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# NOVEL INHIBITORS OF CHOLESTERYL ESTER TRANSFER PROTEIN

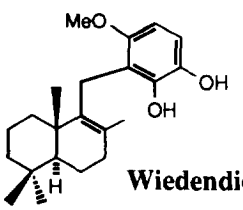
Samuel Chackalamannil,* Yan Xia, Yuguang Wang, Hsingan Tsai, Michael Czarniecki, Suke Wang, Anthony Clemmons, Ho-Sam Ahn, and George Boykow

*Schering-Plough Research Institute*
*2015 Galloping Hill Rd., Kenilworth, New Jersey 07033, U.S.A.*

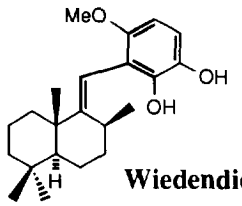
**Abstract:** The synthesis and CETP inhibitory activity of a series of compounds related to wiedendiols (**1a,1b**) are reported. It is proposed that a two point pharmacophore consisting of a catechol group and a large hydrophobic anchor is necessary for activity.

Cholesteryl ester transfer protein (CETP) is a plasma neutral glycoprotein which mediates the net transfer of cholesteryl ester from high density lipoprotein (HDL) into low density lipoprotein (LDL).[1] Since low levels of HDL cholesterol and high levels of LDL cholesterol are directly correlated with increased coronary artery diseases,[2] CETP may play a role in the pathogenesis of atherosclerosis. There have been several reports indicating the relevance of CETP to atherosclerosis suggesting that therapeutic inhibition of CETP may be an attractive target in reducing the risk of coronary artery disease.[3,4]

The sesquiterpenoid marine natural products wiedendiol A (**1a**) and wiedendiol B (**1b**) were identified as CETP inhibitors in a scintillation proximity assay.[5] In mechanism based assays, these compounds were found




**Wiedendiol A (1a)**



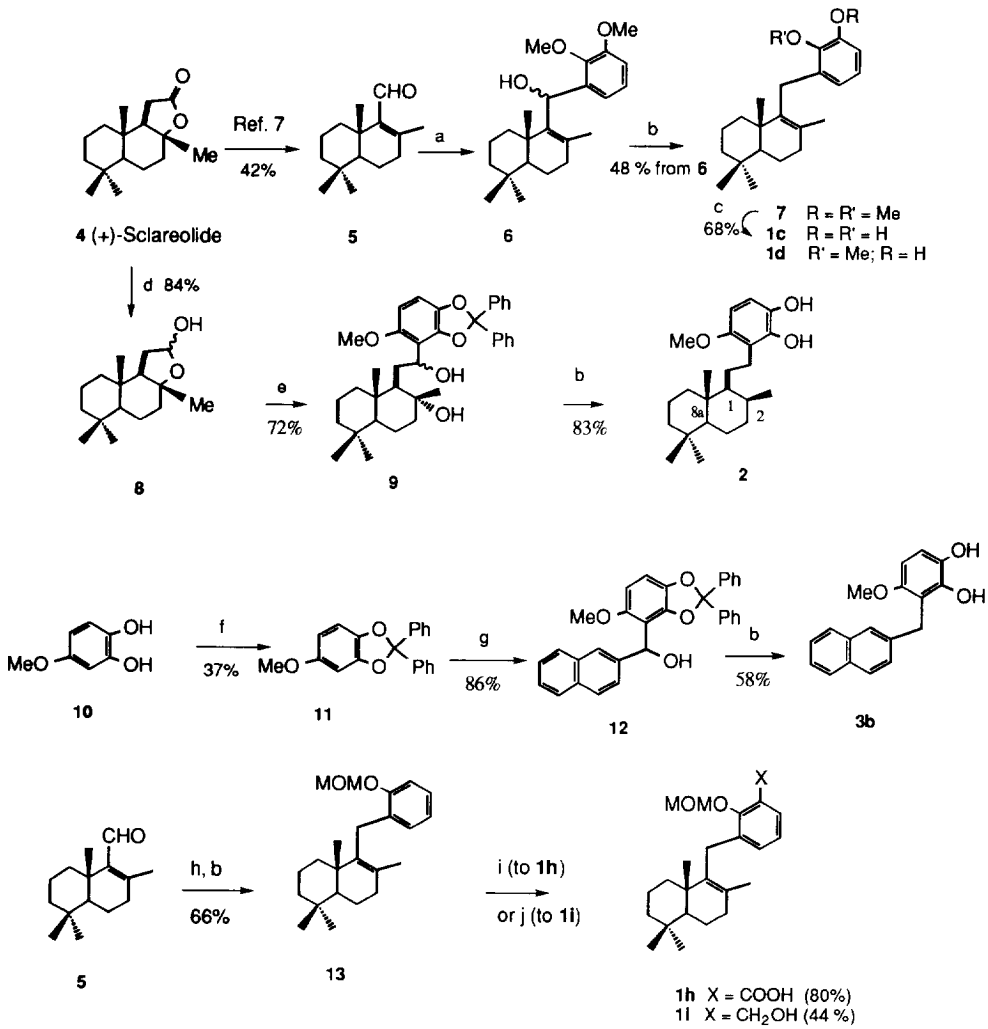

**Wiedendiol B (1b)**

to displace radiolabelled cholesteryl ester from CETP.[6] The isolation and characterization[5] of wiedendiol A and wiedendiol B as well as the chemical synthesis[7] of wiedendiol A have been reported. Herein we report the results of our studies on the structure-activity relationship (SAR) of synthetic analogs related to wiedendiols.

The syntheses of compounds which are described here are outlined in the Schemes 1 and 2. Compounds represented by structures **1a - 1i** (Table I) differ in the pattern and nature of substitution in the aromatic ring. The key optically pure intermediate enal **5** for the synthesis of these compounds was derived from commercially available (+)-sclareolide (**4**) in a multi-step process.[7] Addition of suitably substituted aryl lithium reagents, generated from the corresponding aromatic compounds *via* metalation,[8] gave rise to the intermediate alcohol **6**. Benzyl alcohol derivative **6** under ionic hydrogenation conditions[9] gave the deoxygenated product **7** which,

upon O-deprotection, yielded compound **1c** along with small amounts of monodeprotected compound **1d**. The ratio of products in favor of the latter could be enhanced by employing shorter reaction period.

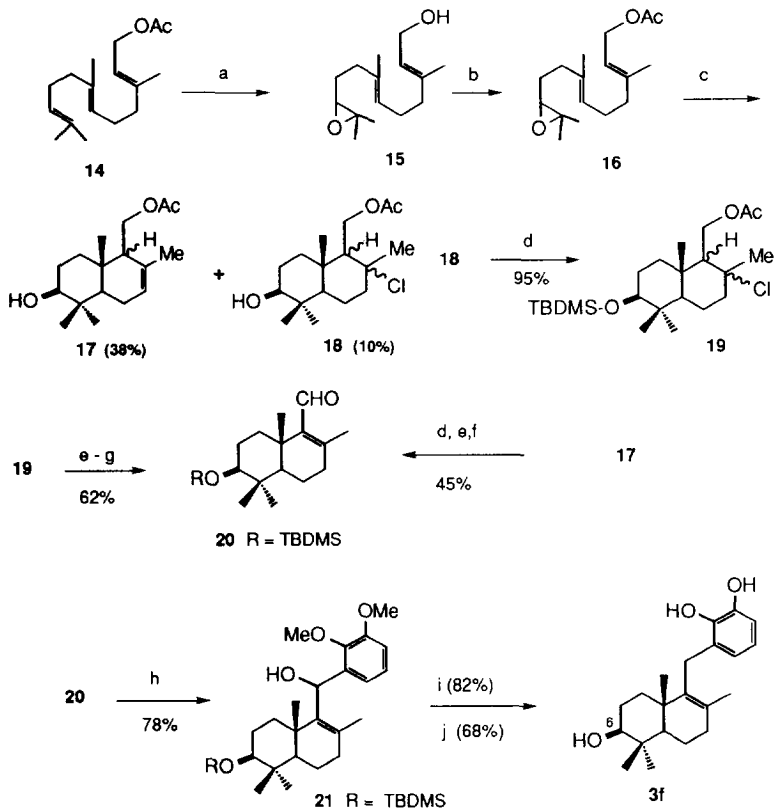
**Scheme 1**




**Reagents and conditions:** a. 1,2-Dimethoxybenzene (**22**)/THF/-78 °C/n-BuLi (1 eq); TMEDA (THF:TMEDA = 2:1, v/v); 0 °C, 2.5 h; then **5**, 1h b. $CH_2Cl_2$-TFA (3:1, v/v)/$Et_3SiH$ (10 eq) rt c. (i) TMSI-Py/150 °C; (ii) HOAc-MeOH/RT d. DIBAL-$CH_2Cl_2$(dropwise)/ $CH_2Cl_2$/-78 °C e. Same as in **a** except **11** instead of **22** and **8** instead of **5** f. $Cl_2CPh_2$/Py/110 °C g. n-BuLi/THF; TMEDA (THF:TMEDA = 2:1, v/v)/ -78 °C to rt; -78 °C then 2-naphthaldehyde, to rt h. Same as in **a** except (methoxymethyl) benzene instead of **22** i. (i) n-BuLi/THF-TMEDA (2:1 v/v), then DMF ; (ii) $NaClO_2$, $NaH_2PO_4$, 2-methyl-2-butene, t-BuOH j. n-BuLi/THF-TMEDA (2:1 v/v), then $(CHO)_n$.

Compound **2**, which represents the carbon chain homologated analogs of wiedendiol A (**1a**), was readily accessible from (+)-sclareolide (**4**) as shown in Scheme 1. Diisobutylaluminum hydride reduction of lactone **4** gave the lactol **8** which, upon treatment with the lithium anion of aromatic compound **11**,[10] gave rise to the diol derivative **9**. Compound **9**, upon treatment with trifluoroacetic acid in the presence of triethylsilane, underwent benzylic deoxygenation, stereospecific reduction of the tertiary alcohol group as well as hydrolysis of the diphenylmethylene ketal group to generate the catechol **2**. The relative stereochemistry of the newly generated asymmetric centers of the decalin derivative **2**, with regard to the angular methyl group, was established by NOE studies.[11] The aromatic derivatives **3a - d** (Table II) were prepared in a manner similar to that described above starting from the appropriate carbonyl precursors.

**Scheme 2**

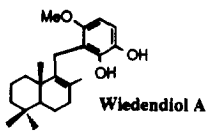
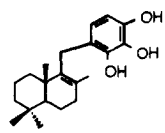
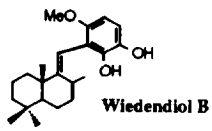
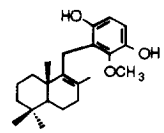
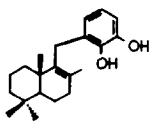
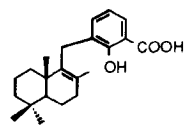
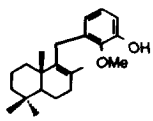
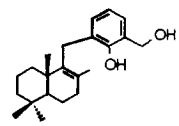
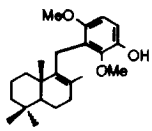
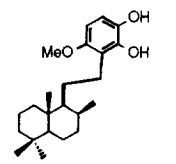



**Reagents and conditions**: a. (i) NBS/t-BuOH-$H_2O$; (ii) $K_2CO_3$/MeOH (ref.12) b. $Ac_2O$/Py /RT c. $MeAlCl_2/CH_2Cl_2$/-78 °C to rt d. TBDMS-Cl/DMF/Im/RT e. KOH/MeOH/RT f. PCC-NaOAc/$CH_2Cl_2$/RT g. $K_2CO_3$/MeOH/RT h. 1,2-dimethoxybenzene/THF-TMEDA (2:1, v/v)/n-BuLi-hexane (1.2 eq)/ -78 °C to 0 °C (2h); -78 °C then **20**; to rt i. $Et_3SiH$/TFA-$CH_2Cl_2$/-78 °C to rt j. (i) TMSI/Py/150 °C; (ii) HOAc/MeOH/RT.

Synthesis of compound **3f**, which bears a hydroxyl group at the site corresponding to C-3 of cholesterol, is outlined in Scheme 2. Lewis acid mediated cyclization[12] of the known epoxide **16**[13] yielded the decalin derivatives **17** and **18** in 38% and 10% yields respectively. These compounds were converted to the enal derivative **20** as shown. Reaction of aldehyde **20** with the aryl lithium reagent generated from 1,2-dimethoxybenzene, followed by deoxygenation and deprotection, as described above, gave final product **3f**.

Table I summarizes the $IC_{50}$ values[14] of compounds **1a** - **1i**. $IC_{50}$ values were determined in a scintillation proximity assay as previously described.[5] The natural products **1a** and **1b** have the same $IC_{50}$ values suggesting that both compounds achieve the same binding conformation despite the more restricted conformations available to **1b**. It is apparent from the data that the 1,2-dihydroxyl substitution (catechol moiety) is essential for optimal activity. The mono-hydroxy derivatives **1d** and **1e** as well as the *para* dihydroxy isomer of **1g** are much less potent. Compound **1c**, which replaces the methoxy substituent of compound **1a** by a

**Table I**

| Entry | | $IC_{50}$ (μM) | Entry | | $IC_{50}$ (μM) |
|---|---|---|---|---|---|
| **1a** |  Wiedendiol A | 5.2 | **1f** |  | 34 |
| **1b** |  Wiedendiol B | 5.2 | **1g** |  | >50 |
| **1c** |  | 16 | **1h** |  | Inactive* |
| **1d** |  | 47 | **1i** |  | >50 |
| **1e** |  | 46 | **2** |  | 6.9 |

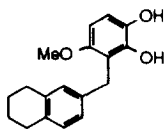
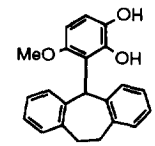
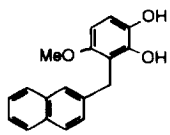
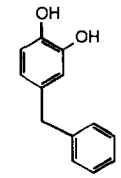
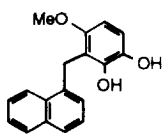
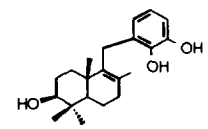
*0% inhibition @ 50 μM.

hydrogen atom, has activity similar to that of the parent compound **1a**. The pyrogallol derivative **1f** has diminished potency suggesting that addition of an extra hydroxyl group to the catechol moiety interferes with the binding. Compounds **1h** and **1i** bear surrogates for the catechol functionality. Compound **1h** has a salicylic

acid group and **1i** has an *o*-hydroxy benzyl alcohol function substituting the catechol group (Scheme 1). These compounds lack potency compared to **1a** (Table I). The relevance of the methylene spacer between the decalin ring system and the aromatic group was also examined. Compound **2** is a homologated analog of **1a**. The $IC_{50}$ value of this compound suggests that homologation of the methylene bridge does not alter potency.

Compounds **3a** to **3f** (Table II) represent structural variations in the carbocyclic region of the natural product **1a**. The data presented in Table II indicate that the carbocyclic region of **1a** shows considerable tolerance to modification. Tetralin derivative **3a** is equipotent to **1a** and **1b** while naphthalene derivatives **3b** and **3c** show only a modest decrease in inhibition. Indeed, even the dibenzosuberane analog **3d** shows potent CETP inhibition. A minimum size requirement for the hydrophobic moiety, however, is clearly indicated by the reduced activity observed with **3e**.[15] Finally, compound **3f**, in which a single hydroxyl group is added to the decalin ring of **1c**, is inactive.

Table II

| Entry | | $IC_{50}$ (μM) | Entry | | $IC_{50}$ (μM) |
|---|---|---|---|---|---|
| **3a** |  | 4.3 | **3d** |  | 2 |
| **3b** |  | 18 | **3e** |  | >50 |
| **3c** |  | 25 | **3f** |  | Inactive* |

*0% inhibition @ 50μM

In conclusion, the data presented here reveal the following structural information regarding the CETP inhibitory properties of the sesquiterpenoid natural products **1a** and **1b** and their analogs. First, the catechol moiety seems to be essential for good activity. None of the compounds we examined without a 1,2-dihydroxyl bearing aromatic ring system showed potent CETP inhibition. Secondly, there is considerable latitude with regard to the structural properties of the hydrophobic region of this molecule. The decalin ring system could be replaced by a naphthalene, tetralin or dibenzosuberane ring system without significant loss of activity. However, hydrophilic functional groups in this region are not tolerated as indicated by the loss of activity for compound **3f** which has a hydroxyl group at the C-6 position of the decalin ring system. The data is consistent with the idea

that the CETP inhibition of these compounds is mediated by a two point pharmacophore with requirements for a catechol binding site and a large hydrophobic anchor. Finally, it should be emphasized that among a wide array of analogs of the natural products **1a** and **1b** that we examined (including others not described here), none turned out to be much more potent than the parent compounds themselves. This data may suggest that the two point pharmacophore proposed in these studies does not contain sufficient binding determinants to achieve more potent inhibition of CETP.

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## References and Notes

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10. Bengtsson, S.; Hogberg, T. *J. Org. Chem.* **1989**, *54*, 4549. The reported procedure was modified by addition of excess of pyridine in the absence of which side reactions occurred.
11. Compound **2** showed positive NOE effect between methyl groups at C-8a and C-2, and the methylene substituent at C-1 indicating their mutual *cis* relationship.
12. Corey, E.J.; Lee, J. *J. Am. Chem. Soc.* **1993**, *115*, 8873 and references cited therein.
13. *Org. Synthesis* Coll.Vol. VI, 560.
14. The $IC_{50}$ values were determined as described in reference 5. The reported $IC_{50}$ values of wiedendiol A and wiedendiol B are 2 μM and 12 μM respectively.[5] However, when repeated, the $IC_{50}$ was found to be 5.2 μM for both compounds.
15. Compound **3e** is commercially available.

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