DOI: 10.1002/chem.201300389

Aerobic Iron-Based Cross-Dehydrogenative Coupling Enables Efficient Diversity-Oriented Synthesis of Coumestrol-Based Selective Estrogen Receptor Modulators

Umesh A. Kshirsagar,[a] Regev Parnes,[a] Hagit Goldshtein,[b] Rivka Ofir,[b, c] Raz Zarivach,[d] and Doron Pappo*[a]

Abstract: An iron-based cross-dehydrogenative coupling (CDC) approach was applied for the diversity-oriented synthesis of coumestrol-based selective estrogen receptor modulators (SERMs), representing the first application of CDC chemistry in natural product synthesis. The first stage of the two-step synthesis of coumestrol involved a modified aerobic oxidative cross-coupling between ethyl 2-(2,4-dimethoxybenzoyl)acetate and 3-methoxyphenol, with $FeCl_3$ (10 mol%) as the catalyst. The benzofuran coupling product was then subjected to sequential deprotection and lactonization steps, affording the natural product in 59% overall yield. Based on this new methodology other coumestrol analogues were prepared, and their effects on the proliferation of the estrogen receptor (ER)-dependent MCF-7 and of the ER-independent MDA-MB-231 breast cancer cells were tested. As a result, new types of estrogen receptor ligands having an acetamide group instead of the 9-hydroxyl group of coumestrol were discovered. Both 9-acetamido-coumestrol and 8-acetamidocoumestrol were found more active than the natural product against estrogen-dependent MCF-7 breast cancer cells, with IC_{50} values of 30 and 9 nM, respectively.

Keywords: cross-coupling · iron · natural products · structure–activity relationships · total synthesis

Introduction

The cross-dehydrogenative coupling (CDC) reaction has become a powerful synthetic tool for the formation of new carbon–carbon bonds. Starting from two different C–H bonds, a new C–C bond is formed through an oxidative coupling process catalyzed by earth-abundant metals, such as copper and iron, in the presence of an oxidant, usually an organic peroxide.[1] Since the pioneering work of Chao-Jun Li,[2] many types of weak C–H bonds have been activated under CDC conditions,[3] thereby enabling easy access to many complex molecular structures.[4] Despite the fact that iron and copper CDC chemistry can offer opportunities for the synthesis of natural products in a practical manner and in an environmental friendly way[5]—in keeping with the demands of modern chemistry—the true value of these reactions in target- and diversity-oriented syntheses has not been examined.[5]

Oxidative cross-coupling reactions have garnered much attention in recent years, because they offer rapid access to late intermediates. Indeed, many exciting transformations based on copper and iron oxidants have successfully been applied in natural product synthesis,[6] but the downside of most of these reactions is that they require supra-stoichiometric amounts of the metal oxidant.[1a] Of particular importance is the homodimerization of two phenol (or protected phenol) units by a stoichiometric amount of iron oxidant—a common protocol in organic chemistry[7] whose application in natural product synthesis goes back to the work of Barton.[8] However, oxidative cross-coupling reactions of phenols by stoichiometric amount of iron oxidants suffer from low efficiency as a result of poor chemo- and regioselectivity,[9] which makes these reactions not particularly suitable for target-oriented synthesis.

In contrast to the above reactions, any iron-based CDC strategy that requires only catalytic amounts of the metal salt offers opportunities for developing biomimetic coupling

[a] Dr. U. A. Kshirsagar,[+] R. Parnes,[+] Dr. D. Pappo
Department of Chemistry
Ben-Gurion University of the Negev
Beer-Sheva 84105 (Israel)
Fax: (+972) 8-6428693
E-mail: pappod@bgu.ac.il

[b] H. Goldshtein, Dr. R. Ofir
Dead Sea & Arava Science Center
Ben-Gurion University of the Negev
Beer-Sheva 84105 (Israel)

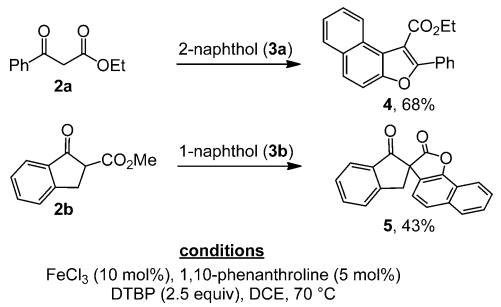
[c] Dr. R. Ofir
Department of Microbiology & Immunology
Ben-Gurion University of the Negev
Beer-Sheva 84105 (Israel)

[d] Dr. R. Zarivach
Department of Life Sciences
Ben-Gurion University of the Negev
and the National Institute for Biotechnology
Ben-Gurion University of the Negev
Beer-Sheva 84105 (Israel)

[+] These Authors contributed equally to this work.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201300389.

reactions of simple phenols with various active CH atoms. Indeed, a number of practical catalytic systems for the coupling of 2-naphthol (**3a**) with sp^2 and sp^3 carbons have recently been developed.[10] In 2009, the group of Zhiping Li reported the formation of substituted benzofurans (such as **4**, Scheme 1) through direct coupling of β-ketoesters such as



Scheme 1. Iron-catalyzed oxidative coupling of phenols and β-ketoesters. Reagents and conditions: $FeCl_3$ (10 mol%), 1,10-phenanthroline (5 mol%), DTEP (2.5 mmol), DCE, 70°C

2a with phenol derivatives, with $FeCl_3{\cdot}(H_2O)_6$ (10 mol%) and di-*tert*-butyl peroxide (DTBP; 2 equiv) serving as the oxidant (in dichloroethane (DCE) at 100°C).[11] Under these reaction conditions, annulation and dehydration steps take place.[11] Although this reaction proved to be successful for a variety of phenols (mainly phenols bearing alkyl substitutions), it required a large excess of the phenol partner (3 equiv) and it suffered from moderate chemoselectivity as a result of Friedel–Craft side reactions.

Recently, our group developed a method for coupling electron-rich phenol and naphthol derivatives with cyclic and acyclic α-substituted-β-ketoesters ($FeCl_3$: 10 mol%, 1,10-phenanthroline: 5 mol%, DTBP (2.5 equiv), DCE; 70°C, Scheme 1).[12] As a result of this transformation, a new quaternary carbon bond is formed within a polycyclic hemiacetal or polycyclic spirolactone architecture such as **5**, which contains the polycyclic core of lachnanthospirone natural product.[12] In our method, the introduction of a ligand was found to dramatically improve the chemoselectivity and the efficiency of the reactions and to reduce the formation of Friedel–Crafts by-products. Our conditions were also applied for the synthesis of benzofuran **4** from ethyl 2-benzyloxyacetate (**2a**) and 2-naphthol (**3a**), giving an improved 68% yield.[12]

Coumestrol is the most important member of the coumestan family of phytochemicals[13] containing a 6*H*-benzofuro-[3,2-*c*][1]benzopyran-6-one skeleton.[14] The group comprises hundreds of molecules with different oxygenation patterns. The coumestans are found in a variety of plant species that are commonly used in traditional medicine. They exhibit a range of biological activities, including estrogenic,[14,15] antibacterial, antifungal, and snake anti-venom[16] activities and phytoalexine effects.[17] Among the coumestans, coumestrol **1** is an important dietary ingredient that is found not only in forage plants, but also in cabbages and soybeans;[18] its role in human nutrition has thus been studied comprehensively.[14],[19]

In vitro studies found that coumestrol bind to estrogen receptors (ERs),[20] ERα and ERβ. These two subtypes of the receptor, which belong to the nuclear hormone family of intracellular receptors, play essential roles not only in development and maintenance of normal sexual and reproductive function but also in the progression of cancer and other diseases.[21] Importantly, whereas the natural estrogen, 17α-estradiol (E_2, Figure 1) binds to both ER subtypes with similar

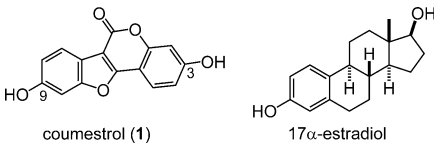
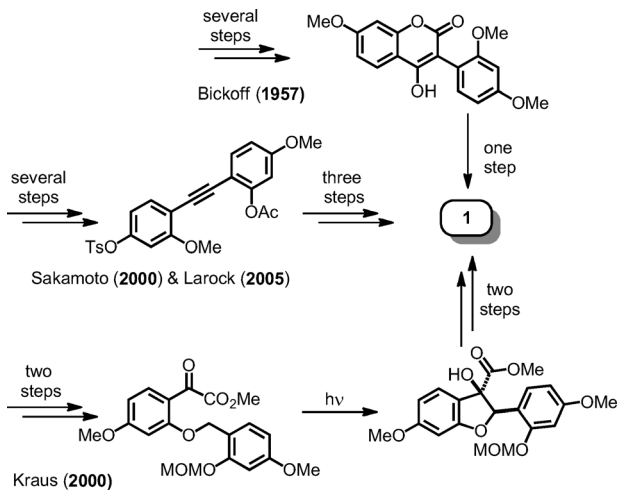


Figure 1. The structure of coumestrol (**1**) and 17α-estradiol (E_2).

affinity, the phytoestrogen coumestrol (**1**, Figure 1) binds with essentially the same affinity as E_2 to ERβ but with lower affinity than that for the α-subtype.[22] The ability to distinguish between the ER subtypes is of high value as it greatly improves the side-effect profile of a drug. Indeed, much effort is currently being invested in developing such selective estrogen-receptor modulators (SERMs).[23–25]

Despite significant potential of coumestrol as a drug, the absence of an efficient synthetic strategy that can provide the natural product and its unnatural analogues in sufficient amounts for biology studies has frustrated any further developments. Several total syntheses of coumestrol have been reported (see Scheme 2),[26] but these usually involve multistep syntheses, which afford only small quantities of the natural product, leaving the production problem unsolved.[26a,b,d] The synthesis of other members of the coumestan family has also been documented,[17b,27] and recently an efficient approach for the synthesis of coumestans was developed by Du and Zhao.[28]

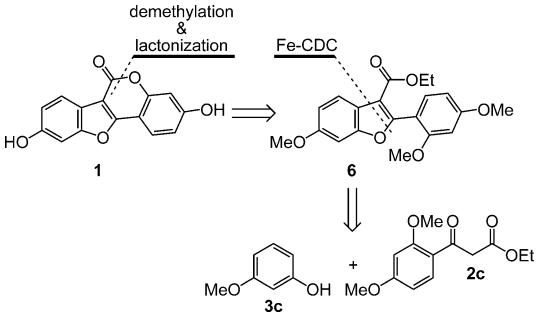


Scheme 2. Selected total syntheses of coumestrol (**1**).

Here, we report the first application of iron-based CDC chemistry in the context of natural product synthesis. A diversity-oriented synthesis for a library of coumestrol-based SERMs was developed utilizing a modified aerobic iron-catalyzed coupling reaction of β-ketoesters and phenols. The work included a gram-scale total synthesis of coumestrol itself. The estrogenicity of the different coumestrol analogues that were synthesized was evaluated by testing their effects on the proliferation of two breast cancer cell lines, the ER-dependent MCF-7 line and the ER-independent MDA-MB-231 line. It was found that new coumestrol analogues, having either an 8- or a 9-NHAc group instead of the 9-OH group of coumestrol, exhibited high potency against the MCF-7 cell line.

Results and Discussion

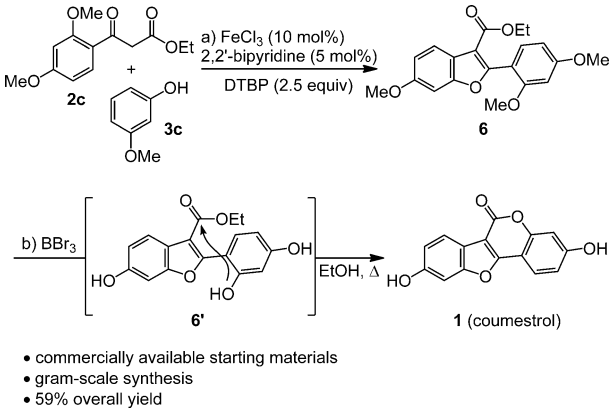
The synthetic work in this project was started by developing an efficient entry to the coumestan family. Our retrosynthetic analysis of coumestrol is illustrated in Scheme 3. The



Scheme 3. General retrosynthetic analysis of coumestans

strategy was based on our prediction that the coumestan structural motif could be synthesized from the corresponding benzofurans **6** through sequential demethylation and lactonization steps, with the latter may be prepared by using iron-catalyzed CDC reactions between ethyl 2-benzoylacetate **2c** and 3-methoxyphenol (**3c**).

Our two-step total synthesis of coumestrol (**1**) started with the iron-based cross-coupling reaction of ethyl 2-(2,4-dimethoxybenzoyl)acetate (**2c**, 1 equiv) and 3-methoxyphenol (**3c**, 1.1 equiv), both commercially available,[29] by using $FeCl_3$ (10 mol%) and 2,2′-bipyridine (5 mol%) as additives[30] and DTBP (2.5 equiv) as the oxidant, in DCE (0.5 M) at 70 °C for 8 h (Scheme 4). Under these conditions, benzofuran **6** was obtained in a moderate 59% yield. The conversion of benzofuran **6** to coumestrol **1** was carried out by using a one-pot protocol: First, removal of the methyl groups (BBr_3, 6 equiv, CH_2Cl_2, RT, overnight) afforded the intermediate **6′** (not isolated). Thereafter, by switching the solvent to boiling ethanol, the lactonization step was accomplished, and the resulting insoluble yellowish solid was filtered off to afford pure coumestrol (**1**) in 97% yield. To

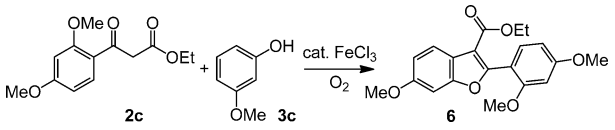


Scheme 4. Total synthesis of coumestrol. Conditions: a) $FeCl_3$ (10 mol%), 2,2′-bipyridine (5 mol%), *t*BuOO*t*Bu (2.5 equiv), DCE, 70 °C, 8 h, 61% yield (gram-scale yield); b) BBr_3 (1 M in CH_2Cl_2), CH_2Cl_2, 18 h; then EtOH, 80 °C, 4 h, 97% yield.

demonstrate the possibility of scaling up this method, a gram-scale (10 mmol) synthesis of coumestrol was successfully accomplished; over 1.6 g of the natural product was prepared (in 59% overall yield) by an undergraduate student in as little as three days.

After succeeding in solving the production problem of coumestrol, we applied our protocol to the synthesis of other natural members of the coumestan family, namely, coumestan (**20**) and 8,9-dihydroxycoumestrol (**22**)[31] (entries 1 and 3, Table 2). Thus, the coupling reaction between

Table 1. Optimization of the CDC reaction of β-ketoester **2c** and phenol **3c** under oxygen and aerobic conditions.[a]



Entry	Conditions	Yield[b] [%]
1	$FeCl_3$ (10 mol%), NHPI (5 mol%), O_2	61
2	$FeCl_3$ (10 mol%), NHPI (20 mol%), O_2	53
3	$FeCl_3$ (10 mol%), O_2	63
4	$FeCl_3$ (10 mol%), 2,2′-bipyridine (5 mol%), O_2	[26][c]
5	$FeCl_3$ (10 mol%), atmospheric air[d]	52

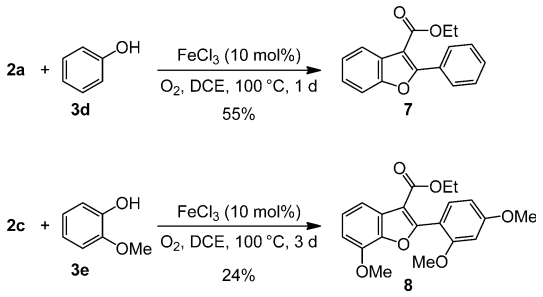
[a] All reactions were carried out with **2c** (0.5 mmol) and **3c** (0.65 mmol) in DCE (0.25 M) at 100 °C for 24 h. [b] Yields of the product. [c] Yields determined by NMR spectroscopy are given in square brackets. [d] 48 h in DCE or 9 h in toluene. 1,3,5-trimethoxy benzene was used as the internal standard. NHPI = *N*-hydroxyphthalimide

ethyl 2-(2-methoxybenzoyl)acetate (**2d**) and phenol (**3d**) afforded benzofuran **9** (73% yield), which was converted to coumestan in 90% yield. Compound **22** was synthesized starting from β-ketoester **2c** and 3,4-dimethoxyphenol (**3f**) in 52% yield for the two steps. This compound could be converted to the medicagol natural product in a single synthetic step.[31] Whereas ethyl 2-benzoylacetates having a single *ortho*-methoxy group (such as **2c** and **2d**) reacted well and the method could be applied in the synthesis of

many members of the coumestan family, other ethyl 2-benzoylacetates having two *ortho*-substituents, such as ethyl 2-(4-bromo-2,6-dimethoxybenzoyl)acetate and ethyl 2-(6-bromo-2,4-dimethoxybenzoyl)acetate, which upon successful coupling could provide an entry to wedelolactone natural product,[17] were found to be inactive.

Although the coupling of phenols **2** and β-ketoesters **3** provides easy access to variety of coumestrol derivatives, the reaction requires the use of the hazardous DTBP as the oxidant.[11,12] Indeed, one of the weaknesses of many of the CDC reactions is the need for organic oxidants that constitute safety concerns, which are particularly troublesome for future industrial applications. Since Li and co-workers reported the first example of an iron-CDC reaction in 2007,[32] most of the transformations developed subsequently have required the use of organic oxidants such as DTBP (*t*BuOO*t*Bu),[33] TBHP (*t*BuOOH)[34] or 2,3-dichloro-5,6-dicyano-1,4-benzoqinone (DDQ).[1c,35] Exceptions are the alkylation reaction of 1,3-dicarbonyl compounds and benzylic substrates in the presence of $FeCl_2$, CuCl, and *N*-hydroxyphthalimide (NHPI) under an oxygen atmosphere[36] and Katsuki's Fe(salan) complex, which catalyzes enantioselective aerobic oxidative cross-coupling reactions of naphthol derivatives.[4,37]

The NHPI/O_2 oxidation system was assumed to be a good solution not only from the safety point of view, but also because it facilitates more environmentally friendly and economical reactions and, in the case of phenol coupling reactions, it should eliminate the Friedel–Crafts alkylation side reaction that occurs with DTBP and TBHP. The oxidative abilities of the NHPI/O_2 system in hydrocarbon oxidations has been studied extensively and reviewed,[38] and the ability of that system to oxidize Fe^{III} to Fe^{IV} species in CH oxidation reactions has also been reported.[39] Therefore, it was logical to explore that direction. Indeed, when ethyl 2-(2,4-dimethoxybenzoyl)acetate (**2c**, 1 equiv) and 3-methoxyphenol (**3c**, 1.3 equiv) were mixed in DCE at 100 °C in the presence of $FeCl_3$ (10 mol %) and NHPI (5 mol %) under an oxygen atmosphere (O_2 balloon), the reaction went to completion within 24 h, isolating the coupling product **6** in 61 % yield (Table 1, entry 1). Increasing the amount of NHPI to 20 mol % had a negative effect on the yield (53 %, Table 1, entry 2). Furthermore, when the reaction was performed in the absence of NHPI, benzofuran **6** was isolated in a moderate 63 % yield (Table 1, entry 3), which indicates that NHPI does not play a role in the reaction mechanism. The addition of 2,2′-bipyridine (5 mol %) to the reaction mixture slowed down the process, and after 24 h only partial conversion was observed (Table 1, entry 4). To simplify the method even further, we performed the reaction under air atmosphere (open flask). Whereas the reaction in DCE was much slower and required a longer reaction time (48 h), the reaction in toluene went to completion in only 9 h. In both cases, the desired coupling product **6** was isolated in 52 % yield. In addition, the modified conditions were examined for the coupling of ethyl benzyloxyacetate (**2a**) with phenol (**3d**). Previously, the corresponding benzofuran **7** (Scheme 5) was detected in 75 % yield by using NMR spectroscopy ($FeCl_3$·$(H_2O)_6$/DTBP catalytic system), however it was contaminated with Friedel–Crafts alkylation byproducts.



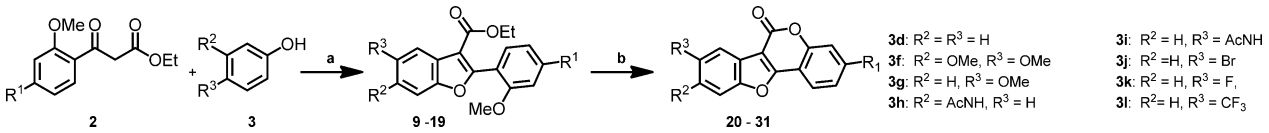
Scheme 5. $FeCl_3/O_2$ Oxidative coupling of β-ketoesters with phenols.

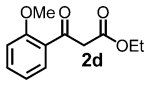
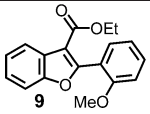
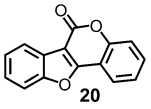
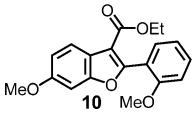
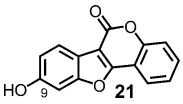
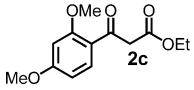
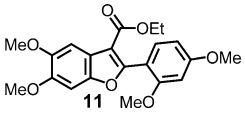
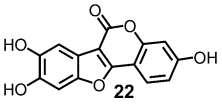
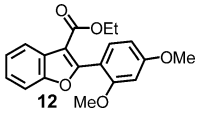
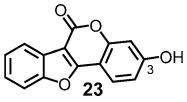
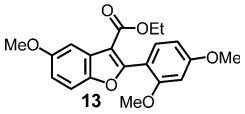
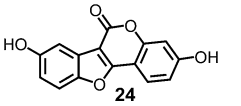
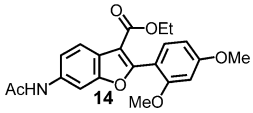
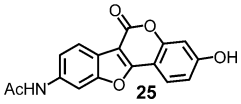
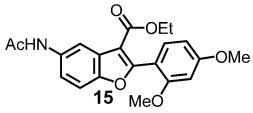
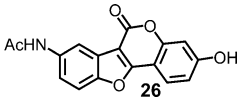
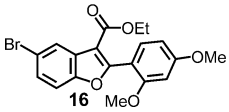
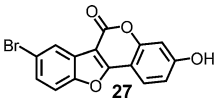
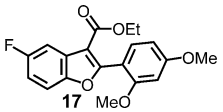
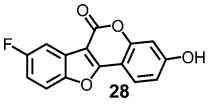
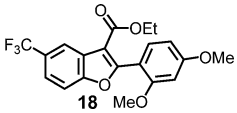
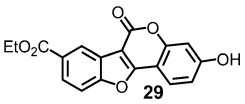
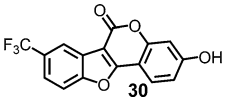
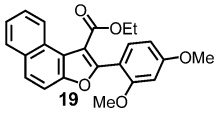
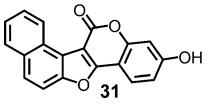
As a result, a pure compound **7** could only be obtained by preparative-HPLC separation and in an unreported yield of the isolated product.[11] Under our modified aerobic coupling conditions benzofuran **7** was isolated in 55 % yield. Moreover, sensitive phenols, such as 2-methoxyphenol (**3e**, Scheme 5), which had failed to react when DTBP was used as the oxidant, now became a suitable partner; benzofuran **8** was obtained in 24 % yield.

Encouraged by the success of our syntheses, we shifted our attention to the synthesis of unnatural coumestrol analogues suitable for a structure–activity relationship study. Based on preliminary biology results (see below), 2-benzyloxyacetates **2c** and **2d** were chosen as the coupling partners for building our library. These β-ketoesters were thus treated with a variety of phenol derivatives by using the $FeCl_3$/bipyridine/DTBP catalytic system (Table 2). The oxidative coupling reaction of compounds **2c** and **2d** with phenols bearing *meta* and *para* electron-neutral and electron-rich substituents (**3c**–**3i**) afforded benzofurans **9**–**15** in moderate-to-good yields (53–77 %; Scheme 4 and Table 2, entries 1–7). Electron-deficient phenols bearing *p*-Br (**3j**), *p*-F (**3k**) and *p*-CF_3 (**3l**) groups were also found to be good partners, and benzofurans **16**–**18** were isolated in 65, 73, and 51 % yields, respectively. Less-activated phenols, such as 4-cyanophenol, 4-formylphenol and 4-(ethoxycarbonyl)phenol, failed to react. For comparison reasons, our modified aerobic oxidative coupling conditions were also examined affording the desired products in moderate yields.

The conversion of benzofurans **9**–**18** and **19** to the corresponding coumestrol analogues was performed in good-to-excellent yields by using the deprotection–lactonization protocol developed for the synthesis of coumestrol (BBr_3 in CH_2Cl_2, then boiling ethanol). However, initial attempts to convert benzofuran **18** bearing the trifluoromethyl group afforded the 9-ethoxycarbonyl-coumestrol derivative **29** in 84 % yield, as a result of acid-catalyzed alcoholysis of the acid-sensitive CF_3 group.[40] Alternatively, when compound **18** was first deprotected with BBr_3 (CH_2Cl_2, room temperature) and then heated at reflux in toluene in the presence of a catalytic amount of triethylamine (50 mol %) for 30 min,

Table 2. Synthesis of coumestans (compounds **20**–**31**) through the direct coupling of β-ketoesters (**2**) and phenols (**3**).[a]



Entry	β-Ketoester	Phenol	Benzofuran	"DTBP" yield [%][b]	"Aerobic" yield [%][b]	Coumestan	Yield [%][b]
1		**3d**		73	–		90
2	**2d**	**3c**		55	34		89
3		**3f**		53	–		89
4	**2c**	**3d**		77	–		83
5	**2c**	**3g**		58	51		91
6	**2c**	**3h**		63	–		92
7	**2c**	**3i**		68	56		93
8	**2c**	**3j**		65	23		85
9	**2c**	**3k**		73	–		97
10	**2c**	**3l**		51	–		83
11	–	–	–	–	–		92[c]
12	**2c**	**3a**		65	–		67

[a] i) "DTBP" conditions: **2** (1 mmol), **3** (1.1 mmol), $FeCl_3$ (10 mol%), 2,2′-bipyridine (5 mol%), *t*BuOO*t*Bu (2 mmol), DCE (0.5 M), 70 °C, N_2 atmosphere; "aerobic" conditions: **2** (1 mmol), **3** (1.1 mmol), $FeCl_3$ (10 mol%), DCE (0.5 M), 100 °C, O_2 atm; ii) **7**, BBr_3 (1 M in CH_2Cl_2), CH_2Cl_2, RT, then EtOH, reflux. [b] Yield of the isolated product. [c] Alternative conditions: **18**, triethylamine (TEA, 50 mol%), toluene, 70 °C, 1 h.

the desired 3-trifluoromethylcoumestrol **30** was isolated in 92% yield after column chromatography; previous attempts to prepare CF_3-substituted coumestan derivatives by using different synthetic approaches failed.[28]

Biological evaluation: In parallel to our synthetic effort to establish the methodology for the synthesis of coumestrol and coumestrol analogues based on CDC technology, we sought to utilize the developed chemistry in a structure–activity relationship study of **1**. For that purpose, molecular-modeling techniques together with estrogenic response evaluations were integrated with our synthetic capabilities.

With the aim of designing a library of SERMs based on coumestrol, we examined the binding mode of the natural product in the estrogen receptor ligand-binding site by using computational modeling techniques. The dimensions of the ER binding sites, as reflected in many solved crystal structures,[41] suggest that the recognition of coumestrol takes place inside the hydrophobic pocket in one of two directionally different binding modes, as presented in Figure 2: either the 3-hydroxy group or the 9-hydroxy group interacts through a hydrogen bond with a buried water molecule in the structurally conserved polar pocket formed by the Glu_{305} and Arg_{346} residues (binding models A and B, respectively, Figure 2). In both cases, several hydrophobic interactions with surrounding hydrophobic amino acids (such as Leu_{298} and Phe_{356}) restrict the conformational freedom of the ligand. Finally, the remaining hydroxyl group can bind at the end of the cavity with the flexible His_{475} residue.[41] The two different binding models represent inverted conformational arrangements of **1** in the hydrophobic pocket.[42] An X-ray co-crystal structure of coumestrol complexed to ERα or ERβ would provide the needed evidence as to the preferred binding form of coumestrol, but such a crystal structure is not available.

The difference in pK_a values of the two hydroxyl groups (7.5 and 9.1, for the 3- and 9-hydroxyl groups, respectively),[45] the structures of co-crystals of ERα and ERβ with other ER ligands,[43] and the structure of co-crystal of coumestrol with 17β-HSD (17β-hydroxysteroid dehydrogenase)[46] all indicate that the conformation in which the 3-hydroxy group interacts with the Glu_{305} and Arg_{346} residues (binding model A) is the more likely of the two options. To provide support for this premise, the proliferation of the ER-positive breast cancer line, MCF-7, was evaluated in response to exposure to 9-hydroxycoumestan **21** and 3-hydroxycoumestan **23**.[47] Whereas compound **23** exhibited moderate activity, with an IC_{50} value of 153 nM (Table 3, entry 5), 9-hydroxycoumestan **21** was inactive at concentrations lower than 10^{-6} M (entry 3). Moreover, coumestan **20**, which lack the two-hydroxyl groups, was found to be inactive as well. These results support our hypothesis that the 3-hydroxy group is important for binding to the ER, and in terms of structure–activity considerations the 9-hydroxy group can be removed and replaced with other substituents.

To provide proof that the inhibitory effect of our compounds on MCF-7 breast cancer cells is indeed ER-dependent, all the compounds were tested against the estrogen-independent MDA-MB-321 breast cancer cell line.[47] Not surprisingly, all tested compounds were found to be inactive against these cells at wide range of concentrations (from 10^{-6} to 10^{-9} M), showing that the activity of our modified

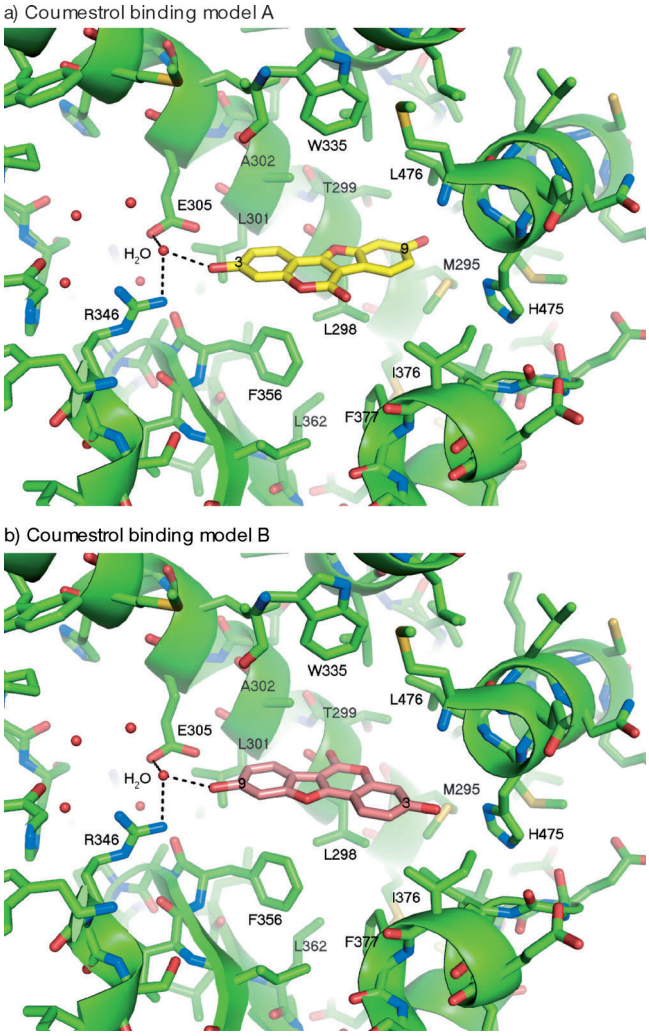
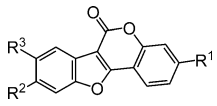


Figure 2. Schematic representation showing the interactions between coumestrol (**1**) and ERβ-ligand binding domain (LBD) (1U9E).[44] Zoom-in view of two possible coumestrol binding modes that are dependent on the hydroxyl location. a) Coumestrol (yellow sticks) is directed by the 3-hydroxy group (binding model A); b) Coumestrol (pink sticks) is directed by the 9-hydroxy (binding model B). ERβ-LBD is represented as green sticks and ribbons. Overall, red represents oxygen atoms and blue represents nitrogen atoms.[44]

coumestrol derivatives does indeed involve binding to the ER. Moreover, these results indicate that the tested compounds are not toxic to other cellular processes beyond the ones that are regulated by the ER. The results for selected compounds are given in Figure 3.

In this study, we addressed only the estrogenicity of coumestrol derivatives having different substituents at the C8 and C9 positions. The effects of all the compounds on the proliferation response of the MCF-7 estrogen-dependent cells was evaluated at different concentrations (10^{-6} to 10^{-9} M), and the IC_{50} values are given in Table 3. The superior anti-proliferative activity of coumestrol over other members of the coumestan family[14] is in consistent with our findings that synthetic coumestans (**20**–**24**) having oxygenation patterns that differ from the pattern of coumestrol **1**

Table 3. Inhibition of proliferation of MCF-7 breast cancer cells by coumestrol and its derivatives and by synthetic coumestans.[a]



Entry	Compound	R^1	R^2	R^3	IC_{50} [10^{-9} M][b]
1	**1**	OH	OH	H	73±38
2	**20**	H	H	H	NA[c]
3	**21**	H	OH	H	NA[c]
4	**22**	OH	OH	OH	NA[c]
5	**23**	OH	H	H	153±12
6	**24**	OH	H	OH	NA[c]
7	**25**	OH	NHAc	H	30±19
8	**26**	OH	H	NHAc	9±5
9	**27**	OH	H	Br	NA[c]
10	**28**	OH	H	F	220±51
11	**29**	OH	H	CO_2Et	58±2
12	**30**	OH	H	CF_3	170±17
13	**31**	OH	naphthyl		180±42

[a] For experimental details see the Supporting Information. [b] IC_{50} = the concentration of the compound that leads to 50% inhibition of cell survival ±SEM values. [c] NA = not active at concentrations lower than 10^{-6} M.

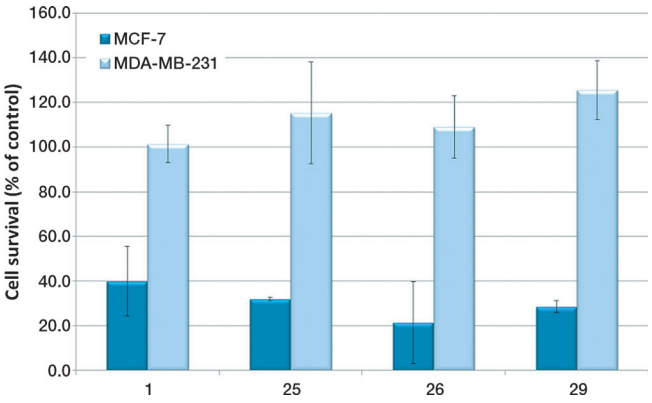


Figure 3. The proliferative response of selected compounds on estrogen-dependent (MCF-7) and estrogen-independent (MDA-MB-231) cells at 10^{-7} M after 6 days in culture. MCF-7 cells and MDA-MB-231 cells were cultured in DCS/MEM for 1 week. Cells were plated in 96-well plates (5,000 cells/well and 2500 cells/well, respectively, in 100 µL of medium), allowed to attach overnight, and treated the next day (day 0). Cell survival was quantified by using the thiazolyl blue tetrazolium bromide (MTT) assay.[48] Data represents the mean of two experiments (four wells for every treatment in every experiment) ±SEM values.

are at least one order of magnitude less active. However, when the 9-hydroxyl group was replaced with hydrophobic groups such 8-CF_3 (**30**) or a fused ring, as in naphthocoumestrol **31**, the estrogenic activity was increased, with IC_{50} values of 170 and 180 nM, respectively.

The substitution of the 9-hydroxy group of coumestrol with 8-CO_2Et (**29**), 9-NHAc (**25**), or 8-NHAc (**26**) groups resulted with improved estrogenic activity, with IC_{50} values of 58, 30, and 9 nM, respectively. A docking study of 9-acetamidocoumestrol (**25**) into the ligand-binding domain of ERβ (Figure 4) suggests that the NH atoms of the latter

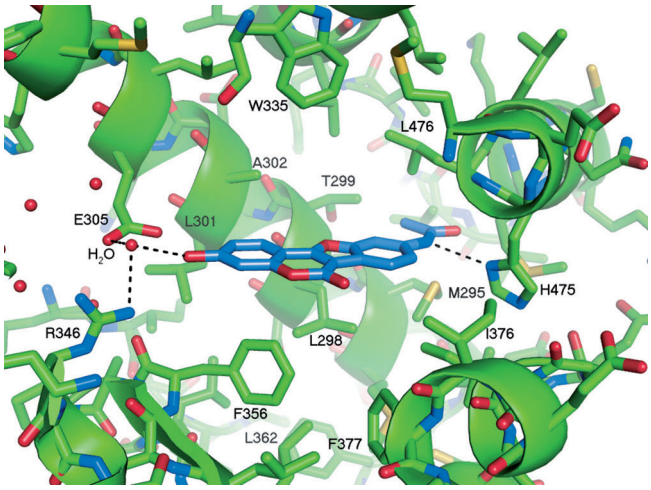


Figure 4. Zoom-in view of 9-acetamidocoumestrol (**25**) (light-purple sticks) docked into ERβ-LBD (green sticks and ribbons). Red represents oxygen atoms, and blue represents nitrogen atoms.

ligand are located in the correct position and orientation to form a hydrogen bond with the His_{475} residue. In addition, hydrophobic interactions can take place between the acetamide group of **25** with close hydrophobic amino acid residues such as Leu_{476} (≈2.5 Å distance), Met_{479} (≈2.8 Å), Met_{295} (≈3.1 Å), and Thr_{299} (≈3.4 Å). Studies of the docking of compound **26** having an acetamide group at C8 into the ERβ ligand-binding domain showed only poor compatibility at the end of the cavity, which suggests that upon binding a conformational change of the protein must occur. Indeed, a previous structural study of ERs has shown that the conformational flexibility of the ER allows it to exist in a spectrum of conformations, from active to inactive, depending on the nature of the binding ligand.[21b]

Importantly, our results on the inhibitory effect of coumestrol in the proliferation of MCF-7 cells are not in agreement with the observations of Matsumara et al. who reported that coumestrol leads to a concentration-dependent enhancement in the proliferation of MCF-7 cells.[49] This discrepancy in the results could be explained by the differences in the culture conditions used by the two laboratories.

Despite the fact that the incorporation of an amide group into SERMs seems logical, we could not find any precedents for such an approach, and we intend to investigate this direction further in the future. Hopefully, in the long-term, this work will open the way to the development of a new class of SERMs for the treatment of breast cancer and other diseases associated with ERs.

Conclusion

This work describes the first application of the CDC strategy in target- and diversity-oriented synthesis. We have developed an efficient, scalable, economical, and sustainable synthesis of coumestrol based on aerobic iron oxidative

cross-coupling of phenols with ethyl 2-benzoylacetate derivatives. A preliminary SAR study was performed in which the coumestrol derivatives prepared in this study were found to inhibit the proliferation of estrogen-dependent MCF-7 breast cancer cells but not of estrogen-independent MDA-MB-321 breast cancer cells, suggesting that these compounds act through the ERs. In addition, the importance of the 3-hydroxy group for the anti-proliferative activity was demonstrated, and an improved estrogenic activity was found when the 9-hydroxy group found in the natural product was replaced with an acetamide group. Whereas the inhibitory activity of 9-acetamidocoumestrol (**25**) of MCF7 cell proliferation was found to be of the same order of magnitude as that of the natural compound coumestrol **1**, 8-acetamidocoumestrol (**26**) was about 8 times more active than **1**.

As part of the interest of our group in developing new methods for the functionalization of phenols based on copper and iron oxidative coupling reactions, we intend to further apply the developed chemistry in the diversity-oriented synthesis of phenolic compounds of pharmacological interest. In addition, structure–activity analysis of compounds **25** and **26** and others in the ER(α and β) ligand-binding domains, assessment of the selectivity for ER subunits of the new class of SERMs and further study of their mode of action are also part of our ongoing medicinal-chemistry program.

Experimental Section

Ethyl-2-(2,4-dimethoxyphenyl)-6-methoxybenzofuran-3-carboxylate (6): A stirred solution of ethyl 3-(2,4-dimethoxyphenyl)-3-oxopropanoate (2 g, 7.94 mmol, 1 equiv), 3-methoxy phenol (1.08 g, 8.73 mmol, 1 equiv), and $FeCl_3$ (0.13 g, 0.8 mmol, 0.1 equiv) in 1,2-dichloroethane (0.5 M) under an oxygen atmosphere was heated to 100 °C for 24 h. The mixture was cooled to room temperature, quenched with saturated $NaHCO_3$ (10 mL), and extracted with EtOAc (3×10 mL). The combined organic layer was washed with saturated $NaHCO_3$ (10 mL) and water (10 mL) and dried over Na_2SO_4. The solvent was filtered and removed under reduced pressure, and the residue purified by flash column chromatography over silica gel (ethyl acetate/hexanes, 1:4) affording compound **6** (1.72 g, 63 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, J = 8.6 Hz, 1H), 7.48 (d, J = 8.5 Hz, 1H), 7.04 (d, J = 2.2 Hz, 1H), 6.96 (dd, J = 8.6, 2.2 Hz, 1H), 6.59 (dd, J = 8.5, 2.2 Hz, 1H), 6.54 (d, J = 2.2 Hz, 1H), 4.3 (q,J = 7.1 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.79 (s, 3H), 1.29 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0, 162.4, 158.9, 158.1, 157.6, 154.9, 132.3, 122.0, 120.0, 112.5, 112.2, 110.3, 104.3, 98.6, 95.6, 60.1, 55.6, 55.5, 55.4, 14.2 ppm; IR (KBr): $\tilde{\nu}$ = 1700.9, 1623.8, 1500.4 cm^{-1}; HRMS (ESI): m/z calcd for $C_{20}H_{21}O_6$: 357.1332 $[M+H]^+$; found: 357.1323.

Coumestrol (1): A solution of BBr_3 (1 M in DCM, 29 mL, 0.029 mol) was added dropwise to a stirred solution of benzofuran **6** (1.72 g, 4.83 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C under a nitrogen atmosphere. The mixture was allowed to warm to room temperature and further stirred overnight. After quenching the reaction with EtOH (1 mL), the volatiles were removed under reduced pressure, and the residue was dissolved in EtOH (5 mL). The mixture was heated at reflux for 3 h until TLC showed complete conversion. The mixture was cooled to room temperature and the desired product was filtered off, washed with EtOH (1 mL) and dried under vacuum, affording coumestrol (1.26 g, 97 %) as a yellow solid. 1H NMR (400 MHz, [D$_6$]DMSO): δ = 10.71 (s, 1H), 10.04 (s, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.16 (d, J = 2.0 Hz, 1H), 6.86–6.98 ppm (m, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 161.7, 160.1, 158.2, 157.5, 156.5, 155.2, 123.3, 121.2, 115.1, 114.6, 114.3, 104.7, 103.6, 102.6, 99.2 ppm.

Acknowledgements

We wish to thank Dr. Amira Rudi (BGU) for NMR spectroscopic assistance and Prof. Ashraf Brik (BGU) for useful discussions. U.A.K is grateful to the PBC fellowship program. This research was supported by the Israel Science Foundation (Grant No. 1406/11).

[1] a) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215–1292; b) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780–1824; c) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Rev.* **2011**, *111*, 1293–1314.
[2] C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335–344.
[3] a) W. Liu, J. Liu, D. Ogawa, Y. Nishihara, X. Guo, Z. Li, *Org. Lett.* **2011**, *13*, 6272–6275; b) H.-F. Jiang, J.-H. Li, Z.-W. Chen, *Tetrahedron* **2010**, *66*, 9721–9728; c) C. M. R. Volla, P. Vogel, *Org. Lett.* **2009**, *11*, 1701–1704; d) Y.-Z. Li, B.-J. Li, X.-Y. Lu, S. Lin, Z.-J. Shi, *Angew. Chem.* **2009**, *121*, 3875–3878; *Angew. Chem. Int. Ed.* **2009**, *48*, 3817–3820; e) C.-X. Song, G.-X. Cai, T. R. Farrell, Z.-P. Jiang, H. Li, L.-B. Gan, Z.-J. Shi, *Chem. Commun.* **2009**, 6002–6004; f) X. Guo, S. Pan, J. Liu, Z. Li, *J. Org. Chem.* **2009**, *74*, 8848–8851; g) L. Zhao, C.-J. Li, *Angew. Chem.* **2008**, *120*, 7183–7186; *Angew. Chem. Int. Ed.* **2008**, *47*, 7075–7078; h) Z. Li, R. Yu, H. Li, *Angew. Chem.* **2008**, *120*, 7607–7610; *Angew. Chem. Int. Ed.* **2008**, *47*, 7497–7500; i) Y. Zhang, C.-J. Li, *Eur. J. Org. Chem.* **2007**, 4654–4657; j) Y. Zhang, C.-J. Li, *Angew. Chem.* **2006**, *118*, 1983–1986; *Angew. Chem. Int. Ed.* **2006**, *45*, 1949–1952; k) Z. Li, D. S. Bohle, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 8928–8933; l) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 3672–3673; m) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2004**, *126*, 11810–11811; n) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 6968–6969.
[4] H. Egami, K. Matsumoto, T. Oguma, T. Kunisu, T. Katsuki, *J. Am. Chem. Soc.* **2010**, *132*, 13633–13635.
[5] P. A. Wender, B. L. Miller, *Nature* **2009**, *460*, 197–201.
[6] a) K. C. Nicolaou, R. Reingruber, D. Sarlah, S. Brase, *J. Am. Chem. Soc.* **2009**, *131*, 2086–2087; b) M. P. DeMartino, K. Chen, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 11546–11560; c) E. S. Krygowski, K. Murphy-Benenato, M. D. Shair, *Angew. Chem. Int. Ed.* **2008**, *47*, 1680–1684; d) P. S. Baran, T. J. Maimone, J. M. Richter, *Nature* **2007**, *446*, 404–408; e) P. S. Baran, N. B. Ambhaikar, C. A. Guerrero, B. D. Hafensteiner, D. W. Lin, J. M. Richter, *ARKIVOC* **2006**, *7*, 310–325; f) R. H. Frazier, Jr., R. L. Harlow, *J. Org. Chem.* **1980**, *45*, 5408–5411.
[7] A. A. O. Sarhan, C. Bolm, *Chem. Soc. Rev.* **2009**, *38*, 2730–2744.
[8] D. Barton, A. Deflorin, O. Edwards, *J. Chem. Soc.* **1956**, 530–534.
[9] H. Eickhoff, G. Jung, A. Rieker, *Tetrahedron* **2001**, *57*, 353–364.
[10] a) M. Chandrasekharam, B. Chiranjeevi, K. S. V. Gupta, B. Sridhar, *J. Org. Chem.* **2011**, *76*, 10229–10235; b) H.-P. Bi, W.-W. Chen, Y.-M. Liang, C.-J. Li, *Org. Lett.* **2009**, *11*, 3246–3249.
[11] X. Guo, R. Yu, H. Li, Z. Li, *J. Am. Chem. Soc.* **2009**, *131*, 17387–17393.
[12] R. Parnes, U. A. Kshirsagar, A. Werbeloff, C. Regev, D. Pappo, *Org. Lett.* **2012**, *14*, 3324–3327.
[13] A. L. Ososki, E. J. Kennelly, *Phytother. Res.* **2003**, *17*, 845–869.
[14] M. S. Kurzer, X. Xu, *Annu. Rev. Nutr.* **1997**, *17*, 353–381.
[15] K. R. Price, G. R. Fenwick, *Food Addit. Contam.* **1985**, *2*, 73–106.
[16] P. A. Melo, D. A. Pinheiro, H. D. Ricardo, F. F. A. Fernandes, M. A. Tomaz, C. Z. El-Kik, M. A. Strauch, F. T. F. da, D. N. Sifuentes, S. Calil-Elias, C. D. Buarque, F. V. Brito, P. R. R. Costa, S. A. J. M. Da Silva, *Toxicon* **2010**, *55*, 488–496.
[17] a) K. W. Gaido, L. S. Leonard, S. Lovell, J. C. Gould, D. Babai, C. J. Portier, D. P. McDonnell, *Toxicol. Appl. Pharmacol.* **1997**, *143*, 205–212; b) C. C. Li, Z. X. Xie, Y. D. Zhang, J. H. Chen, Z. Yang, *J. Org. Chem.* **2003**, *68*, 8500–8504.

[18] a) E. M. Bickoff, R. L. Lyman, A. L. Livingston, A. N. Booth, *J. Am. Chem. Soc.* **1958**, *80*, 3969–3971; b) E. M. Bickoff, A. N. Booth, R. L. Lyman, A. L. Livingston, C. R. Thompson, F. Deeds, *Science* **1957**, *126*, 969–970.

[19] a) M. S. Kurzer, *J. Nutr.* **2003**, *133*, 1983S–1986S;

[20] S. Makela, V. L. Davis, W. C. Tally, J. Korkman, L. Salo, R. Vihko, R. Santti, K. S. Korach, *Environ. Health Perspect.* **1994**, *102*, 572–578.

[21] a) N. Heldring, A. Pike, S. Andersson, J. Matthews, G. Cheng, J. Hartman, M. Tujague, A. Strom, E. Treuter, M. Warner, J. A. Gustafsson, *Physiol. Rev.* **2007**, *87*, 905–931; b) B. J. Deroo, K. S. Korach, *J Clin Invest* **2006**, *116*, 561–570.

[22] a) J. K. Hess-Wilson, J. Boldison, K. E. Weaver, K. E. Knudsen, *Breast Cancer Res. Treat.* **2006**, *96*, 279–292; b) S. Gélinas, M.-G. Martinoli, *J. Neurosci. Res.* **2002**, *70*, 90–96; c) G. G. J. M. Kuiper, B. Carlsson, K. Grandien, E. Enmark, J. Häggblad, S. Nilsson, J.-Å. Gustafsson, *Endocrinology* **1997**, *138*, 863–870; d) G. G. J. M. Kuiper, J. G. Lemmen, B. Carlsson, J. C. Corton, S. H. Safe, P. T. van der Saag, B. van der Burg, J.-Å. Gustafsson, *Endocrinology* **1998**, *139*, 4252–4263.

[23] C. Phillips, L. R. Roberts, M. Schade, R. Bazin, A. Bent, N. L. Davies, R. Moore, A. D. Pannifer, A. R. Pickford, S. H. Prior, C. M. Read, A. Scott, D. G. Brown, B. Xu, S. L. Irving, *J. Am. Chem. Soc.* **2011**, *133*, 9696–9699.

[24] L. R. Roberts, D. Armor, C. Barker, A. Bent, K. Bess, A. Brown, D. A. Favor, D. Ellis, S. L. Irving, M. MacKenny, C. Phillips, N. Pullen, A. Stennett, L. Strand, M. Styles, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5680–5683.

[25] A. K. Shiau, D. Barstad, J. T. Radek, M. J. Meyers, K. W. Nettles, B. S. Katzenellenbogen, J. A. Katzenellenbogen, D. A. Agard, G. L. Greene, *Nat. Struct. Biol.* **2002**, *9*, 359–364.

[26] a) T. Yao, D. Yue, R. C. Larock, *J. Org. Chem.* **2005**, *70*, 9985–9989; b) N. Al-Maharik, N. P. Botting, *Tetrahedron* **2004**, *60*, 1637–1642; c) G. A. Kraus, N. Zhang, *J. Org. Chem.* **2000**, *65*, 5644–5646; d) K. Hiroya, N. Suzuki, A. Yasuhara, Y. Egawa, A. Kasano, T. Sakamoto, *J. Chem. Soc. Perkin Trans. 1* **2000**, 4339–4346; e) R. Laschober, T. Kappe, *Synthesis* **1990**, 387–388; f) S. B. Pandit, S. Y. Gadre, *Synth. Commun.* **1988**, *18*, 157–166; g) O. H. Emerson, E. M. Bickoff, *J. Am. Chem. Soc.* **1958**, *80*, 4381–4383.

[27] < a) C.-F. Chang, L.-Y. Yang, S.-W. Chang, Y.-T. Fang, Y.-J. Lee, *Tetrahedron* **2008**, *64*, 3661–3666; b) D.-H. Gong, C.-Z. Li, C.-Y. Yuan, *Chin. J. Chem.* **2010**, *19*, 522–527; c) A. J. M. da Silva, P. A. Melo, N. M. Silva, F. V. Brito, C. D. Buarque, D. V. de Souza, V. P. Rodrigues, E. S. Pocas, F. Noël, E. X. Albuquerque, P. R. Costa, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 283–286; d) B. S. U. Rani, M. Darbarwar, *J. Indian Chem. Soc.* **1986**, *63*, 1060–1062; e) M. Darbarwar, V. Sundaramurthy, N. V. S. Rao, *Proc.-Indian Acad. Sci., Sect. A* **1974**, *80*, 93–96; f) H. W. Wanzlick, R. Gritzky, H. Heidepriem, *Chem. Ber.* **1963**, *96*, 305–307; g) C. Deschamps-Vallet, C. Mentzer, *Compt. Rend.* **1960**, *251*, 736–738.

[28] L. Tang, Y. Pang, Q. Yan, L. Shi, J. Huang, Y. Du, K. Zhao, *J. Org. Chem.* **2011**, *76*, 2744–2752

[29] Ethyl 2-(2,4-dimethoxbenzoyl)acetate is commercially available. In this study we have prepared it from 2′,4′-dimethoxyacetophenone (NaH, diethylcarbonate, toluene).

[30] Both 2,2′-bipyridine and 1,10-phenanthroline can be used as additives in this reaction.

[31] A. L. Livingston, S. C. Witt, R. E. Lundin, E. M. Bickoff, *J. Org. Chem.* **1965**, *30*, 2353–2355.

[32] Z. Li, L. Cao, C. J. Li, *Angew. Chem.* **2007**, *119*, 6625–6627; *Angew. Chem. Int. Ed.* **2007**, *46*, 6505–6507.

[33] P. Liu, Z. Wang, J. Lin, X. Hu, *Eur. J. Org. Chem.* **2012**, 1583–1589.

[34] W. Liu, Y. Li, K. Liu, Z. Li, *J. Am. Chem. Soc.* **2011**, *133*, 10756–10759.

[35] G. Zhang, Y. Zhang, R. Wang, *Angew. Chem.* **2011**, *123*, 10613–10616; *Angew. Chem. Int. Ed.* **2011**, *50*, 10429–10432.

[36] C. A. Correia, C.-J. Li, *Tetrahedron Lett.* **2010**, *51*, 1172–1175.

[37] a) H. Egami, T. Katsuki, *J. Am. Chem. Soc.* **2009**, *131*, 6082–6083; b) T. Oguma, T. Katsuki, *J. Am. Chem. Soc.* **2012**, *134*, 20017–20020.

[38] F. Recupero, C. Punta, *Chem. Rev.* **2007**, *107*, 3800–3842.

[39] S. H. Cho, M. S. Cheong, K. D. Jung, C. S. Kim, S. H. Han, *Appl. Catal., A* **2004**, *267*, 241–244.

[40] K. Ramig, M. Englander, F. Kallashi, L. Livchits, J. Zhou, *Tetrahedron Lett.* **2002**, *43*, 7731–7734.

[41] P. Ascenzi, A. Bocedi, M. Marino, *Mol. Aspects Med.* **2006**, *27*, 299–402.

[42] The size of the hydrophobic pocket permits the rotation of ligands around their horizontal axis (not shown); however, the shape of the polar pocket restricts the phenol group to a specific position and orientation.

[43] E. S. Manas, R. J. Unwalla, Z. B. Xu, M. S. Malamas, C. P. Miller, H. A. Harris, C. Hsiao, T. Akopian, W.-T. Hum, K. Malakian, S. Wolfrom, A. Bapat, R. A. Bhat, M. L. Stahl, W. S. Somers, J. C. Alvarez, *J. Am. Chem. Soc.* **2004**, *126*, 15106–15119.

[44] Details regarding the docking methods are given in the Supporting Information.

[45] O. S. Wolfbeis, K. Schaffner, *Photochem. Photobiol.* **1980**, *32*, 143–148.

[46] A. Cassetta, I. Krastanova, K. Kristan, M. Brunskole Švegelj, D. Lamba, T. Lanišnik Rižner, J. Stojan, *Biochemical J.* **2012**, *441*, 151–160.

[47] E. W. Thompson, D. Katz, T. B. Shima, A. E. Wakeling, M. E. Lippman, R. B. Dickson, *Cancer Res.* **1989**, *49*, 6929–6934.

[48] N. Dudai, Y. Weinstein, M. Krup, T. Rabinski, R. Ofir, *Planta Med.* **2005**, *71*, 484–488.

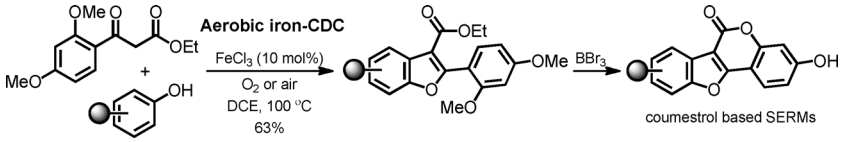
[49] A. Matsumura, A. Ghosh, G. S. Pope, P. D. Darbre, *J. Steroid Biochem. Mol. Biol.* **2005**, *94*, 431–443.

Received: January 31, 2013
Revised: June 12, 2013
Published online: ■■ ■■, 2013

Cross-Coupling

*U. A. Kshirsagar, R. Parnes, H. Goldshtein, R. Ofir, R. Zarivach, D. Pappo** ..... ▮▮▮▮–▮▮▮▮

Aerobic Iron-Based Cross-Dehydrogenative Coupling Enables Efficient Diversity-Oriented Synthesis of Coumestrol-Based Selective Estrogen Receptor Modulators



Green medicinal chemistry: An iron-based cross-dehydrogenative coupling (CDC) approach was applied for the diversity-oriented synthesis of coumestrol-based selective estrogen receptor modulators (SERMs), representing the first application of CDC chemistry in natural product synthesis (see scheme; DCE = dichloroethane).