilide E inhibiting differentiation and driving progenitor expansion. The effects were shown to be reversible, and following transfer of the cells to fresh, compound-free medium, the cells maintained their native potential for differentiation, proliferation, and expansion. Related compounds, such as hyrcanin (**5**) (Figure 1), showed only cytotoxicity toward HSPCs. Notably, together eupalinilide E (**1**) and SR1 (**2**) acted synergistically to increase expansion.[10]

Herein we report an enantioselective synthesis of eupalinilide E accessing >400 mg in a single batch. Starting from (*R*)-carvone (**6**), the crystalline lactone **8** was accessed in four steps through a series of reactions initiated on a 100 g scale (Figure 2).[11] Favorskii


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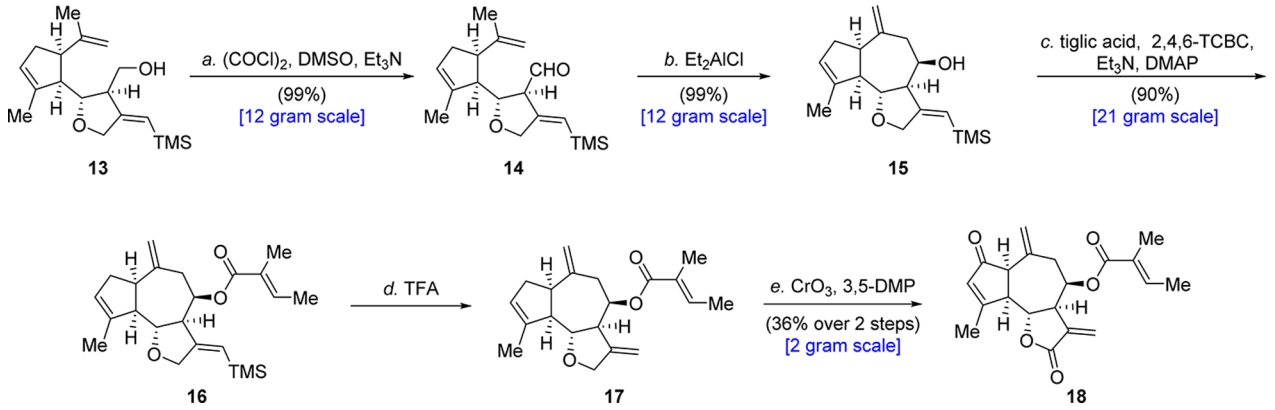


**Figure 3.** Expedited access to the oxidized guaianolide core. Conditions: (*a*) **13**, $(COCl)_2$, DMSO, triethylamine, $CH_2Cl_2$, −78 °C, 2.5 h (99%); (*b*) **14**, $Et_2AlCl$, $CH_2Cl_2$, −78 °C, 10 min (99%); (*c*) **15**, tiglic acid, 2,4,6-TCBC, triethylamine, DMAP, PhMe, 80 °C, 2 h (90%); (*d*) **16**, TFA, $CH_2Cl_2$, 23 °C, 2 h; (*e*) **17**, $CrO_3$, 3,5-DMP, $CH_2Cl_2$, 0 °C, 30 min (36% over two steps). $(COCl)_2$, oxalyl chloride; $Et_2AlCl$, diethylaluminum chloride; 2,4,6-TCBC, 2,4,6-trichlorobenzoyl chloride; DMAP, 4-dimethylaminopyridine; TFA, trifluoroacetic acid; $CrO_3$, chromium(VI) oxide; 3,5-DMP, 3,5-dimethylpyrazole.

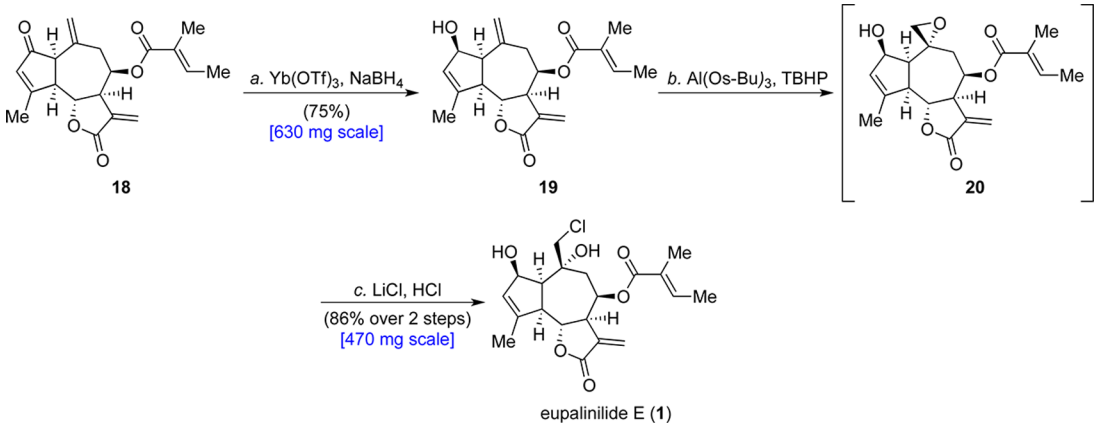


**Figure 4.** Selective reduction and epoxidation completes the synthesis of eupalinilide E. Conditions: (*a*) **18**, $Yb(OTf)_3$, $NaBH_4$, MeOH/THF, −78 °C, 2 h (75%); (*b*) **19**, $Al(Osec\text{-}Bu)_3$, TBHP, $CH_2Cl_2$, 0 to 23 °C, 40 min, then **20**, LiCl, HCl, THF, 23 °C, 5 min (86% over two steps). $Yb(OTf)_3$, ytterbium(III) trifluoromethanesulfonate; $NaBH_4$, sodium borohydride; $Al(Osec\text{-}Bu)_3$, aluminum *sec*-butoxide; LiCl, lithium chloride.

reactions have been previously applied to the syntheses of guaianolide natural products.[12−18] However, lactone **8**, prepared from tribromide **7**, had yet to be employed and provides a generally useful starting material for complex molecule synthesis given the ease and scale with which it is prepared and its inherent crystallinity (mp 33−35 °C). The bicyclic lactone **8** was reduced with lithium aluminum hydride, and the diol was subjected to in situ acetate formation/pyrolysis to give olefin **9**. Lithium aluminum hydride-mediated acetate cleavage and Dess−Martin oxidation of the resulting primary alcohol afforded unconjugated aldehyde **10**.[19] Vinyllithium, generated from tetravinyltin, added with high diasteroselectivity into the aldehyde, generating an intermediate lithium alkoxide that was directly made to react with propargyl bromide in the presence of HMPA. The alkyne of trienyne **11** was deprotonated with *n*-butyllithium, and the acetylide anion was silylated to cleanly afford trienyne **12**.

Providing a new strategy for the assembly of guaianolide natural products,[20] a borylative enyne cyclization of **12** (21 g scale) generated the cyclized product **13** (after oxidative conversion of the boronate to a primary alcohol) with the correct diastereomeric configuration (as confirmed by X-ray crystallography) in 62% yield (Figure 2).[21−23] This transitioned well to the formation of the last carbocyclic ring through a two-step sequence consisting of Swern oxidation of **13** to generate intermediate aldehyde **14** followed by direct cyclization of **14** through an ene reaction promoted by diethylaluminum chloride to form **15** possessing the tricyclic system of eupalinilide E (Figure 3).[18] The secondary alcohol of **15** was converted to the tigloyl ester using Yamaguchi conditions to yield **16**, with the reaction conducted on 21 g of **15**.[24]

With all of the carbons installed, oxidation of four C−H bonds through allylic oxidation of both the substituted furan and cyclopentene was sought directly following clean removal of the vinyl trimethylsilyl group of **16** with TFA to form **17** (Figure 3). Through an extensive inspection of reagents leading to chromium trioxide and 3,5-dimethylpyrazole, the corresponding enone/butyrolactone product **18** was generated in 36% yield over two steps, providing the optimal yield starting from 2 g of **16**.[25,26] This was a crucial success, as late-stage introduction of the carbonyls enabled earlier chemistry by minimizing functional group incompatibility to this point in the synthesis.[27] Selective 1,2-reduction of the unsaturated ketone of **18** under modified Luche conditions using $Yb(OTf)_3$ afforded allylic alcohol **19** in 75% yield (Figure 4).[28] In view of the high reactivity of the $\alpha$-methylene-$\gamma$-butyrolactone, conventional Luche conditions failed to adequately suppress the 1,4-reduction. Diastereoselective hydroxyl-directed epoxidation of the homoallylic olefin over the allylic olefin of **19** proved challenging, as mixtures of epoxides were generated with a number of reagents. Similarly reagent-controlled reactions exploiting matched and mismatched


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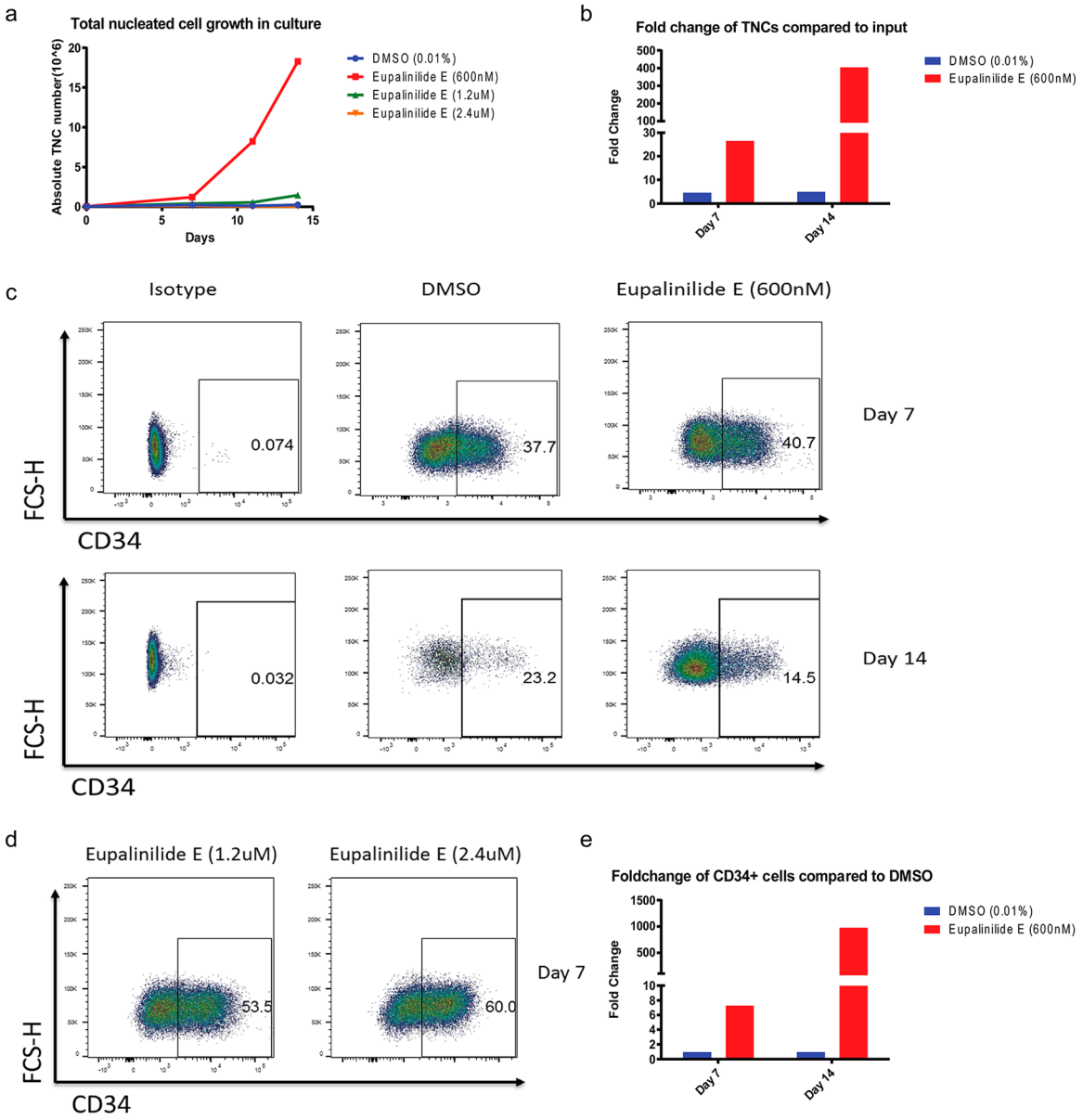


**Figure 5.** Synthesized eupalinilide E can expand human HSPCs ex vivo. (a) Eupalinilide E (600 nM) largely expands the total nucleated cell (TNC) number in culture. The $4.5 \times 10^4$ human cord blood CD34+ cells were cultured in HSC expansion medium containing 0.01% DMSO vehicle or 600 nM, 1.2 $\mu$M, or 2.4 $\mu$M eupalinilide E. The number of cells was counted at days 0, 7, 11, and 14. (b) TNCs were increased to 27-fold at day 7 and 406-fold at day 14 in the cells treated with eupalinilide E (600 nM) relative to the input number of cells ($4.5 \times 10^4$). (c) Flow cytometry analysis of CD34 expression at days 7 and 14 on cultured cells treated with 0.01% DMSO vehicle or 600 nM eupalinilide E. The CD34+ cells were similarly maintained while the total cells were markedly expanded in cells treated with 600 nm eupalinilide E compared with DMSO-treated cells. (d) Flow cytometry analysis of CD34 expression on cultured cells treated with 1.2 or 2.4 $\mu$M eupalinilide E at day 7. The results show that a higher concentration of eupalinilide E retained a higher percentage of CD34+ cells, although the total TNCs were only slightly increased with 1.2 $\mu$M eupalinilide E or even decreased with 2.4 $\mu$M eupalinilide E compared with DMSO-treated cells. (e) Fold change in the absolute CD34+ cell number upon treatment with 600 nM eupalinilide E compared with DMSO-vehicle-treated cells at days 7 and 14. After 14 days of culture, eupalinilide E (600 nM) led to a 983-fold increase in CD34+ cells compared with 0.01% DMSO vehicle.

combinations were unsuccessful. The use of aluminum *sec*-butoxide in combination with *tert*-butyl hydroperoxide successfully formed the desired epoxide **20**, which was telescoped directly to eupalinilide E (**1**).[29] Opening of the epoxide of **20** was achieved in a lithium chloride-saturated THF solution with dry hydrochloric acid to cleanly provide the chlorohydrin and complete the total synthesis of eupalinilide E (**1**), providing 466 mg of natural product. Full $^1$H and $^{13}$C NMR spectral analysis matched the reported values[9] and was corroborated by 2D NMR experiments.

To confirm the activity of eupalinilide E, cord blood CD34+ cells were cultured in HSPC expansion medium containing 0.01% DMSO and eupalinilide E at 600 nM, 1.2 $\mu$M, or 2.4 $\mu$M. DMSO-vehicle-treated cells were used as a negative control. We examined three different dosages of eupalinilide E in our study to identify the effect of the concentration on HSPC culture. The starting number of cells was $4.5 \times 10^4$ for all of the conditions. As shown in Figure 5a, eupalinilide E (600 nM) markedly increased the total nucleated cells (TNCs) with time up to 1.2 million cells at day 7 and 18 million cells at day 14. Relative to the input number of


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cells, cells treated with 600 nM eupalinilide E led to a 27-fold increase in TNCs at day 7 and a 406-fold increase at day 14 (Figure 5b). In contrast, the DMSO-vehicle-treated cells gave a 4.7-fold increase in the number of TNCs at day 7 and a minimal increase for the next week to only 5.2-fold at day 14. Compared with DMSO vehicle, eupalinilide E (600 nM) largely expanded the TNCs by 5.6-fold at day 7 and 77-fold at day 14. Interestingly, treatment with 1.2 $\mu$M eupalinilide E increased total cultured cells only 1.6-fold at day 7 and 6-fold at day 14 compared with DMSO treatment. A higher dosage of eupalinilide E (2.4 $\mu$M) resulted in a decreased number of TNCs to 2-fold at day 7 and 11-fold at day 14. Retesting for cytotoxicity toward A549 cells demonstrated attenuated activity relative to the isolation data at 660 nM (see the Supporting Information).

One major challenge of HSPC expansion ex vivo is that the culture of HSPCs results in a loss of multipotency, as indicated by the loss of the HSPC marker CD34+. To measure the percentage of CD34+ cell fraction during culture, we analyzed the CD34+ surface antigen expression on cultured cells at days 7 and 14 (Figure 5c). Cells treated with 600 nM eupalinilide E maintained 40.7% and 14.5% of CD34+ cells at days 7 and 14, respectively, which were comparable to the results for DMSO-vehicle-treated cells. Interestingly, treatment with 1.2 and 2.4 $\mu$M eupalinilide E retained 53.5% and 60% of CD34+ cells at day 7, respectively, which were significantly higher compared with DMSO-treated cells (Figure 5d).

To measure the total expansion of CD34+ cells in culture, we calculated the absolute number of CD34+ cells by multiplying the total TNCs by the frequency of CD34+ cells in the total cells. The results showed that upon treatment with 600 nM eupalinilide E, the number of CD34+ cells was expanded from $4.5 \times 10^4$ initially to $4.3 \times 10^5$ at day 7 and $1.7 \times 10^6$ at day 14, corresponding to 9- and 37-fold increases relative to the starting CD34+ cell count. Compared with DMSO treatment, treatment with 600 nM eupalinilide E promoted CD34+ expansion by 7-fold and 983-fold at days 7 and 14, respectively (Figure 5e).

## DISCUSSION

Late-stage C−H oxidation chemistry has enabled a laboratory synthesis of eupalinilide E that can access >400 mg in a single batch. In addition to a double allylic C−H oxidation, the synthetic route utilized reactions that were conducted on useful scales with notable simplifying transformations: a diastereoselective borylative enyne cyclization, a hyperselective Luche reduction, and an aluminum-mediated epoxidation reaction that favors oxidation of homoallylic alkenes over allylic alkenes. With access to synthetic eupalinilide E, retesting and confirmation of the natural product's ability to promote HSPC expansion was possible. The natural eupalinilide E was shown previously to retain a higher percentage of CD34+ cells at a dosage of 600 nM compared with cells treated with 0.1% DMSO, although the cell growth remained similar during the first 10 days.[10] However, in our study, cells treated with 600 nM synthetic eupalinilide E outgrew control cultures much earlier (~4 days), and a significant increase in TNCs was observed at day 7. However, the CD34+ percentage in cells treated with 600 nM eupalinilide E was not significantly increased compared with DMSO-treated cells. We noticed that cells treated with 1.2 $\mu$M eupalinilide E behaved similarly to cells treated with 600 nM natural eupalinilide E as described previously,[10] with a higher percentage of CD34+ cell fraction and less total cell expansion during the short time culture. This inconsistency could be due to the variations between different laboratories or the different responses of cells from various sources to the compound. It may also suggest that synthesized eupalinilide E requires a relatively higher concentration to achieve the same level of activity as natural eupalinilide E. Since 2.4 $\mu$M eupalinilide E resulted in a decrease of cellularity but retained a higher percentage of CD34+ cells, these data together indicate that eupalinilide E expansion of HSPCs is dose-sensitive. If the dosage is too high (2.4 $\mu$M), the compound will likely kill the cells although it retains high percentage of CD34+ cells. A lower dosage of eupalinilide E (1.2 $\mu$M) tends to promote total cell growth and maintain relatively high CD34+ cell fraction in the population compared with DMSO-treated cells. Treatment with 600 nM eupalinilide E is capable of enhancing cell proliferation without loss of cell identity. Further study is required to optimize the concentration of eupalinilide E for the best potential effect on HSPC expansion and to explore the underlying mechanisms.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b03055.

Experimental details, X-ray crystallographic data, spectral data, activity of eupalinilide E against A549 cells, and HSPC expansion methods (PDF)

Crystallographic data for **13** (CIF)

## AUTHOR INFORMATION


### Corresponding Author

*drsiegel@ucsd.edu


### Notes

The authors declare no competing financial interest.

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