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FULL PAPER

Construction of a Meroterpenoid-like Compounds Library Based on Diversity-Enhanced Extracts

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Abstract: The structural diversity of natural products and their derivatives have long contributed to the development of new drugs. However, the difficulty in obtaining compounds bearing skeletally novel structures has recently led to the decline of pharmaceutical research into natural products. In this paper, we report the construction of a meroterpenoid-like library containing 25 compounds with diverse molecular scaffolds obtained from diversity-enhanced extracts. This method constitutes an approach for increasing the chemical diversity of natural-product-like compounds by combining natural product chemistry and diversity-oriented synthesis. Extensive pharmacological screening of the library revealed promising compounds for anti-osteoporotic and anti-lymphoma/leukemia drugs. This result indicates that the use of diversity-enhanced extracts is an effective methodology for producing chemical libraries for the purpose of drug discovery.

Introduction

Natural products and their derivatives have long played an essential role in the development of novel drugs because of their structural diversity. However, pharmaceutical research into natural products has recently declined because of factors such as more difficulty of collecting novel compounds with skeletally novel structures from natural resources than from combinatorial synthetic libraries.[1,2] Therefore, new approaches for augmenting the chemical diversity of these compounds are crucial to retaining the usefulness of natural products and their derivatives.

Recently, we proposed the use of "diversity-enhanced extracts",[3,4] which is an approach for increasing the chemical diversity of natural-product-like compounds through a combination of natural product chemistry and diversity-oriented synthesis.[5] Diversity-enhanced extracts are obtained from chemical reactions that remodel molecular scaffolds directly in the extracts of natural resources. The subsequent isolation of each compound produced from such reactions affords a diverse natural-product-like library of new molecular scaffolds. There have also been some reports on similar methods that chemically convert natural extracts.[6–11] However, we defined diversity-enhanced extracts as natural extracts formed by multiple diversity-generating reactions that not only convert functional groups, but also form new carbon–carbon bonds and modify the molecular scaffolds similarly to diversity-oriented synthesis.

Meroterpenoids are natural products of mixed biosynthetic origin that are partially derived from terpenoids.[12a] Particularly, meroterpenoids derived from polyketide and terpenoid precursors contain sp^3-rich terpenoid scaffolds and sp^2-rich polyketide scaffolds, which confer various pharmacological activities. Meroterpenoids are often isolated from fungi and marine organisms. On the other hand, plants can produce limited types of meroterpenoids, such as cannabinoids and polyprenylated phloroglucinols,[12] though plants are rich sources of several types of terpenoids. If meroterpenoid-like compounds based on terpenoids derived from plants can be produced, then they can be useful in constructing a chemically diverse compound library for drug discovery.

In this paper, we report the construction of a library of meroterpenoid-like compounds with diverse scaffolds based on the diversity-enhanced extracts of classical medicinal plants. Among these compounds, anti-osteoporotic and antiviral compounds were obtained via extensive pharmacological screening.

Results and Discussion

Preparation of diversity-enhanced natural extracts.

Although typically diverse in structure, phenolic meroterpenoids such as siccanin[13] and pyrone-type meroterpenoids such as pyripyropene A[14] possess polyketide-derived meroterpenoid structures. More specifically, they contain a cyclic ether moiety fused with a benzene or pyrone ring (Scheme 1). Thus, we planned to construct such cyclic ether moieties to produce meroterpenoid-like compounds in diversity-enhanced extracts. Two successive reactions, ortho-iodophenyl etherification of allyl or homoallyl alcohol moiety in terpenoids and a ring formation by Mizoroki-Heck reaction[15] would produce cyclic ether moieties in phenolic meroterpenoid-like compounds. Reacting these compounds with iodo-α-pyrone instead of *o*-iodophenol would result in the formation of pyrone-type meroterpenoids.

Cyperus rotundus is a traditional medicinal plant used as both an antipyretic and an aromatic stomatic. The main constituents of *C. rotundus* are sesquiterpenoids such as α-cyperone and cyperotundone, which contain an allyl alcohol or α,β-unsaturated ketone moiety.[16] Methanol extracts of *C. rotundus* were treated with DIBAL to produce chemically reduced extracts. The use of

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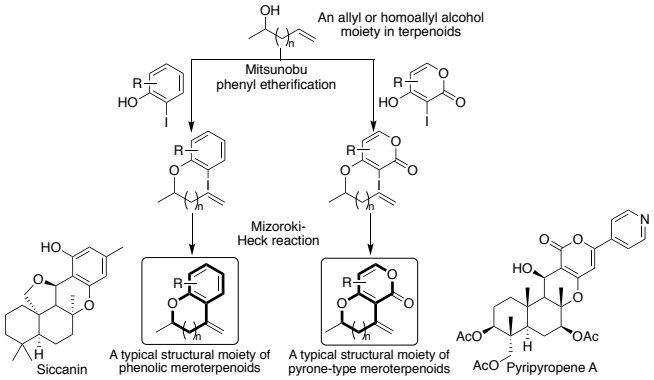


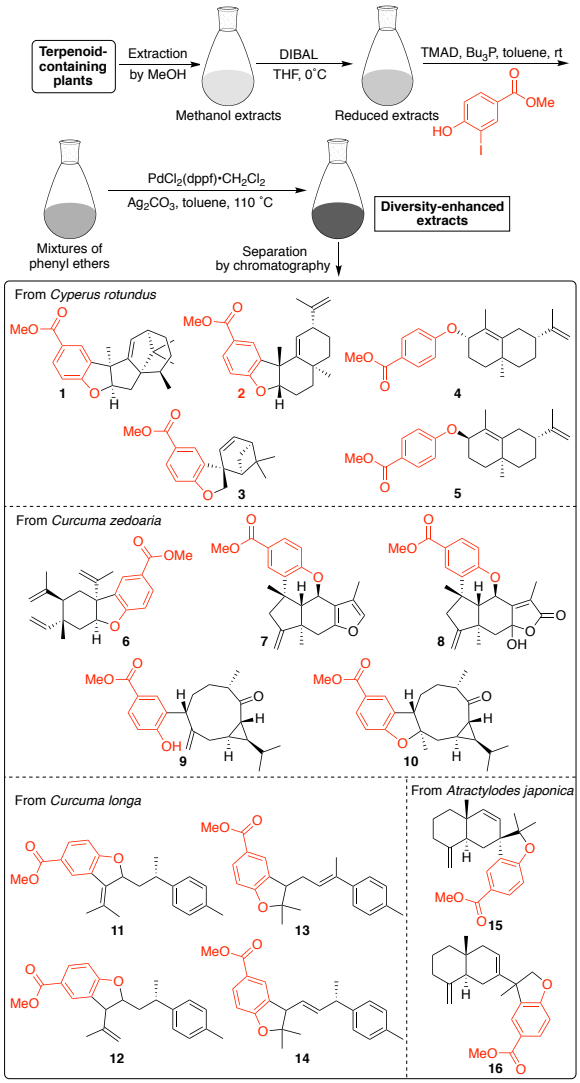
Scheme 1. Synthetic route for obtaining meroterpenoid-like compounds.

such conditions enabled the reduction of α,β-unsaturated ketones into the allyl alcohols. Next, the etherification of the allyl alcohols was carried out by Mitsunobu reaction with methyl 4-hydroxy-3-iodobenzoate in the presence of *N*,*N*,*N*',*N*'-tetramethylazodicarboxyamide and tributylphosphine[17] to afford mixtures of aryl ethers. Finally, these mixtures were subjected to intramolecular Mizoroki–Heck reaction conditions to obtain diversity-enhanced extracts containing phenolic meroterpenoid-like compounds with cyclic ether moieties (Scheme 2). On the other hand, the etherification of the chemically reduced extracts using 4-hydroxy-3-iodo-6-methyl-2*H*-pyran-2-one instead of iodobenzoate was carried out to produce diversity-enhanced extracts containing pyrone-type meroterpenoid-like compounds.

Curcuma zedoaria,[18] *Curcuma longa*,[19] and *Atractylodes japonica*[20] are also traditional medicinal plants that are rich sources of sesquiterpenoids. Diversity-enhanced extracts containing meroterpenoid-like compounds were also prepared from the methanol extracts of these medicinal plants using similar procedures.

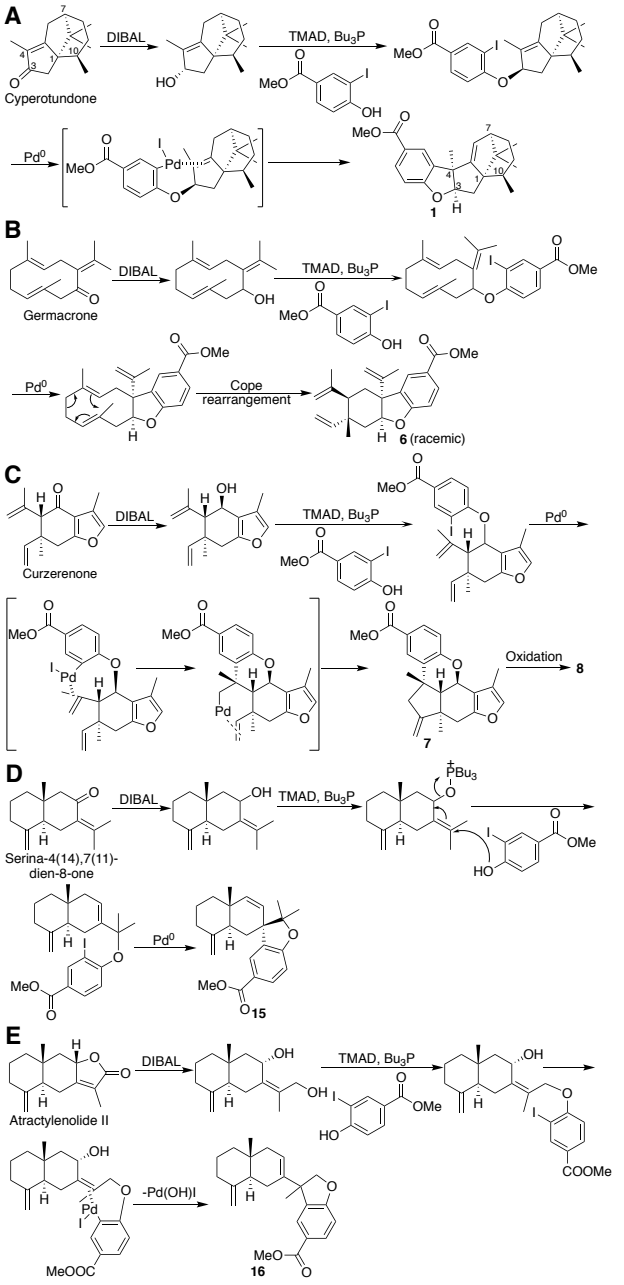
Isolation and structure elucidation of phenolic meroterpenoids.

The diversity-enhanced extracts of *C. rotundus*, *C. zedoaria*, *C. longa*, and *A. japonica* conjugated with hydroxyiodobenzoates were separated by repeated column chromatography. Five phenolic meroterpenoid-like compounds (**1**–**5**) were isolated from the extracts of *C. rotundus* (Scheme 2), while five (**6**–**10**), four (**11**–**14**), and two (**15**, **16**) compounds were isolated from those of *C. zedoaria*, *C. longa*, and *A. japonica*, respectively. The structures including the relative stereochemistry of these compounds were established using NMR spectroscopy (see Supporting Information). The isolated compounds are assumed to be produced from the constituents of their plant sources (Scheme S1~4). For example, compound **1** is assumed to be produced from cyperotundone,[16a] a constituent of *C. rotundus*, via reduction, etherification, and cyclization, as expected (Scheme 3A). Because the stereochemistry at C-1, C-7, and C-10 should be retained through these reactions, the absolute configurations at C-1, C-7, and C-10 in **1** are assumed to be *R*, *R*, and *R*,



Scheme 2. Phenolic meroterpenoid-like compounds isolated from the diversity-enhanced extracts of sesquiterpenoid-containing medicinal plants.

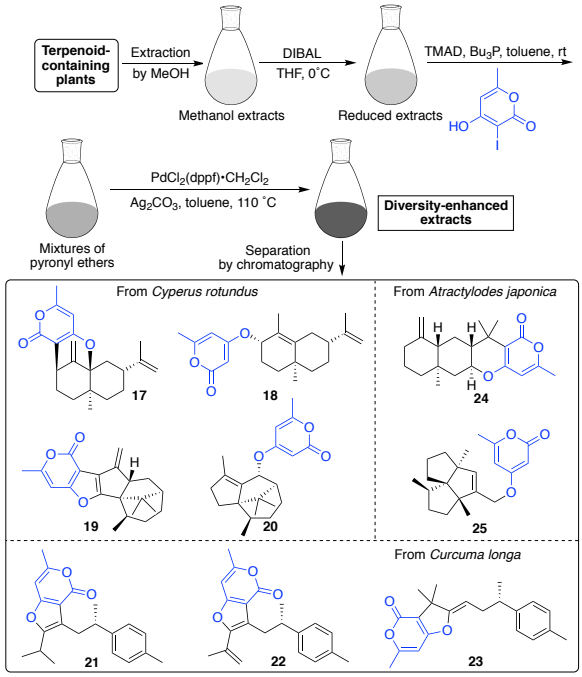
respectively, which are the same as those in cyperotundone. Compounds **2**, **4**, and **5** are assumed to be produced from α-cyperone or cyperol,[16b] even though cyclic ether moieties were not formed in **4** and **5**. On the other hand, some isolated compounds are assumed to be produced by unexpected reactions. For example, compound **6** is produced from germacrone,[18d] a constituent of *C. zedoaria*, by sequential reduction, etherification, cyclization, and additional Cope rearrangement[21] (Scheme 3B). Compounds **7** and **8** are produced from curzerenone by sequential reduction, etherification, and bicyclization caused by tandem Mizoroki–Heck reactions (Scheme 3C). Compound **15** is produced from selina-4(14),7(11)-dien-8-one[20b] via S_N2'-type Mitsunobu etherification (Scheme 3D). Compound **16** is produced from atractylenolide II with the elimination of Pd(OH)I at Mizoroki–Heck reaction (Scheme 3E).



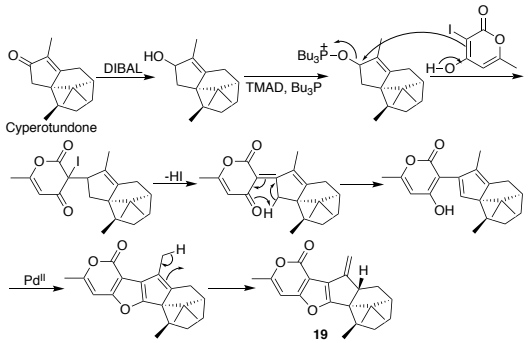
Scheme 3. Plausible pathways for the synthesis of phenolic meroterpenoid-like compounds **1**, **6**, **7**, **8**, **15** and **16**.

Isolation and structure elucidation of pyrone-type meroterpenoids.

The diversity-enhanced extracts of *C. rotundus*, *C. longa*, and *A. japonica* conjugated with hydroxyiodopyrones were separated by repeated column chromatography. Four pyrone-type meroterpenoids (**17**–**20**) were isolated from the extracts of *C. rotundus* (Scheme 4), while three (**21**–**23**) and two (**24**, **25**) compounds were isolated from those of *C. longa* and *A. japonica*, respectively. These isolated compounds are also assumed to be produced from the constituents of their plant sources (see Supporting Information). Compound **24** is formed from selina-4(14),7(11)-dien-8-one via reduction, etherification, and cyclization, as expected. Cyclic ether moieties were not formed in compounds **18**, **20**, and **25**, although the triangle triquinane **25** is assumed to be produced from 3a,5a,8-trimethyl-1,2,3,3a,5a,6,7,8-octahydrocyclopenta[*c*]pentalene-4-carboxylic acid, which has been previously reported to be a constituent of *Ligularia caloxantha*.[22] Compounds **17**, **21**, and **22** are produced through S_N2'-type Mitsunobu etherification. On the other hand, **19** is assumed to be produced from cyperotundone through C–C bond formation under Mitsunobu reaction conditions resulting in hydroiodination, followed by Wacker-type oxidation and the transfer of double bonds (Scheme 5).



Scheme 4. Pyrone-type meroterpenoids isolated from the diversity-enhanced extracts of sesquiterpenoid-containing medicinal plants.



Scheme 5. Plausible pathways for the synthesis of pyrone-type meroterpenoid **19**.

Evaluation of the chemical diversity of the meroterpenoid-like compound library.

We evaluated the chemical diversity of the meroterpenoid-like compound library by calculating Tanimoto coefficients based on 2D molecular fingerprints.[23] A Tanimoto coefficient is obtained for a pair of compounds on a scale of 0 to 1, with 0 and 1 representing perfect dissimilarity and similarity, respectively. It has been reported that the Tanimoto coefficient is generally greater than 0.7 between a parent compound and its simply modified compound (e.g., following alkylation, oxidation/reduction, and substitution of functional groups).[24,25] A similarity matrix for the meroterpenoid-like library (Figure 1) shows that the average of the calculated Tanimoto coefficients is 0.230, indicating that the meroterpenoid-like compounds in the library are structurally different from one another. The averages of the groups of phenolic (**1**–**16**) and pyrone-type meroterpenoids (**17**–**25**) are 0.318 and 0.268, respectively, indicating that these compounds, in which the same polyketide moiety has been introduced, are also structurally different from one another. Thus, the use of the diversity-enhanced extracts produced a structurally diverse meroterpenoid-like library, which cannot be obtained solely by simple modification of known natural products.

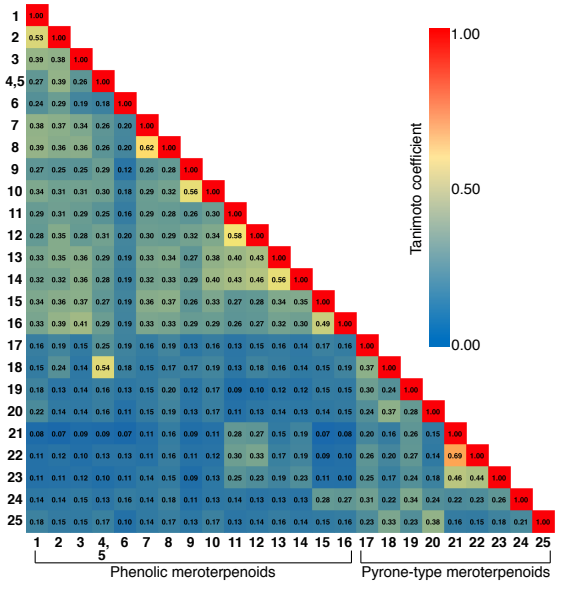


Figure 1. Matrix of Tanimoto coefficients for the meroterpenoid-like library obtained from the diversity-enhanced extracts. The Tanimoto coefficients were calculated using KNIME® Analytic Platform version 3.5.2 based on ECFP4 molecular fingerprints. The fingerprints of compounds **4** and **5** are identical because they are diastereomeric.

Evaluation of the biological activities of the meroterpenoid-like compound library.

To verify the usefulness of the library of meroterpenoid-like compounds for drug discovery and to discover new pharmacologically active compounds, the library was extensively screened for biological activities. As a result, some compounds in the library have been found to have two types of biological activities.

Osteoclasts are multinucleated cells that resorb bone tissue. They are formed by the fusion of mononuclear monocyte/macrophage lineage precursor cells. Excessive bone resorption often results in osteoporosis and rheumatoid arthritis.[26] To assess the effect on osteoclastogenesis, monocytic RAW264.7 cells were treated with the meroterpenoid-like compounds in the presence of receptor activator of NF-κB ligand (RANKL) and measured activity of tartrate-resistant acid phosphatase (TRAP), which is an osteoclast specific marker enzyme.[27] We found that compound **16** suppressed RANKL-induced TRAP activity with an IC_{50} value of 6.2 μM (Figure 2 and Figure S1) without showing cytotoxicity at the effective concentrations (data not shown); this suggests that compound **16** is an inhibitor of osteoclastogenesis and a possible lead compound for the development of new drugs for treating osteoporosis.

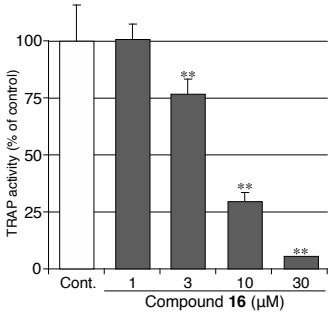


Figure 2. Osteoclastogenesis-suppressive activity of compound **16**. RAW264.7 cells were treated with various concentrations of **16** in the presence of the receptor activator of the NF-κB ligand (RANKL) for four days. After fixation with 10% formalin and 100% ethanol, TRAP activity was measured. Data are expressed as percentages in relation to the mean value of the control cells. The bars indicate the standard deviation of the three wells. The statistical significance of the differences was determined by Dunnett's test. **p < 0.01 vs. control.

The Epstein–Barr virus (EBV) has been strongly associated with the onset of several types of cancer, including both B-cell and T/NK-cell lymphomas.[28] Because EBV infection is prevalent worldwide, the development of new anti-EBV drugs or drugs for treating the associated tumors due to this virus is urgent. We screened the meroterpenoid compound library using an EBV-infected KAI3 cell line (T/NK-cell lymphoma) to find compounds that show selective toxicity against the lymphoma cells. As a result, **17** was found to show toxicity against KAI3 cells at a concentration of less than 0.5 μM. In addition, **17** exerted similar cytotoxic effects on an adult T-cell leukemia cell line, MT-2, without demonstrating apparent cytotoxicity to a hepatoma cell line, HepG2, at a concentration up to 5 μM. These results indicate that **17** has selective cytotoxic effects toward lymphoma/leukemia cells.

Conclusions

We constructed a library of meroterpenoid compounds from the diversity-enhanced extracts of medicinal plants. The library contains 25 compounds that have diverse molecular scaffolds and are difficult to obtain by other synthetic methods, as they were derived from the combination of the original diverse natural products of medicinal plants and diversity-generating reactions. The structural diversity of the compounds in the library was confirmed by using a Tanimoto similarity matrix. In the preparation of diversity-enhanced extracts, almost all compounds present in the natural extracts may be converted. Thus, unexpected and unique compounds such as **25** can be obtained by the conversion of undiscovered minor components that are present in the natural extracts. The occurrence of unexpected sequenced reactions also provided unexpected unique compounds, which enhanced the structural diversity of the compounds in the library. The isolation of each meroterpenoid-like compound from the diversity-enhanced extracts may appear tedious in comparison with common chemical synthetic procedures, but only two to three successive column chromatography steps were necessary to separate these products, similar to the methods utilized for the isolation of common natural products. To expand the chemical diversity of the compound library, more meroterpenoid-like compounds will be obtained by using other types of terpenoid-containing plants as starting materials. The use of structure-modifying chemicals other than 2-iodophenol or iodopyrone will also produce more diverse meroterpenoid-like compounds. After extensive pharmacological screening of the meroterpenoid-like compounds, **16** and **17** were identified as seed compounds for anti-osteoporosis and selective anti-lymphoma/leukemia drugs, respectively. This result indicates that the use of diversity-enhanced extracts is an effective methodology for constructing chemical libraries that may be screened for biologically active compounds.

Experimental Section

Preparation of phenolic meroterpenoids-containing diversity-enhanced extracts. Rhizomes (209 g) of *Cyperus rotundus*, which was purchased from Kinokuniyakanyakkyoku Co., Ltd. (Tokyo, Japan), were extracted twice with methanol (1.60 L) at room temperature to give the extract. This extract was partitioned with ethyl acetate and water to yield the ethyl acetate solubles (13.14 g).

Diisobutylaluminium hydride (1.0 M solution in toluene) (80 mL) was added to a solution of the ethyl acetate solubles (8.55 g) in THF (80 mL) at 0 ˚C. After being stirred for 3 hours at 0 ˚C, the reaction mixture was poured into saturated potassium sodium tartarate solution, and the mixture stirred for 30 minutes. Then, the mixture was extracted with ethyl acetate three times. The combined organic layer was washed with water and brine, dried over sodium sulfate, and concentrated *in vacuo* to the reduced extracts (7.52 g).

Tri-n-butylphosphine (2.5 mL, 10 mmol) was added dropwise to the solution of *N*,*N*,*N*′,*N*′-tetramethylazodicarboxyamide (1.72 g, 10 mmol) in toluene (10 mL) at 0 ˚C. Then, the solution of the reduced extracts (3.00 g) and methyl 4-hydroxy-3-iodobenzoate (1.47 g, 5.30 mmol) in toluene (20 mL) was added dropwise to the reaction mixture. After being stirred for 12 hours at room temperature, the mixture was extracted with ethyl acetate three times. The combined organic layer was washed with water and brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was chromatographed over silica gel eluted by hexane-ethyl acetate (19:1 to 4:1) to the mixture of phenyl ethers (1.83 g).

The mixture of phenyl ethers (1.83 g), $PdCl_2$(dppf) complex with dichloromethane (196 mg, 0.24 mmol), 1,1'-bis(diphenylphosphino)ferrocene (266 mg, 0.48 mmol) and silver carbonate (1.65 g, 6.0 mmol) were suspended in toluene (25 mL), and the mixture was refluxed for 12 hours under argon atmosphere. After being cooled into room temperature, the reaction mixture was filtered through a silica gel pad, which was eluted by ethyl acetate. The filtrate was concentrated *in vacuo* to afford the diversity-enhanced extracts containing phenolic meroterpenoid-like compounds (476 mg).

By the use of the same procedure described above, the phenolic meroterpenoids-containing diversity enhanced extracts of *Curcuma zedoaria* (570 mg), *Curcuma longa* (2.99 g) and *Atractylodes japonica* (1.00 g) were afforded from the methanol extracts of rhizomes of *C. zedoaria* (101 g), *C. longa* (151 g) and *A. japonica* (150 g), respectively.

Separation of the phenolic meroterpenoids-containing diversity-enhanced extracts of *C. rotundus*. The diversity-enhanced extracts (476 mg) of *C. rotundus* were chromatographed over silica gel and the column eluted with hexane-ethyl acetate mixtures with increasing polarity to afford hexane-ethyl acetate (19:1) eluent (fraction A, 201 mg), which was further separated by ODS column using water-acetonitrile solvent system to give water-acetonitrile (3:7) eluent (fraction A-1, 16.6 mg), water-acetonitrile (2:8) eluent (fraction A-2, 53.0 mg) and water-acetonitrile (1:9) eluent (fraction A-3, 11.1 mg).

Fraction A-1 was subjected to recycle preparative HPLC (column, YMC-GPC T-2000 (ϕ 20 mm x 600 mm, YMC Co., Ltd.); solvent, ethyl acetate) to give compound **3** (1.8 mg). Fraction A-2 was also subjected to recycle preparative HPLC (column, YMC-GPC T-2000 (ϕ 20 mm x 600 mm, TMC Co., Ltd.); solvent, ethyl acetate) to give compounds **1** (5.4 mg) and **2** (4.3 mg). Fraction A-3 was subjected to reverse phase HPLC (column, Wakopak Navi C30-5 (ϕ 20 mm x 250 mm, Wako Pure Chemical Industries, Ltd.); solvent, water–acetonitrile (9:1)) to give compounds **4** (5.3 mg) and **5** (2.8 mg).

Preparation of pyrone-type meroterpenoids-containing diversity-enhanced extracts. Tri-n-butylphosphine (3.7 mL, 15 mmol) was added dropwise to the solution of *N*,*N*,*N*′,*N*′-tetramethylazodicarboxyamide (2.58 g, 15 mmol) in toluene (10 mL) at 0 ˚C. Then, the solution of the reduced extracts of *C. rotundus* (3.24 g) and 4-hydroxy-3-iodo-6-methyl-2-pyrone (2.51 g, 10.0 mmol) in toluene (30 mL) was added dropwise to the reaction mixture. After being stirred for 12 hours at room temperature, the mixture was extracted with ethyl acetate three times. The combined organic layer was washed with water and brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was chromatographed over silica gel eluted by hexane-ethyl acetate (2:1 to 1:3) to the mixture of pyronyl ethers (1.74 g).

The mixture of pyronyl ethers (1.74 g), $PdCl_2$(dppf) complex with dichloromethane (183 mg, 0.22 mmol), 1,1'-bis(diphenylphosphino)ferrocene (251 mg, 0.45 mmol) and silver carbonate (1.54 g, 5.6 mmol) were suspended in toluene (20 mL), and the mixture was refluxed for 12 hours under argon atmosphere. After being cooled into room temperature, the reaction mixture was filtered through a silica gel pad, which was eluted by ethyl acetate. The filtrate was concentrated *in vacuo* to afford the diversity-enhanced extracts containing pyrone-type meroterpenoids (1.07 g).

By the use of the same procedure described above, the pyrone-type meroterpenoids-containing diversity enhanced extracts of *Curcuma longa* (3.15 g) and *Atractylodes japonica* (1.05 g) were afforded from the methanol extracts of rhizomes of *C. zedoaria*, *C. longa* and *A. japonica*, respectively.

Separation of the pyrone-type meroterpenoids-containing diversity-enhanced extracts of *C. rotundus*. The diversity-enhanced extracts (1.07 g) were chromatographed over silica gel and the column eluted with hexane-ethyl acetate mixtures with increasing polarity to afford hexane-ethyl acetate (19:1) eluent (fraction A, 100 mg), hexane-ethyl acetate (9:1) eluent (fraction B, 147 mg) and hexane-ethyl acetate (4:1) eluent (fraction C, 251 mg).

Fraction A was separated by ODS column using water-acetonitrile solvent system to give water-acetonitrile (2:8) eluent (fraction A-1, 15 mg), which was subjected to recycle preparative HPLC (column, YMC-GPC T-2000 (ϕ 20 mm x 600 mm, TMC Co., Ltd.); solvent, ethyl acetate) to give compound **19** (5.1 mg).

Fraction B was separated by ODS column using water-acetonitrile solvent system to give water-acetonitrile (4:6) eluent (fraction B-1, 11 mg) and water-acetonitrile (3:7) eluent (fraction B-2, 19 mg). Fraction B-1 was subjected to recycle preparative HPLC (column, YMC-GPC T-2000 (ϕ 20 mm x 600 mm, TMC Co., Ltd.); solvent, ethyl acetate) to give compounds **17** (2.7 mg). Fraction B-2 was subjected to reverse phase HPLC (column, Mightysil RP-18GP (ϕ 20 mm x 250 mm, Kanto Chemical Co., Inc.); solvent, water–acetonitrile (3:7)) to give compound **20** (1.0 mg).

Fraction C was separated by ODS column using water-acetonitrile solvent system to give water-acetonitrile (3:7) eluent (fraction C-1, 16 mg), which was subjected to reverse phase HPLC (column, Mightysil RP-18GP (ϕ 20 mm x 250 mm, Kanto Chemical Co., Inc.); solvent, water–acetonitrile (3:7)) to give compound **18** (9.0 mg).

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Keywords: Diversity-enhanced extracts •Diversity-oriented synthesis • Meroterpenoids • Chemical library

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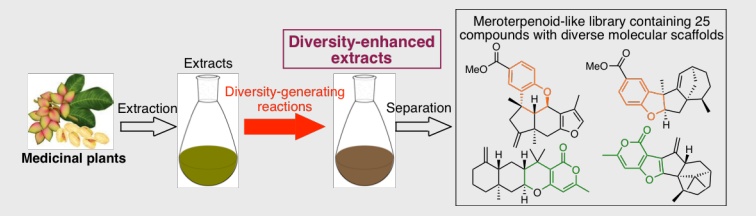

A meroterpenoid-like library containing 25 compounds with diverse molecular scaffolds was constructed from diversity-enhanced extracts, which constitutes an approach for increasing the chemical diversity of natural-product-like compounds by combining natural product chemistry and diversity-oriented synthesis. Extensive pharmacological screening of the library revealed promising compounds for anti-osteoporotic and anti-lymphoma/leukemia drugs.

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Development of Terpenoid Alkaloid-like Compound Library Based on a Humulene Skeleton