Supporting Materials and Methods

Algorithm to Identify the Parent Scaffold of Each Individual Natural Product (NP) Scaffold. A list of possible parent candidates was generated by substructure matching of all available scaffolds to the scaffold under study (child scaffold) and collecting those that are substructures of the child.

For the identification of the parent scaffold the following prioritization rules were determined:

1. The parent scaffold had to be a substructure of the child scaffold.
2. The parent scaffold had to have fewer rings than the child scaffold.
3. Breaking of ring bonds was not allowed.
4. In case there were several possible parent candidates, the parent scaffold was selected such that it contained the maximum number of heteroatoms.
5. If rule 4 was not applicable, the parent with the larger scaffold was chosen.
6. If parent assignment based on rules 4 and 5 was not possible, the more frequent scaffold among NPs was selected as parent.

The following *in silico* procedure (shown as JAVA-based pseudo code) was developed based on these rules:

```
parent = null;
// loop through all available candidates (passing rules 1-3) to select the parent
for each (candidate) {
// do not allow ring opening in the children scaffold
if (candidate.max_ring_size > child.max_ring_size) continue;
// parent should be the largest candidate (if other criteria fit)
if (candidate.number_of_atoms > parent.number_of_atoms + 2) {
parent = candidate;
continue;
}
```

```
if (parent = = null) parent = candidate;
// select paring with maximal number of ring bonds
if (candidate.nonring_bond_count > parent.nonring_bond_count) continue;
// take parent with more heteroatoms
if (candidate.number_of_heteroatoms > parent.number_of_heteroatoms) {
parent = candidate;
continue;
}
// if still more possibilities, take the most common scaffold
if (candidate.frequency > parent.frequency) {
parent = candidate;
continue;
}
}
```

Synthesis of the Compound Collection. Differently functionalized octahydronaphthalene scaffold derivatives were synthesized in solution and subsequently attached to a solid support by means of an alcohol for library synthesis on the polymeric carrier. 3,4,8,8a-tetrahydronaphthalene-1,6(2*H*,7*H*)-diones (**6**; see Scheme 1) were synthesized in solution employing the enantioselective Robinson anellation(1, 2) as the key C–C-bond forming step. Compounds of type **6** were reduced to the respective 4,4a,5,6,7,8-hexahydro-5-hydroxynaphthalin-2(3*H*)-one compounds (**7**). As shown in Scheme 1 for compound **8** as a representative example, scaffolds were then immobilized on Merrifield resin equipped with a dihydropyranyl linker (3) through their hydroxy function and then subjected to aldol condensation reactions with different aldehydes leading to exocyclic *E*-configured olefins (**9**).

The immobilized aldol condensation products then were subjected to a variety of different transformations to increase the diversity of the library. As shown in Scheme 1, reactions included, for example, Sonogashira and Wittig reactions.

Compounds were released from the solid support by treatment with trifluoroacetic acid (TFA) and purified to homogeneity by means of preparative HPLC. In total, 162 compounds were synthesized in multimilligram amounts.

General Procedures. *General procedure for resin loading* (*GP 1*). Dihydropyran-functionalized resin (1.0 eq) is pretreated for swelling for 15 min with dichloromethane (15 ml/g). The alcohol (5 eq) to be coupled then is added along with *p*-toluene sulfonic acid monohydrate (0.5 eq), and the mixture is shaken overnight. The resin is filtered and washed three times each with dichloromethane, dichloromethane:methanol (1:1, vol/vol), methanol, dichloromethane:methanol (1:1, vol/vol), and dichloromethane. The resin is then dried *in vacuo*.

Loading determination procedure. The resin is pretreated for 15 min with dichloromethane, then 5 ml of a 10% solution of trifluoroacetic acid in dichloromethane is added, and the mixture is shaken for 10 min. The solution then is filtered and coevaporated with 3 ml of toluene. The loading of the resin is calculated from the amount of the released alcohol.

General procedure for solid-phase aldol reaction (*GP 2*). Butyl lithium in hexane (9 eq) is added to a solution of diisopropyl amine (10 eq) in tetrahydrofuran (THF) (1 ml/mmol) at –78°C. The solution is warmed to room temperature and added to the resin (1 eq), which was washed twice and pretreated with 15 ml THF. The mixture is shaken at room temperature for 30 min, then cooled to 0°C. The aldehyde (12 eq) is added, and the mixture is shaken for a further 30 min at 0°C, then for 2 h at room temperature. After filtration of the solvent, the resin is washed three times each with THF, dichloromethane:MeOH (1:1, vol/vol), MeOH, dichloromethane:MeOH (1:1, vol/vol), and dichloromethane. The resin then is dried *in vacuo*.

General procedure for the Wittig reaction on the solid support (*GP 3*). The polymer-bound ketone (1.0 eq) is suspended in toluene (2 ml/g resin) and shaken for 15 min. Triphenylphosphine bromide (10 eq) and butyl lithium (8 eq) in toluene then are added,

and the mixture is shaken for 15 min at room temperature then overnight at 100°C. The resin is filtered and washed three times with toluene, dichloromethane:toluene (1:1, vol/vol), dichloromethane:MeOH (1:1, vol/vol), MeOH, dichloromethane:MeOH (1:1, vol/vol), and dichloromethane and dried *in vacuo*.

General procedure for release of the products from the solid phase (*GP 4*). The dry resin (30 mg) is pretreated with 2 ml of dichloromethane for 15 min. After filtration of the solvent, 3 ml of a 10% TFA solution in dichloromethane is added, and the mixture is shaken for 10 min. The solution is filtered, and the resin is washed twice with the TFA solution. Toluene (3 ml) is added to the combined filtrates, and the solution is evaporated under reduced pressure. The crude product is dissolved in ≈100 μl of acetonitrile and purified by means of HPLC.

General procedure for the Sonogashira reaction on the solid phase (*GP 5*). The resin (1 eq) is combined under argon atmosphere with CuI (1.0 eq), $Pd(PPh_3)_4$ (0.5 eq), DMF (15 ml/g), diisopropylethyl amine (20 eq), and the terminal alkyne (15 eq). The mixture is shaken overnight at 90°C. The solution is filtered, and the resin is washed three times with THF:H_2O (2:1), dichloromethane:MeOH (1:1, vol/vol), MeOH, dichloromethane:MeOH (1:1, vol/vol), and dichloromethane, then dried under reduced pressure.

Glucocorticoid Receptor (GR)-Dependent Transactivation Assay. HEK-293 cells were grown on poly(L-lysine)-coated 12-well plates containing 1 ml of DMEM and 10% FCS. Subconfluent cells (200,000 cells per well) were transfected with 300 ng of pMMTV-LacZ reporter plasmid, 100 ng of pCMV-LUC control plasmid, 300 ng of GR expression vector, and either 300 ng of 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1) or empty pcDNA3 vector. After 6 h, cells were washed twice carefully with steroid-free medium. 11βHSD1 inhibitor, GR antagonist, and steroid hormone were added, and the cells were incubated for an additional 24 h. Cells were lysed in 50 μl of lysis buffer, and lysates were analyzed with the luciferase assay system (Promega) and the β-galactosidase galacto-light plus kit (Tropix, Bedford, MA). Galactosidase activity

was normalized to the internal luciferase control. Data (mean ± SD) were expressed as percentage relative to the control in presence of steroid but absence of inhibitor and were obtained from three independent experiments.

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