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Scale-Up Syntheses of Two Naturally Occurring Procyanidins: (−)-Epicatechin-(4β,8)-(+)-catechin and (−)-Epicatechin-3-*O*-galloyl-(4β,8)-(−)-epicatechin-3-*O*-gallate†

Pradeep K. Sharma,‡ Alexander Kolchinski,‡ Hélène A. Shea,§ Jayesh J. Nair,§ Yanni Gou,|| Leo J. Romanczyk, Jr.,*,⊥ and Harold H. Schmitz#

Chemical Process Research & Development, Catalytic Services, and Analytical Division, Johnson Matthey Pharmaceutical Materials, Inc., 25 Patton Road, Devens, Massachusetts 01434, U.S.A., Masterfoods USA, A MARS Incorporated Company, 800 High Street, Hackettstown, New Jersey 07840, U.S.A., and MARS, Incorporated, 6885 Elm Street, McLean, Virginia 22101, U.S.A.

Abstract:

A scaleable process for the synthesis of two naturally occurring procyanidins, namely (−)-epicatechin-(4β,8)-(+)-catechin (1) and (−)-epicatechin-3-*O*-galloyl-(4β,8)-(−)-epicatechin-3-*O*-gallate (2), is described. The key steps were highlighted by improvements for the benzylation of (+)-catechin (3), stereoselective reduction of the C-3 keto group of (2*R*)-5,7,3′,4′-tetrakis(benzyloxy)flavan-3-one (10), and coupling between 4-hydroxyethoxy-5,7,3′,4′-tetra-*O*-benzyl-(−)-epicatechin (11) and 5,7,3′,4′-tetra-*O*-benzyl-(+)-catechin (4) or 5,7,3′,4′-tetra-*O*-benzyl-(-)-epicatechin (6), respectively. The debenzylation performed in a biphasic system resulted in an improved yield and purity of the target compounds. The chemistry was scaled-up to produce multigram quantities of the title compounds (1 and 2) for various *in vitro*, *ex vivo*, and *in vivo* studies. Moreover, the scale-up process provided a detailed description for the preparation of multihundred to kilogram scale quantities of intermediates used in the synthesis of these two titled procyanidins.

Introduction

Polyphenols are an important class of natural products. Such compounds are widely distributed in nature and possess a diverse range of biological activities. These include, but are not limited to, the inhibition of HIV 1 replication *in vitro*,[1] reducing the risk of heart disease,[2] suppressing ulcer formation,[3] possessing antimutagenic,[4] neuroprotective,[5] anti-inflammatory,[6] antibacterial,[7] and hypotensive[8] properties, and can inhibit the growth of cancer cells.[9]

Our interest is focused mainly at the cancer and vascular biology areas, where initial observations have shown different procyanidins to evoke different activities.[10−23] To unequivocally determine the natural oligomeric procyanidins associated with these activities and to confirm the structures assigned to these compounds, a synthesis program was initiated.[24−27] A series of oligomers of defined regio- and stereochemistry were synthesized for comparison to oligomers purified from cocoa extracts for structure−activity

* To whom correspondence should be addressed. E-mail: leo.romanczyk@mss.effem.com. Telephone: (908) 892-1125. Fax: (908) 892-1196.

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‡ Chemical Process Research & Development, Johnson Matthey Pharmaceutical Materials, Inc.

§ Catalytic Services, Johnson Matthey Pharmaceutical Materials, Inc.

|| Analytical Division, Johnson Matthey Pharmaceutical Materials, Inc.

⊥ Masterfoods USA.

MARS, Incorporated.

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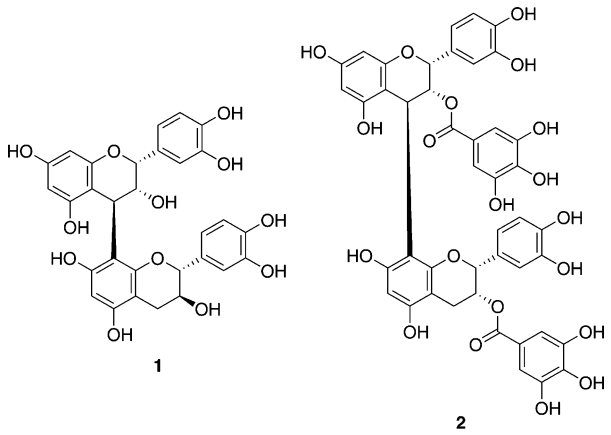

Figure 1.

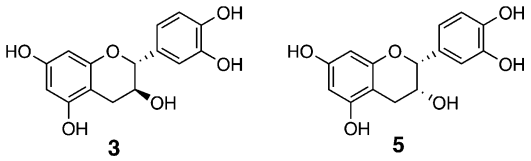

Figure 2.

relationships in various *in vitro*, *ex vivo*, and *in vivo* models of assessment. The results from these initial studies has addressed some of the complex, synthetic challenges posed by the proanthocyanidins (condensed or nonhydrolyzable tannins) related to the difficulty in controlling the interflavan regio- and stereochemistry, as well as the sensitivity of the unprotected compounds to acid,[28] alkali,[29] and oxidizing[30] environments. Through these efforts, 10−100 milligram quantities of some of these compounds have been made to confirm much of the *in vitro* results elaborated by the natural products.[24,27] However, in order to fully develop the potential clinical applications for this class of compounds and address pharmacological and toxicological requirements, 100 g to 1000 g levels of material are essential for full investigations. To this end, we report on the process scale-up conditions

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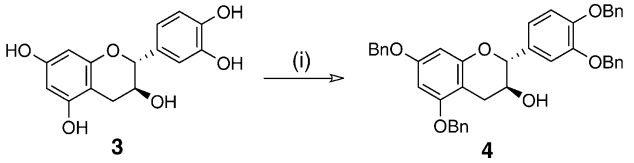
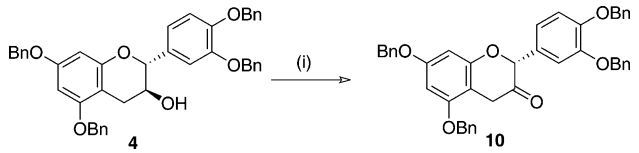
Scheme 1[a]



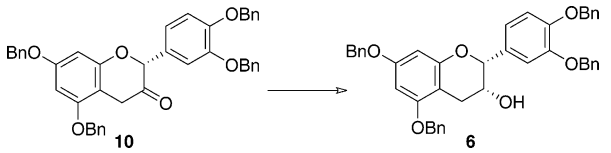
[a] Reagents and conditions: (i) BnBr, NaH, DMF.

Scheme 2[a]



[a] Reagents and conditions: (i) Dess−Martin periodinane reagent, wet CH_2Cl_2, RT.

Scheme 3



required for the multigram synthesis of two naturally occurring procyanidin dimers.

These conditions are applicable to pilot manufacture at the kilogram level through the manipulation of the chemistry accomplished earlier.[24−27] The target dimers selected for scale-up syntheses were **1** and **2** (Figure 1). To the best of our knowledge, this effort represents the first large-scale synthesis for this class of compounds.

The total synthesis of the target dimers, if developed, would obviously require a lengthy synthetic sequence involving several stereoselective steps. The preparations of the target dimers, however, can be greatly simplified by using naturally occurring **3** and **5** as the starting materials (Figure 2).

The literature describes a semisynthetic route (Scheme 1)[24a] that is based on naturally occurring **3**, exclusively. This route gives reliable results for 100 mg to 1 g scales but requires several HPLC purifications and involves other protocols, which are difficult to implement and/or have safety issues at the industrial scale. Following the same sequence of transformations we significantly modified the existing procedures and developed a process applicable for the preparation of the target dimers in kilogram quantities sufficient for a variety of *in vitro*, *ex vivo*, and *in vivo* studies.

Naturally occurring **3**, which serves as a major building block in this synthetic sequence, is available in kilogram quantities from commercial sources. Incorporation of **5** as the other starting material could have provided much easier access to the midstream intermediate **6**, rather than oxidation and stereoselective reduction of **3** (Schemes 2 and 3). Our lengthy outsourcing attempts, however, brought us to the realization that pure **5** was not available in sufficient quantities. Hence, similar to the literature route,[24a] we based

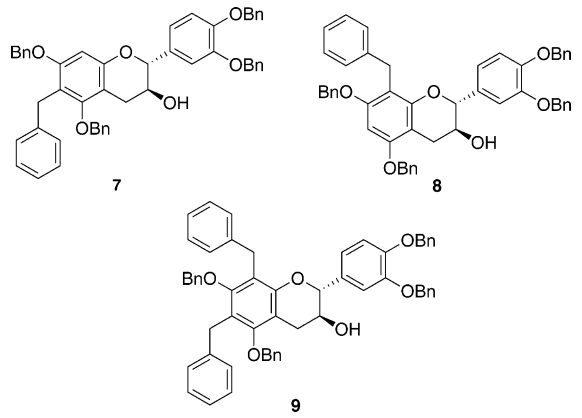


Figure 3.

our development work on **3** as the only flavan-3-ol starting material.

Results and Discussion

Most synthetic transformations required for the preparation of dimeric species from unprotected **3** are poorly compatible with free phenolic functionalities. Other properties of free polyphenols, such as their air sensitivity and complicated extractive behavior, also pose handling problems for the phenolic intermediates. For this reason, protection of the free phenolic functionalities before executing core synthetic transformations, followed by the deprotection step, proved to be the most fruitful in the synthesis of the procyanidins.[24] Benzylation was used as the most common way to protect the phenolic functionalities of procyanidins and related molecules.

1. Benzylation of 3. The original protocol for the benzylation of **3** (Scheme 1) employed BnBr/NaH in DMF to produce **4** in 20% yield.[24a] The major byproducts, **7**, **8**, and **9** (Figure 3), were removed by column chromatography followed by crystallization. These experimental conditions also lead to partial penta-*O*-benzylation of **3**.[26] In addition, NaH in DMF represents a significant safety hazard and is known to have caused several incidents in industrial settings.[31−33]

Multiple alternative benzylation protocols of **3** and **5** are described in the literature.[24b] Other methods for benzylation, which were attempted in our laboratory, involved the use of various bases such as K_2CO_3, DBU, Et_3N, Cs_2CO_3, $NaHCO_3$, Na_2CO_3, and Hünig's base in various solvents such as DMF, acetone, EtOAc, water, and EtOAc/water with and without phase transfer catalyst (nBu_4NI) at RT, at moderate temperature (40−45 °C), or at reflux. These experiments only allowed for incremental yield increases and purity improvements having C-benzylated compounds as major byproducts (**7**, **8**, and **9**).

The best conditions, which were eventually scaled up, involved slow addition of BnBr to a stirred suspension of **3** and K_2CO_3 in DMF at <30 °C. The suspension was then allowed to stir at rt for 18 to 24 h. The solids were removed through a celite pad, and the filtrate was diluted with EtOAc. This was washed sequentially with dilute hydrochloric acid and water to produce product, which was subsequently purified by crystallization (see Table 1).

Table 1. **Crystallization of 4**

entry	solvent/conditions	yield[a]	purity of **4**
1	EtOH/ −5° C	76%	63 (%AUC)
2	EtOH/EtOAc (8/2)/ RT	78%	67 (%AUC)
3	MTBE/ RT	50%	76 (%AUC)
4	CH_2Cl_2/ −20° C		
5	PhMe/ RT	82%	70 (% AUC)
6	CF_3Ph/ RT	80%	70 (%AUC)
7	$ClCH{=}CCl_2$/ −20° C	46%	>97 (%AUC)

[a] All values are isolated yields.

In order to avoid the use of silica gel chromatography or a silica gel plug, variations in trituration or recrystallization procedures of **4** were attempted. Table 1 shows the various conditions employed.

In the most successful experiment (Table 1, entry 7), **4** was treated with hot trichloroethylene followed by cooling to −20 °C for 24 h to afford product in 45−50% yields having >97% (AUC) purity. These yields and purities were obtained on a consistent basis for the synthesis of **4**.

2. Oxidation of 4 to 10. Our efforts to obtain **5** in large quantities from commercial sources were not successful. In addition, compound **5** is considerably more expensive than **3**. Thus, it was decided to use **4** as starting material for **6** by inverting the stereochemistry at the C-3 position (Schemes 2 and 3) through an oxidation/stereoselective reduction sequence. The use of Dess-Martin periodinane in the oxidation of **4** to **10** is known to give reproducible yields of 92% after column chromatography.[24a] However, the cost of Dess−Martin periodinane reagent, and the potential interruptions with its supply prompted us to look for a replacement.

There are several published reports that claim low yield for the oxidation of the C-3 alcohol to the ketone under the following conditions; DMSO/Ac_2O,[34] CrO_3 activated with DMSO,[35] PDC,[36] NMO/catalytic tetrapropylammonium peruthenate,[24a] or Oppenauer conditions (fluorenone, $KOCMe_3$).[24a] In our studies we also found these conditions to be impractical as a mixture of products, and incomplete reactions were observed. Our attempts to apply previously untested Swern oxidation and sodium hypochlorite/TEMPO or MnO_2 for the preparation of **10** did not produce the desired ketone. Rather a complex mixture of products was observed. Even the application of the synthetically equivalent, stabilized IBX did not produce the desired ketone. The lack of practical alternatives resulted in our return to Dess−Martin periodinane (Scheme 2). The isolation protocol was significantly modified where the column chromatography step was

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Table 2. **Stereoselective reduction of 10 to 6 using Ru catalysts[a]**

entry	catalyst	additive solvents	condition	yield
1	Cl_2Ru(II)-(*R*)-BINAP (0.1 equiv)	THF	H_2 (50 psi), RT, 7 h	**10** (100%)
2	(dppb)Ru(II)Cl_2 (0.1 equiv)	THF	H_2 (50 psi), RT, 7 h	**10** (100%)
3	Cl_2Ru(II)-(*R*)-BINAP (0.1 equiv)	Cs_2CO_3 (0.1 equiv), THF	H_2 (50 psi), 50 °C, 7 h	**4** (3%) **6** (5%) **10** (69%)
4	(dppb)Ru(II)Cl_2 (0.1 equiv)	Cs_2CO_3 (0.1 equiv), THF	H_2 (50 psi), 50 °C, 7 h	**10** (100%)
5	5% Ru/C 10 wt %	THF, MeOH	H_2 (100 psi), 50 °C, 65 h	**10** (100%)
6	Ru(II)-(*R*)-BINAP (0.1 equiv)	Cs_2CO_3 (0.1 equiv), THF	H_2 (200 psi), 50 °C, 65 h	**4** (5%) **6** (82%) **10** (1.5%)
7	Ru(II)-(TsDPEN)[b] (0.011 equiv)	KOH (0.1 equiv), THF/IPA	RT, 15 h	**10** (100%)
8	Ru(II)-(TsDPEN)[b] (0.011 equiv)	KOH (0.1 equiv), THF/IPA	80 °C, 15 h	**4** (4%) **6** (19%) **10** (45%)
9	Ru(II)-dppb[c] (0.01 equiv)	Cs_2CO_3 (0.1 equiv), THF	H_2 (50 psi), 50 °C, 16 h	**4** (33%) **6** (0%) **10** (59%)
10	Ru(II)-dppb[c] (0.01 equiv)	Cs_2CO_3 (0.1 equiv), THF	H_2 (200 psi), 50 °C, 16 h	**4** (3%) **6** (0.3%) **10** (56%)
11	Cl_2Ru(II)-(*R*)-BINAP (0.01 equiv)	Cs_2CO_3 (0.1 equiv), THF	H_2 (50 psi), 75 °C, 4 h	**4** (3.4%) **6** (16%) **10** (42%)
12	Cl_2Ru(II)-(*R*)-BINAP (0.01 equiv)	Cs_2CO_3 (0.1 equiv), THF	H_2 (200 psi), 75 °C, 4 h	**4** (2.8%) **6** (25%) **10** (48%)
13	Ru(II)-dppb[c] (0.01 equiv)	Cs_2CO_3 (0.1 equiv), THF	H_2 (50 psi), 75 °C, 4 h	**4** (8%) **6** (0.7%) **10** (38%)
14	Ru(II)-dppb[c] (0.01 equiv)	Cs_2CO_3 (0.1 equiv), THF	H_2 (200 psi), 75 °C, 4 h	**4** (3.6%) **6** (1.4%) **10** (36%)
15	Cl_2Ru(II)-(*R*)-BINAP (0.01 equiv)	Cs_2CO_3 (0.1 equiv), THF	H_2 (200 psi), 75 °C, 16 h	**4** (6%) **6** (84%) **10** (5%)
16	Cl_2Ru(II)-(*R*)-BINAP-(2*R*)-(−)-1,1-bis(4-methoxyphenyl)-3-methyl-1,2-butadiene (0.1 equiv)	Cs_2CO_3 (0.1 equiv), THF	H_2 (200 psi), 75 °C, 16 h	**4** (5%) **6** (83%) **10** (6%)
17	$RuCl_2(PPh_3)_2$ (0.02 equiv)	THF	H_2 (200 psi), 75 °C, 16 h	**4** (9%) **6** (8%) **10** (61%)
18	$RuCl_2(PPh_3)_2$ (0.02 equiv)	Cs_2CO_3 (0.1 equiv), THF	H_2 (200 psi), 75 °C, 16 h	**4** (17%) **6** (19%) **10** (29%)
19	$RuCl_2(PPh_3)_2$ (0.02 equiv)	IPA/THF	reflux, 16 h	**4** (2%) **6** (0%) **10** (78%)
20	$RuCl_2(PPh_3)_2$ (0.02 equiv)	Cs_2CO_3 (0.1 equiv), IPA/THF	reflux, 16 h	**4** (1%) **6** (2%) **10** (10%)
21	$RuCl_2(PPh_3)_2$ (0.02 equiv)	LiBr (6 equiv), THF	reflux, 16 h	**4** (2%) **6** (2%) **10** (68%)
22	$RuCl_2(PPh_3)_2$ (0.02 equiv)	KOH (6 equiv), THF/IPA	reflux, 16 h	**4** (2%) **6** (9%) **10** (0%)
23	Ru(II)-*rac*-BINAP (0.1 equiv)	THF	H_2 (200 psi), 75 °C, 16 h	**4** (66%) **6** (27%) **10** (0%)

[a] All the reactions were performed at the 100 mg to 400 mg scale. The completion of the reaction was monitored by HPLC. [b]Obtained in situ from [Ru(*p*-cymene)Cl_2]$_2$+TsDPEN. [c]Obtained in situ from [Cl_2(COD)Ru(II)]polymer+dppb.

eliminated. Instead, the periodinane reduction products were removed from the reaction mixture by crystallization from methylene chloride. This modification resulted in good yield (77−85%) and made isolation significantly less time-consuming and labor-intensive. The oxidation of **4** to **10** was performed at the 440-g scale under Dess−Martin[37] conditions. The crude product was directly purified by crystallization to produce the desired ketone in high purity.

3. Synthesis of 6 from 10. The stereoselective reduction at the C-3 position of **10** to **6** was reported in the literature using L-Selectride and LiBr at −78 °C in THF.[24a] In addition to the low temperature used for the reaction, the use of L-Selectride and dry LiBr were identified as potential problems for scale up because of reaction volume efficiency. Therefore, our initial efforts were focused at finding alternative reagents and conditions for the stereoselective reduction. First, we focused our efforts on a catalytic hydrogenation of the C-3 ketone functionality. There is a great deal of literature precedence for the stereoselective reduction of ketones to alcohols using Ru based catalysts.[38] Noyori's BINAP-Ru (II) catalysts are recognized as general and efficient catalysts for the hydrogenation of ketones to alcohols.[39,40] However, the stereoselective reduction of aliphatic ketones remains a difficult task since it requires the catalyst to differentiate between alkyl groups. Nonetheless, our initial efforts were based upon Ru based catalysts, and the results are summarized in Table 2.

The use of various commercially available Ru catalysts gave satisfactory results. The best catalyst was found to be Ru(II)-(*R*)-BINAP (Entry 6, Table 2), which gave **6** in 82% yield. The final reaction mixture also contained 1.5% unreacted starting material, 5% of the undesired enantiomer, and several small unidentified impurities.

Alternatively, the use of Al(O^{i}Pr)$_3$ with 2-propanol in refluxing PhMe under Meerwein−Ponndorf−Verley reduction conditions[41] resulted in preferential reduction to afford **6**. The ratio between desired diastereomer **6** and unwanted **4** in the crude reaction mixture was found to be 89:7 (% AUC). The diastereomeric purity of **6** was significantly upgraded either by crystallization (most conveniently from partially evaporated reaction mixture) or by trituration with methanol. The combination of these two purification techniques allowed us to improve the diasteriomeric ratios (**6/4**) to 650:1. Compound **6** was obtained in high optical and chemical purity (>99% AUC) and in 80−85% isolated yield.

4. Synthesis of 11. The literature describes a procedure to produce **11** in 40% yield by treating **6** with ethylene glycol

(37) Dess-Martin periodinane (DMP) used in the process was purchased from commercial sources. The literature indicates that the intermediate [1-hydroxy-1, 2-benziodoxol-3(1*H*)-one] is explosive under excessive heating (>200 °C) or impact [J.B. Plumb & D.J. Harper, *Chem. Eng. News* **1990**, July 16, 3]. In our experience, the oxidation of the secondary alcohol was found to be slow when DMP was used in dry methylene chloride and required several hours for the completion of the reaction. However, when wet methylene chloride [S.D. Meyer & S.L. Schreiber, *J. Org. Chem.* **1994**, *59*, 7549] was used, the reaction required only 2 to 3 h for completion and a very mild exotherm was observed (∼5 to 8 °C) at the 440-g scale reaction. We have also observed that the rate of the addition of wet methylene chloride controls the exotherm and rate of the reaction.

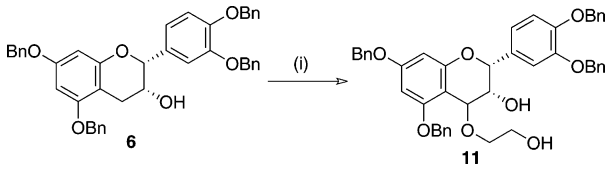
(38) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029 and references cited therein.

(39) Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245.

(40) Ohta, T.; Takaya, H.; Noyori, R. *Inorg. Chem.* **1988**, *27*, 566.

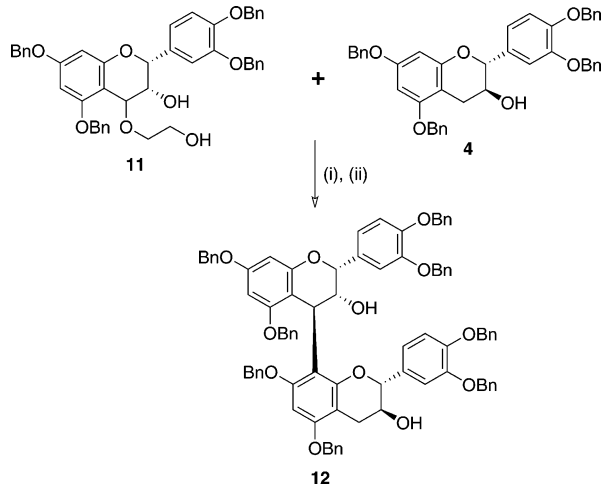
(41) Wilds, A. L. *Org. React.* **1944**, *2*, 178.

Scheme 4[a]



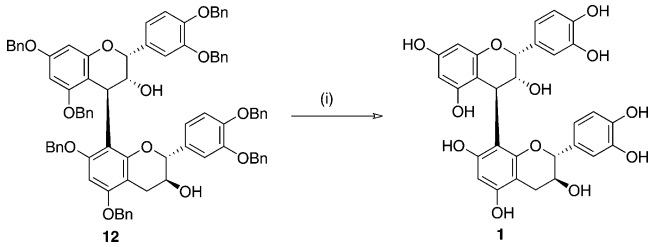
[a] Reagents and conditions: (i) Ethylene glycol, DDQ, DMAP, CH_2Cl_2.

Scheme 5[a]



[a] Reagents and conditions: (i) Bentonite clay K-10, CH_2Cl_2, 0 °C; (ii) column chromatography.

Scheme 6[a]



[a] Reagents and conditions: (i) 20% $Pd(OH)_2/C$ (50% H_2O wet), EtOAc/H_2O (1/3, v/v), RT, 15 psi, 3−4 h.

in DCM with DDQ and DMAP (Scheme 4).[24a] The procedure required repeated column chromatographies to obtain the desired purity.

Our attempt to replace DDQ with less expensive and safer reagents such as IBX or chloranil did not produce even a trace of the desired compound. Thus, it was decided to use DDQ as an oxidizing agent but modify the isolation conditions. Decreasing the concentration of ethyl acetate inthe heptane−ethyl acetate eluent allowed us to replace a two-step column chromatography method with a single column chromatography step. Additional purification of **11** was achieved by crystallization from heptane and ethyl acetate. Compound **11** was obtained in good yield (>70%) and purity (>99% AUC).

5. Synthesis of 12. The coupling reaction between **8** and **4** was performed by using Bentonite clay K-10 at 0 °C as reported by Kozikowski et al.[27] (Scheme 5). In addition to **4** and **12**, higher oligomers were also detected in the reaction mixture.

Initial observations from TLC and HPLC analysis revealed that the low yield of **12** was caused by the formation of the undesired higher oligomers. To suppress the formation of the higher oligomers, the concentration of **4** was increased (from 2.6 to 4 equiv) so that at any given time excess **4** was present to react with the electrophile. As a result, the treatment of 1 equiv of **11** with 4 equiv of **4** improved the ratio of **12** to higher oligomers from 2.6:1 to 4:1. Compound **12** was isolated from silica gel chromatography in 72−76% yield with >96% (AUC) purity.

6. Synthesis of 1. Our initial attempts to prepare compound **1** under the reported conditions[24] led to the desired product at 88% (AUC) purity where the presence of many partially benzylated intermediates necessitated purification by preparative HPLC. The use of reversed phase preparative HPLC for the isolation of **1** would be tedious and not economical for any large-scale production. We also observed that during the workup, the amount of byproducts increased, which indicated the product not to be stable under such conditions. To improve the yield and purity criteria for the debenzylation of **1**, we examined pressure, solvent, catalyst, and time of reaction conditions listed in Table 3. Our evaluations showed that altering the pressure from 1 to 15 psig did not greatly affect the reaction yield (entries 1−4). However, the total amount of time the reaction was allowed to progress greatly affected the yield (entries 3−4) because the dimer **1** would cleave into monomer units. Changing the catalyst from 20% $Pd(OH)_2/C$ to either Pd black or 5% Pd/C did not give favorable results (entries 5−8). Using EtOAc rather than THF and MeOH in the reaction mixtures greatly increased the yield and purity of the final product (entries 9−10, 13−16). We also observed that the reaction could not be done exclusively in H_2O since the substrate was insoluble in H_2O (entry 11). If the reaction was done exclusively in EtOAc, the reaction rate was very fast, but the final yield and purity of the product were <90% (entry 12). Based on the above results and having an understanding of the solubility of **12** (soluble in organic solvent and insoluble in water) and the desired product **1** (soluble in water and partially soluble in organic solvent), it was decided to run the reaction in a biphasic solution so that as the product formed, it would transfer to the aqueous layer (Scheme 6). Thus, the product can be isolated from the aqueous layer, and most of the intermediates/byproducts are removed by simple liquid/liquid extraction.

The final solvent conditions using EtOAc/H_2O gave the desired product in quantitative yield and 98% purity.

7. Synthesis of 13. The aforementioned conditions for the coupling reaction between **11** and **4** in the presence of Bentonite K-10 were also applied to the coupling reaction between **11** and **6** (Scheme 7). Most of the unreacted **6** was removed from the evaporated reaction mixture by crystallization from ethyl acetate.

Final separation was achieved by column chromatography on silica gel. The desired product **13** was isolated in 72−78% yield with >98% purity.

8. Synthesis of 14. The galloylation of **13** using tri-*O*-benzyloxy galloyl chloride in the presence of DMAP in C_5H_5N produced **14** in high yield (Scheme 8). Trituration of the reaction mixture with CH_2Cl_2 at RT caused precipita-

Table 3. **Conditions for the debenzylation of 12**

entry	solvent(s)	temp (°C)	time (h)	pressure (psig)	catalyst	yield
1	THF/MeOH/H_2O	25	1.5	1−2	20% Pd $(OH)_2$/C 30 wt %	18%
2	THF/MeOH/H_2O	25	3	1−2	20% Pd $(OH)_2$/C 30 wt %	88%
3	THF/MeOH/H_2O	25	2	15	20% Pd $(OH)_2$/C 30 wt %	86%
4	THF/MeOH/H_2O	25	5	15	20% Pd $(OH)_2$/C 30 wt %	48%
5	THF/MeOH/H_2O	25	1.5	1−2	Pd Black 60 wt %	84%
6	THF/MeOH/H_2O	25	3	1−2	Pd Black 60 wt %	90%
7	THF/MeOH/H_2O	25	1.5	1−2	Pd Black 5 wt %	0%
8	THF/MeOH/H_2O	25	1	15	5% Pd/C 120 wt %	22%
9	EtOAc/MeOH/H_2O	25	1	10	20% Pd $(OH)_2$/C 30 wt %	88%
10	EtOAc/MeOH/H_2O	25	1	15	20% Pd $(OH)_2$/C 30 wt %	96%
11	H_2O	25	1	15	20% Pd $(OH)_2$/C 30 wt %	0%
12	EtOAc	25	1	15	20% Pd $(OH)_2$/C 30 wt %	82%
13	EtOAc/H_2O	25	1	15	20% Pd $(OH)_2$/C 30 wt %	2%
14	EtOAc/H_2O	25	4	15	20% Pd $(OH)_2$/C 30 wt %	86%
15	EtOAc/H_2O	25	4	15	20% Pd $(OH)_2$/C 30 wt %	96%
16	EtOAc/H_2O	25	4	15	20% Pd $(OH)_2$/C 30 wt %	98%

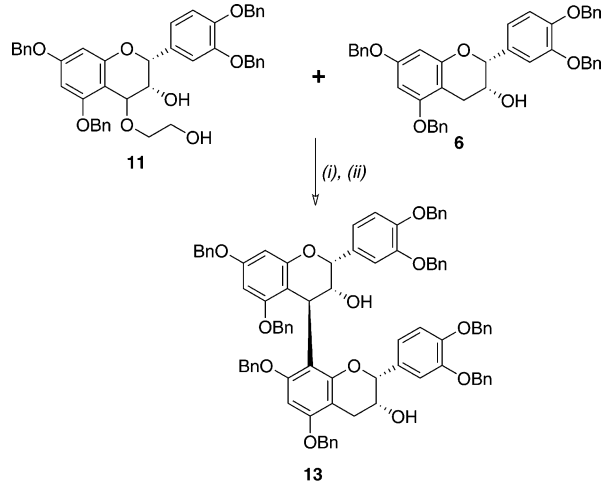
tion of 3,4,5-tri-*O*-benzyl gallic acid, which was removed by filtration. The product was then purified by passage through a silica gel plug. This reaction was efficiently performed several times in the laboratory setting.

9. Synthesis of 2. The hydrogenation of **14** to produce **2** was performed under similar conditions as those previously described for the synthesis of **1**, except for slight modifications in the workup (Scheme 9). These are outlined in the Experimental Section.

Summary

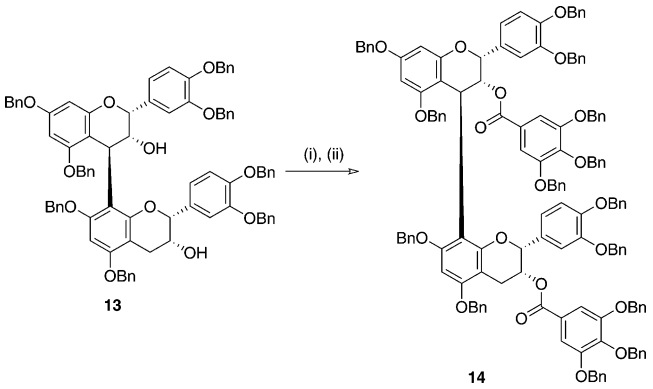
In summary, the scale-up synthesis of compounds **1** and **2** has been described with several improvements. The benzylation of **3** was achieved using K_2CO_3 as a base in DMF, and the desired product was isolated after crystallization. Compounds **10** and **11** were isolated in good yield after improving the reaction and isolation conditions. The conversion of compound **10** to **6** was achieved by stereoselective reduction with $Al(^iOPr)_3$ and IPA and had excellent selectivity. The desired compound was isolated after trituration with methanol. The debenzylation conditions (to obtain **1** and **2**) were optimized using a combination of water and ethyl acetate as a solvent in 3/1 ratio (v/v). The desired compounds were isolated in good yield and high purity after the extractive workup, thus avoiding either the chromatographic or HPLC purification.

Scheme 7[a]



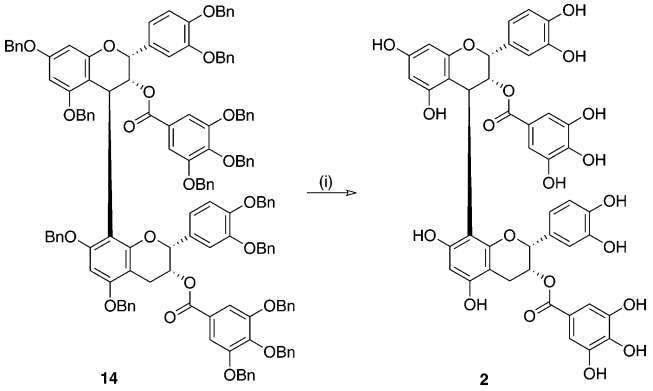
[a] Reagents and conditions: (i) Bentonite clay K-10, CH_2Cl_2, 0 °C; (ii) column chromatography.

Scheme 8[a]



[a] Reactions and conditions: (i) Galloyl acid, $(COCl)_2$, Et_3N, CH_2Cl_2, 0 °C; (ii) silica gel plug.

Scheme 9[a]



[a] Reagents and conditions: (i) 20% $Pd(OH)_2$/C (50% H_2O wet), EtOAc/H_2O (1/3, v/v), RT, 15 psi, 3−4 h.

Experimental Section

General. Solvents and reagents were obtained from commercial sources and were used without any purification. All the reactions were performed in glass reactors. Different HPLC methods were used for the benzylated and phenolic compounds using standard HPLC equipment with PDA detection and data systems. Separations were performed with a Phenomenex Synergi 4 μ Fusion-RP 80 Å (150 mm × 4.6 mm) column and Chiralpak AD-RH (150 mm × 4.6 mm) column. The mobile phase for isocratic and gradient HPLC separations was prepared using 0.01% TFA in water and 0.01% TFA in acetonitrile. All the compounds were monitored against reference materials including the starting materials.

5,7,3′,4′-Tetra-*O*-benzyl-(+)-catechin (4). A dry 12 L, three-necked round-bottom flask equipped with a mechanical stirrer, a dropping funnel, a N_2 inlet, and an internal temperature probe was charged with **3** (400 g, 1.38 mol, 1 equiv) and DMF (4 L, 1 g/10 mL, 10 vol). To this solution was slowly added K_2CO_3 (1430.5 g, 10.38 mol, 7.5 equiv) with stirring. The suspension was allowed to stir at RT for 0.5 h. To this was slowly added BnBr (1180.2 g, 6.9 mol, 5 equiv) via the addition funnel (***Note:*** *A mild exotherm was observed as the internal temperature rose to 30.6 °C from 21.6 °C*). It took about 4.5 h to complete the addition of benzyl bromide at this scale. The suspension was then allowed to stir at RT for 18 h. The consumption of the starting material was monitored by TLC (30% EtOAc/heptane, v/v). After complete consumption of the starting material, the reaction mixture was suction filtered through a pad of celite (500 g) to remove K_2CO_3. The celite pad was washed with EtOAc (3 × 1 L, 3 × 500 mL). The combined filtrates were sequentially washed with 10% aqueous HCl (2 × 1.5 L), H_2O (2 × 1 L), and 30% aqueous NaCl (1 × 2 L). The organic layer was dried over anhydrous $MgSO_4$ (300-g) and filtered, and the solvent was removed under vacuum to afford an off-white to light yellow colored semisolid. The semisolid was chased with heptane (2 × 500 mL). Trichloroethylene (2 L, 1 g/5 mL based on the starting material, **3**) was added to the solid and heated at reflux until a clear orange to red solution was obtained. The solution was first allowed to cool to RT with agitation, and then it was further cooled to −20 to −26 °C in the freezer for 56 h. The solids obtained were suction filtered and washed with cold trichloroethylene (−20 °C, 2 × 500 mL) and cold heptane (−20 °C, 1 × 500 mL). The solids were dried under high vacuum at 50−55 °C for 18 h to produce **4** as an off-white to white solid. Yield = 412 g, 46%. HPLC purity = 98% (AUC).

(2*R*)-5,7,3′,4′-Tetrakis(benzyloxy)flavan-3-one (10). To a solution of **4** (440 g, 0.675 mol, 1 equiv) in dichloromethane (3.2 L) was added at once with stirring at RT Dess−Martin periodinane reagent (315.4 g, 0.74 mol, 1.1 equiv) in one portion. CH_2Cl_2 saturated with water (242 mL) was added dropwise during 1.5 h. The internal temperature (IT) gradually increased from 16 to 24 °C. The IT reached its maximum in approximately 50 min then gradually decreased to 20 °C. HPLC analysis of the reaction mixture showed complete consumption of the starting material. Saturated $NaHCO_3$ (4 L) solution was slowly added, followed by a 10% aqueous solution of sodium thiosulfate pentahydrate (161.5 g /1.6 L in water). The white precipitate formed upon quenching was suction filtered. The filtrate was transferred to a separatory funnel. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (650 mL). The combined organic phase was dried over $MgSO_4$ (*Note: During the drying process, the reduced DMP reagent precipitates*). Once the precipitation process was completed, the reaction mixture was suction filtered, and the solvent was removed under vacuum. The residue was triturated with methanol (600 mL) for 1 h at RT, filtered (filtrate saved), dissolved in boiling dichloromethane (800 mL), and diluted with methanol (1.5 L). Precipitation was observed when the reaction mixture cooled to RT. After stirring for 18 h at RT and subsequently at ice bath temperature for 1 h, the solids were suction filtered and washed with methanol (4 × 100 mL). The re sulting pale pink precipitate was dried *in vacuo* to afford **10**. Yield = 336 g, 76.6%. HPLC purity = 94% (AUC).

5,7,3′,4′-Tetra-*O*-benzyl-(−)-epicatechin (6). A 22-L, three-necked round-bottom flask equipped with a heating mantle, an overhead stirrer, a thermometer, and a distillation unit was charged with **10** (1263 g, 1.95 mol, 1 equiv), PhMe (10 L), $Al(O^iPr)_3$ (796.6 g, 3.9 mol, 2 equiv), and IPA (5 L) with agitation. A slightly yellow turbid solution was obtained after stirring at RT for ∼30 min (*Note: A mild endotherm was observed as the internal temperature dropped to 14.3 °C*). The suspension was heated to reflux with continuous stirring. As the internal temperature increased, the suspension became a clear yellow solution. As the internal temperature reached ≥82 °C (*Note: It took about 1.75 to 2 h at this scale to reach this temperature*), the distillation of the solvent (acetone and IPA) began and was collected in a 2 L round-bottom flask. After collecting about 1400 mL of distillate, HPLC analysis of the reaction mixture indicated the presence of unreacted starting material. Additional IPA (500 mL) was added to the reaction mixture, and the distillation was continued. After an additional 2.2 L of distillate were collected, another sample was submitted for HPLC analysis. (*Note: HPLC results indicated the consumption of the starting material.)* The reaction mixture was cooled to RT (IT = 18.8 °C). To the reaction mixture was slowly added 10% aq. H_2SO_4 (v/v, 3 L) with stirring. The IT rose to 47.2 °C (*Note: Initial addition of aqueous H_2SO_4 resulted in a gel, which dissolved as more acid was added to the reaction mixture with good agitation. At the end of the addition, a clear biphasic solution was obtained*). The mixture was allowed to cool to RT. Once the IT reached RT, the reaction mixture was transferred to a separatory funnel, and the organic layer was separated. The organic layer was washed with 10% aqueous H_2SO_4 (v/v, 1 × 3 L). The combined aqueous layers were washed with toluene (1 × 3 L). The organic layers were combined, washed with 20% aq. NaCl (w/v, 1 × 2.5 L), dried over Na_2SO_4 (750 g), and filtered. The solvent was removed under vacuum keeping

the bath temperature ≤45 °C to produce a light yellow semisolid. The solids were triturated with methanol (1 g/8 mL, 8 L) at RT for 19 h. The solids were suction filtered, washed with methanol (5 × 500 mL), and dried under high vacuum at 40−45 °C for 20 h to give **6**. Yield = 1018.18 g, 80.3%. HPLC purity = 99% (AUC).

5,7,3′,4′-Tetra-*O*-benzyl-4-(2-hydroxyethoxy)-(−)-epicatechin (11). To a stirred solution of **6** (219 g, 0.35 mol, 1.0 equiv) in CH_2Cl_2 (2.2 L) was added anhydrous ethylene glycol (112.5 mL, 2.0 mol, 5.7 equiv) and DDQ (100 g, 0.44 mol, 1.26 equiv) at RT. The color of the reaction mixture turned green and then almost black. After the reaction mixture was stirred at RT for 2 h, a solution of DMAP (87 g, 0.71 mol, 2.0 equiv) in CH_2Cl_2 (500 mL) was added, and the reaction mixture was further stirred for an additional 10 min. Silica gel (1 kg) was added, and the reaction mixture was dried under vacuum for 20 h at RT. The dry silica gel was placed on top of a 400 g silica gel column, and the product was eluted with heptane−ethyl acetate (2/1, v/v, 14 L). Fractions containing pure product (TLC and HPLC analysis) were combined, and the solvent was removed under vacuum. The residue was dissolved in boiling ethyl acetate (200 mL) and upon cooling diluted with heptane (200 mL). Crystallization began after a few minutes. The resulting suspension was vigorously stirred overnight at RT for 18 h. The solid was filtered, washed with heptane, and dried *in vacuo* to afford **11** as an off-white solid. Yield = 171 g, 71.5%. HPLC purity = 99% (AUC).

5,7,3′,4′-Tetra-*O*-benzyl-(−)-epicatechin-(4β,8)-[5,7,3′,4′-tetra-*O*-benzyl-(+)-catechin] (12). To an ice cold (IT <5 °C) suspension of **4** (1189.7 g, 1.83 mol, 4.46 equiv) and Bentonite K-10 (574 g) in CH_2Cl_2 (10 L) under N_2 atmosphere was slowly added a solution of **11** (290 g, 0.41 mol, 1.0 equiv) in CH_2Cl_2 (1 L) with stirring at such a rate that the internal temperature was maintained at <6 °C throughout the addition (*Note: It took ∼1.5 h at this scale for the addition*). The reaction mixture was stirred at this temperature for an additional 1 h (the IT rose to 10 °C). The clay was suction filtered through a pad of celite, and the celite was washed with CH_2Cl_2 (2 L). The filtrates were combined, and the solvent was removed under vacuum to produce an off-white solid. The solid was analyzed by HPLC indicating a mixture of **4** (excess), the desired dimer **12**, and higher oligomers. Most of the unreacted **4** was crystallized from ethyl acetate. The remaining reaction mixture was purified by silica gel chromatography using ethyl acetate and heptane as an eluent to give **12**. Yield = 323.4 g, 61%. HPLC purity = 98.7% (AUC).

5,7,3′,4′-Tetra-*O*-benzyl-(−)-epicatechin-(4β,8)-[5,7,3′,4′-tetra-*O*-benzyl-(−)-epicatechin] (13). A suspension of **6** (306 g, 0.47 mol, 4.0 equiv) and bentonite K-10 (165 g) in CH_2Cl_2 (3650 mL) was cooled in an ice bath under N_2 atmosphere. To this was slowly added a solution of **11** (83.6 g, 0.12 mol, 1.0 equiv) in CH_2Cl_2 (150 mL) with stirring while keeping the IT <5 °C throughout the addition (*Note: It took ∼2.5 h for the addition at this scale*). The reaction mixture was stirred for an additional 1 h at ice-bath temperature (*The internal temperature rose to ∼10 °C*). The completion of the reaction was monitored by HPLC and TLC (EtOAc /$CHCl_3$/heptane: 1/14/14, v/v/v). The reaction mixture was filtered through a pad of celite to remove bentonite K-10. The celite pad was washed with EtOAc (2 × 20 mL). The filtrates were combined, and the solvents were removed under vacuum to afford a foamy solid. Most of the unreacted **6** was isolated by dissolving the foamy solid with boiling EtOAc (750 mL) followed by cooling the solution to RT with agitation. The reaction mixture was then purified by silica gel chromatography using ethyl acetate and heptane as an eluent to afford **13**. Yield = 93 g, 60.8%. HPLC purity = 98.5% (AUC).

5,7,3′,4′-Tetra-*O*-benzyl-3-*O*-(3,4,5-tri-*O*-benzylgalloyl)-(−)-epicatechin-(4β,8)-[5,7,3′,4′-tetra-*O*-benzyl-3-*O*-(3,4,5-tri-*O*-benzylgalloyl)-(−)-epicatechin] (14). To a suspension of tri-*O*-benzyl gallic acid (206.96 g, 470 mol, 5 equiv) and DMF (1.62 mL, catalytic amount) in anhydrous CH_2Cl_2 (3.27 L) was slowly added oxalyl chloride (65.33 g, 44.9 mL, 515 mol, 5.5 equiv) at RT with agitation under N_2. The reaction mixture was stirred for 1 h at RT. Additional oxalyl chloride (4 mL) and DMF (0.5 mL) were added to the reaction mixture. After 1.5 h, the reaction mixture was concentrated under vaccum. The residue was chased with PhMe (2 × 500 mL). To this was then added a solution of **13** (122 g, 93.8 mol, 1 equiv) in dry pyridine (2.72L), and the reaction mixture was stirred at RT for 90 h. H_2O (135 mL) was added to the reaction mixture, and the stirring was continued for an additional 4 h at RT. The reaction mixture was diluted with CH_2Cl_2 (6 L) and 25% aq HCl (600 mL), respectively. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (1 × 2 L). The combined organic layers were washed with brine (750 mL), dried over Na_2SO_4 (some of the tri-*O*-benzyl gallic acid was precipitated during the storage at RT), and was filtered. The solvent was removed *in vacuo* to afford a semisolid, which was purified by a silica gel plug (2.5 kg) using CH_2Cl_2 as an eluent. The crude product was further purified on a silica gel column using heptane/$CHCl_3$ /EtOAc, 14 /14/1 (v/v/v) to produce **14** as an off-white foamy solid. Yield = 161 g, 80%. HPLC purity = 96% (AUC).

(−)-Epicatechin-(4β,8)-(+)-catechin (1). To a 6 L pressure bottle was added 20% $Pd(OH)_2$/C (50% wet, 48 g, 60 wt %). To this a solution of **12** (80 g, 0.062 mol) in EtOAc (HPLC grade, 300 mL) was added followed by H_2O (HPLC grade, 900 mL). The bottle was sealed and purged with N_2 (15 psi) three times and then with H_2 at 15 psi (three times). The reactor was pressurized with hydrogen (15 psi), and stirring was started. After stirring for 3 h at RT, the reactor was vented and purged with N_2 (three times). The reaction mixture was filtered through a cartridge (Millipore, Opticap 4″, 0.22 μm) directly into a separatory funnel containing hexane (300 mL). The aqueous layer was separated. The vessel and cartridge were washed with H_2O (2 × 1 L). Each time the aqueous layer was separated and combined with the other aqueous layers. The aqueous layer was frozen and lyophilized to afford **1** as a pale yellow solid. Yield = 35.1 g, quantitative. HPLC purity = 96% (AUC).

(−)-Epicatechin-3-*O*-galloyl-(4β,8)-(−)-epicatechin-3-*O*-gallate (2). In a 6 L hydrogenation glass apparatus was added a solution of **14** (41.6 g, 0.466 mol, 96% purity) in EtOAc (228 mL) to a suspension of 20% $Pd(OH)_2$/C (60 wt % wet, 25 g) in water (HPLC grade, 685 mL) at RT with stirring. The reaction vessel was purged with N_2 (twice) followed by H_2, and the reaction was allowed to stir at RT in the presence of 15 psi H_2 for 4 h. After the reaction mixture was purged with N_2, it was filtered through a filter cartridge (Millipore, Opticap, 4″, 0.22 μm). The cartridge was washed with H_2O (300 mL), EtOAc (1 L), and warm water (25−30 °C, 1 L). The combined washes were transferred to a 6 L separatory funnel, and hexane (300 mL) was added (*Note: the organic layer turns cloudy. Also, addition of hexane helps in the separation of the layers*). The aqueous layer was separated. The cartridge was again washed with EtOAc (1 L) and warm water (25−30 °C, 1 L). Again the aqueous layer was separated. The organic layers were combined and washed with H_2O (1 L). The aqueous layers were frozen and lyophilized for 72 h to afford **2** as an off-white solid. Yield = 15.6 g, 91%. HPLC purity = 98.5% (AUC).

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The authors are grateful to Drs. Heather Taft, Daniel Coughlin, and Richard Lombardy for their support, encouragement, and valuable discussions during the course of this work.

Supporting Information Available

HPLC characterization data and NMR spectra assignments for **1**, **2**, **4**, **6**, **10**, **11**, **12**, **13**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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