Articles

Free-Radical-Mediated Conjugate Additions. Enantioselective Synthesis of Butyrolactone Natural Products: (−)-Enterolactone, (−)-Arctigenin, (−)-Isoarctigenin, (−)-Nephrosteranic Acid, and (−)-Roccellaric Acid

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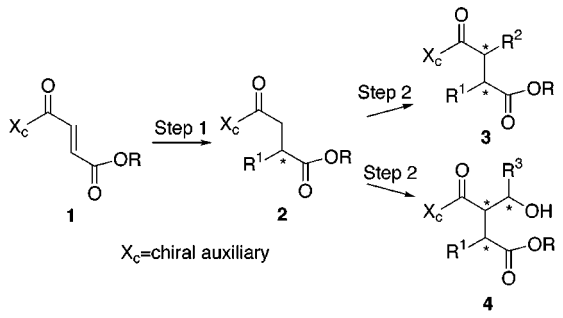
Lewis acid-mediated conjugate addition of alkyl radicals to a differentially protected fumarate **10** produced the monoalkylated succinates with high chemical efficiency and excellent stereoselectivity. A subsequent alkylation or an aldol reaction furnished the disubstituted succinates with syn configuration. The chiral auxiliary, 4-diphenylmethyl-2-oxazolidinone, controlled the stereoselectivity in both steps. Manipulation of the disubstituted succinates obtained by alkylation furnished the natural products (−)-enterolactone, (−)-arctigenin, and (−)-isoarctigenin. The overall yields for the target natural products were 20−26% over six steps. Selective functionalization of the disubstituted succinates obtained by aldol condensation gave the paraconic acid natural products (−)-nephrosteranic acid (**8**) and (−)-roccellaric acid (**9**). The overall yield of the natural products **8** and **9** over four steps was 53% and 42%, respectively.

Introduction

The readily available simple four-carbon dicarboxylic acids, succinic, fumaric, and maleic acid, serve as important building blocks in organic chemistry. Recently, succinates with substituents on the carbon backbone have received attention because of their potential use as components in the development of metalloproteinase inhibitors.[1] In this regard, a differentially protected succinate is an extremely useful synthon for ready functionalization of the carbon backbone. We have recently shown that conjugate radical additions to enoates proceed with high chemical efficiency and excellent stereoselectivity.[2] In an effort to expand the utility of this chemistry in total synthesis, we have undertaken the regio- and stereocontrolled radical additions to differentially protected fumarates.[3] This should allow for the ready preparation of functionalized succinates as shown in Scheme 1. In step 1, the remote chiral center is established through a regio- and stereoselective radical addition to the fumarate **1** (X_c = chiral auxiliary). In step 2, the chiral auxiliary controls the regio- and stereochemistry in the introduction of the second substituent by an alkylation or an aldol process. Thus, a single chiral center in the auxiliary allows for the sequential introduction of multiple stereocenters with control over both regio- and stereochemistry of each substituent.

Scheme 1



Natural products containing the butyrolactone skeleton continue to attract considerable attention due to their interesting biological profile.[4,5] For example, enterolactone (**5**), a lignan present in human urine, has been

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† Taken in part from the MS thesis of Pingrong Liu, North Dakota State University, September 2000.

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(2) For Lewis acid-mediated conjugate radical additions, see: (a) Sibi, M. P.; Ji, J.; Sausker J. B.; Jasperse, C. P. *J. Am. Chem. Soc.* **1999**, *121*, 7517. (b) Sibi, M. P.; Jasperse, C. P.; Ji, J. *J. Am. Chem. Soc.* **1995**, *117*, 10779. (c) Sibi, M. P.; Ji, J.; Wu, J. H.; Gürtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200. (d) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1997**, *62*, 3800. (e) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1996**, *61*, 6090.

(3) For work on radical addition to fumarates using imides derived from Kemp's triacid, see: (a) Stack, J. G.; Curran, D. P.; Rebek, J., Jr.; Ballester, P. *J. Am. Chem. Soc.* **1991**, *113*, 5918. (b) Stack, J. G.; Curran, D. P.; Geib, S. V.; Rebek, Jr., J.; Ballester, P. *J. Am. Chem. Soc.* **1992**, *114*, 7007. For examination of selectivity in radical addition to fumarates and related systems, see: (c) Porter, N. A.; Bruhnke, J. D.; Wu, W.-X.; Rosenstein, I. J.; Breyer, R. A.; McPhail, A. T. *J. Am. Chem. Soc.* **1992**, *114*, 7664. (d) Giese, B.; Zehnder, M.; Roth, M.; Zeitz, H.-G. *J. Am. Chem. Soc.* **1990**, *112*, 6741. (e) Porter, N. A.; Scott, D. M.; Lacher, B.; Giese, B.; Zeitz, H. G.; Lindner, H. J. *J. Am. Chem. Soc.* **1989**, *111*, 8311. (f) Scott, D. M.; McPhail, A. T.; Porter, N. A. *Tetrahedron Lett.* **1990**, *31*, 1679. (g) Bulliard, M.; Zeitz, H.-G.; Giese, B. *Synlett* **1991**, 423.

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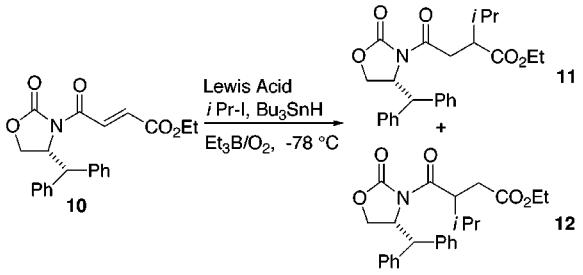
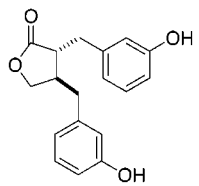
Table 1. Lewis Acid-Mediated Isopropyl Radical Addition to Desymmetrized Fumarate 10



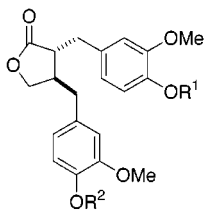
entry	Lewis acid[a] (equiv)	solvent	yield[b] (%)	diastereoselectivity (**11**)[c]	regioselectivity **11**/**12**[d]
1		CH_2Cl_2	92	1.6:1.0	11:1
2	$BF_3{\cdot}Et_2O$ (1)	CH_2Cl_2	86	1.2:1.0	9:1
3	$Mg(OTf)_2$ (1)	CH_2Cl_2	87	1.0:1.0	7:1
4	$Zn(OTf)_2$ (1)	CH_2Cl_2	88	1.6:1.0	33:1
5	$Sc(OTf)_3$ (1)	CH_2Cl_2/THF = 4/1	95	2.1:1.0	6:1
6	$Y(OTf)_3$ (1)	CH_2Cl_2/THF = 4/1	90	21:1	>100:1
7	$Sm(OTf)_3$ (1)	CH_2Cl_2/THF = 4/1	95	29:1	>100:1
8	$Sm(OTf)_3$ (2)	CH_2Cl_2/THF = 4/1	95	5.0:1.0	24:1
9	$Ho(OTf)_3$ (1)	CH_2Cl_2/THF = 4/1	88	13:1	>100:1
10	$Tm(OTf)_3$ (1)	CH_2Cl_2/THF = 4/1	92	47:1	>100:1
11	$Yb(OTf)_3$ (1)	CH_2Cl_2/THF = 4/1	91	10:1	80:1
12	$Lu(OTf)_3$ (1)	CH_2Cl_2/THF = 4/1	95	31:1	87:1
13	$Er(OTf)_3$ (1)	CH_2Cl_2/THF = 4/1	90	33:1	>100:1
14	$Er(OTf)_3$ (3)	CH_2Cl_2/THF = 4/1	91	71:1	>100:1
15	$Er(OTf)_3$ (0.2)	CH_2Cl_2/THF = 4/1	88	3.0:1	11:1
16	$Er(OTf)_3$ (1)	THF	93	53:1	>100:1
17	$Er(OTf)_3$ (1)	Et_2O	90	34:1	>100:1

[a] See the Experimental Section for reaction conditions. [b] Isolated yield. [c] Diastereomeric ratios were determined by ^{1}H 400 MHz NMR of the crude reaction mixture. [d] Regioselectivity was determined by ^{1}H 400 MHz NMR analysis of the crude reaction mixture.

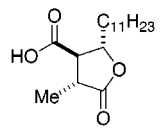
shown to possess protective properties toward certain types of cancers.[6] Arctigenin (**6**), another example of a bisbenzylbutyrolactone lignan, exhibits anti-HIV properties.[7] Besides the disubstituted lignans, there are trisubstituted butyrolactones that contain a carboxylic acid group at the C-4 position, which also show promising biological activities. Nephrosteranic acid (**8**), roccellaric acid (**9**), and methylenolactocin are examples of this class of butyrolactones known as paraconic acids. In this paper, we describe the selective functionalization of fumarates by the strategy outlined in Scheme 1 and apply it in the highly efficient synthesis of enterolactone[8] (**5**) and arctigenin (**6**),[8h,9] and the first enantioselective synthesis of isoarctigenin (**7**).[10] Additionally, the enantioselective synthesis of paraconic acid natural products nephrosteranic (**8**)[11] and roccellaric acid (**9**)[11a,12] is also described.[13]



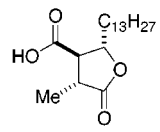
5 (-)-Enterolactone



6 R^1=H, R^2=Me, (-)-Arctigenin
7 R^1=Me, R^2=H, (-)-Isoarctigenin



8 (-)-Nephrosteranic Acid



9 (-)-Roccellaric Acid

Results and Discussion

Application of free-radical-based synthetic methods for the stereoselective construction of carbon−carbon bonds

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has continued to increase.[14] A major breakthrough in this area was the discovery that Lewis acids can be effectively used for obtaining high levels of diastereo- and enantioselectivity in radical reactions.[15] Lewis acid mediated addition of isopropyl radical to desymmetrized fumarate **10**[16] was initially evaluated to establish optimal reaction conditions (Table 1). The auxiliary of choice was the oxazolidinone derived from diphenylalanine[17] since it had shown the best characteristics in our earlier work. Several trends are evidenced from Table 1.

The conjugate addition reaction proceeds in excellent chemical yields. High regio- and diastereoselectivity was observed with lanthanide and pre-lanthanide Lewis acids (Table 1, entries 6, 7, 9, 10, 12, and 13), but the reaction was essentially nonselective in the absence of a Lewis acid (Table 1, entry 1). The regioselectivity in the radical addition experiments was determined by NMR analysis of the reaction mixture. Authentic samples of the racemic regio- and diastereomeric (1:1) monoethyl succinic acids were prepared by independent synthesis[18] and the chiral auxiliary introduced by standard techniques. The four regio- and diastereomeric products show well-separated signals for the methylene protons (400 MHz NMR) to allow for unambiguous determination of product ratios. The regiochemistry in the conjugate addition was further confirmed by the preparation of the natural products (vide infra). Of the lanthanide Lewis acids examined,[19] samarium, thulium, lutetium, and erbium triflates gave the best selectivity (Table 1, entries 7, 10, 12, and 13). Yttrium triflate also gave high regio- and diastereoselectivity (Table 1, entry 6). Stoichiometric amount of Lewis acid was required for high selectivity (compare Table 1, entry 13 with 15). Whereas excess erbium triflate led to a small enhancement in diastereoselectivity, excess samarium triflate greatly lowered both regio- and diastereoselectivity (compare Table 1, entry 13 with 14 and 7 with 8).

These results indicate that a chelating Lewis acid is required for obtaining high selectivity (compare Table 1, entry 10 or 13 with 2). The Lewis acid selectively coordinates to the imide group and activates the substrate for conjugate addition β to the imide carbonyl resulting in high regioselectivity. Chelation to the Lewis acid also locks the substrate in an s-cis rotamer, and radical addition takes place from a face opposite to the bulky diphenylmethyl substituent providing high diastereoselectivity. We have previously established that radical addition to crotonates and cinnamates can be accomplished with substoichiometric amounts of Lewis acid with minimal change in yield and selectivity.[2a] However, with the more reactive fumarate **10**, radical addition to uncomplexed substrate presumably competes effectively (Table 1, entry 1) with substoichiometric Lewis acid−substrate complex (Table 1, entry 15), leading to lower selectivity. The dependence of regio- and diastereoselectivity with variation in chelating Lewis acids remains unexplained.

Having established that regio- and stereocontrolled *i*-Pr radical addition to **10** was feasible, we turned our attention to the introduction of benzylic fragments. Intermolecular conjugate addition of benzylic radicals to enoates has not been reported in the literature. We began our investigation with the addition of benzylic radicals[20] to **10** under the condition established from *i*-Pr radical addition. A stoichiometric amount of $Sm(OTf)_3$ was used as the Lewis acid. The reaction produced the desired products along with ethyl addition product **17**, which was produced from the ethyl radical generated by Et_3B and remaining starting material **10**. However, the benzyl radical added to the β-position of the chiral imide, and only one diastereomer was obtained. After brief optimization of the reaction conditions by variation of the amounts of radical precursors, Bu_3SnH, Et_3B, and multiple addition of those reagents, the reactions went to completion and produced the desired products in 71−84% yields as single diastereomers after purification by flash column chromatography (Table 2). Three-time addition and larger scale of reagents helped to improve the conversions (compare Table 1, entries 2, 3, and 5). The use of iodide instead of bromide decreased the conversion (compare Table 1, entry 4 with 3). Larger scale reaction improved the yield of **14** from 50% to 71% (compare Table 1, entry 5 with 6) and also increased the yield of **15** from 74% to 80% (compare Table 1, entry 8 with 9). 3,4-Dimethoxybenzyl radical was more reactive than 3-methoxybenzyl radical; thus, less radical precursor and shorter reaction time were needed for the reaction, and higher yields and less amount of ethyl product were obtained (compare Table 1, entries 8 and 9 with entries 5 and 6). The addition of 3-methoxy-4-benzyloxybenzyl radical worked quite well. We obtained 84% of isolated yield for the product **16**, with <10% of ethyl product **17** (Table 1, entry 10). However, there was a problem with the simple benzyl radical addition (Table 1, entry 1) experiment. The desired product and ethyl product had the same polarity. Therefore, neither flash column chromatography nor crystallization could completely separate both products.

In conjugate addition reactions using relatively unreactive nucleophilic radicals, competitive ethyl radical addition was a problem when Et_3B was used as an initiator. Recently, Schiesser has reported the utility of 9-BBN as a radical initiator to avoid the competitive addition associated with Et_3B.[21] We found that conjugate

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(14) For discussion on acyclic diastereoselection in radical reactions see: (a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1995. (b) Giese, B. *Radical in Organic Synthesis. Formation of Carbon−Carbon Bond*; Pergamon: Oxford, 1986. (c) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. (d) Smadja, W. *Synlett* **1994**, 1.

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(16) Substrate **10** was prepared in 87% yield by acylation of the chiral auxiliary (*R*)-4-diphenylmethyl-2-oxazolidinone with the acid chloride derived from commercially available monoethyl fumaric acid.

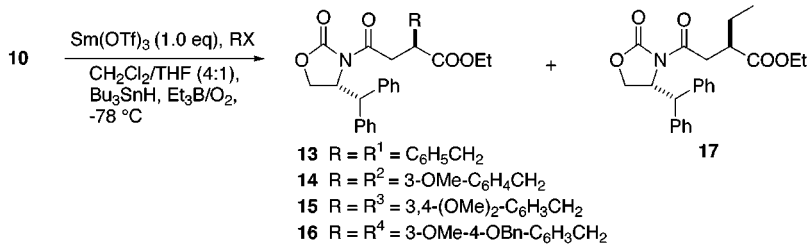
(17) The choice of the 4-diphenylmethyl-2-oxazolidinone as a chiral auxiliary was based on its known superiority in radical reactions. For synthesis of the auxiliary see: Sibi, M. P.; Deshpande, P. K.; La Loggia, A. J.; Christensen, J. W. *Tetrahedron Lett.* **1995**, *36*, 8961. Sibi, M. P. *Aldrichim. Acta* **1999**, *32*, 93. This chiral auxiliary is now available commercially from Aldrich Chemical Co.

(18) For synthesis of the racemic compound, see ref 3b.

(19) Other lanthanide Lewis acids ($La(OTf)_3$, $Gd(OTf)_3$, $Pr(OTf)_3$, $Tb(OTf)_3$, $Eu(OTf)_3$) were also evaluated, but they showed inferior selectivity.

(20) Reaction of benzylic radicals has been noted in the literature. See: Bury, A.; Cooksey, C. J.; Funabiki, T.; Gupta, B. D.; Johnson, M. D. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1050.

Table 2. Benzylic Radical Conjugate Addition to 10 Initiated by Et_3B



13 R = R^1 = $C_6H_5CH_2$
14 R = R^2 = 3-OMe-$C_6H_4CH_2$
15 R = R^3 = 3,4-$(OMe)_2$-$C_6H_3CH_2$
16 R = R^4 = 3-OMe-4-OBn-$C_6H_3CH_2$

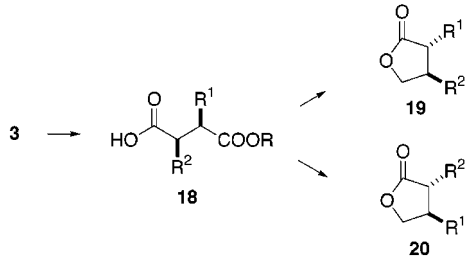
entry[a]	RX/(equiv)	Bu_3SnH (equiv)	Et_3B (equiv)	time (h)	**10**/product/**17**[b]	product/yield[c](%)	yield[c] of **17** (%)
1	R^1Br/10.0	6.0[d]	3.0[d]	3	1:6:2		
2	R^2Br/10.0	5.0	2.0	3	2:2:1		
3	R^2Br/10.0	5.0	2.0[d]	3	2:3:1		
4	R^2I/10.0	5.0	2.0[d]	3	6:3:1		
5	R^2Br/10.0[d]	6.0[d]	3.0[d]	3	1:6:3	**14**/50	27
6[e]	R^2Br/10.0[d]	6.0[d]	3.0[d]	3	0:3.5:1	**14**/71	19
7	R^3Br/10.0	6.0[d]	3.0[d]	2	0:4.6:1		
8	R^3Br/8.0	6.0[d]	3.0[d]	2	0.1:4:1	**15**/74	17
9[f]	R^3Br/8.0	6.0[d]	3.0[d]	2	0:5.3:1	**15**/80	12
10	R^4Br/10.0	6.0[d]	3.0[d]	2	0:8:1	**16**/84	<10

[a] 0.2 mmol scale reaction unless otherwise noted. [b] Product ratios were determined by ^{1}H 500 MHz NMR of the crude reaction mixture. [c] Isolated yield. [d] Three-time addition of the reagent. [e] 2.6 mmol scale reaction. [f] 4.52 mmol scale reaction.

addition of benzyl radical to **10** using 9-BBN as an initiator (1 equiv of $Sm(OTf)_3$, −78 °C, CH_2Cl_2/THF (4:1), 10 equiv of benzyl bromide, 2 equiv of 9-BBN (0.5 M in THF), and 5 equiv of Bu_3SnH) provided the desired product **13** with reaction going to completion. Similar results were obtained from the substituted benzylic radicals furnishing products **14**−**16**. The regio- and diastereoselectivity in the benzylic radical additions were similar irrespective of the initiator (Et_3B or 9-BBN) used for the reaction. But the reactions with 9-BBN were difficult to control; sometimes reactions were very messy and the byproducts were hard to separate.

Generally, the benzyl radicals are stable and undergo reduction (hydrogen atom transfer) rather than intermolecular addition to simple esters or amides. The reasons for the successful formation of benzylic radical conjugate addition products are 2-fold. Compound **10** is a highly activated substrate by the presence of the two electron poor functional groups, an imide and an ester. The reactivity of the substrate is further enhanced by chelation of the Lewis acid to the imide. Additionally, the nucleophilic character of the benzylic radical complements the electrophilicity of the fumarate **10**. The preferential chelation of the Lewis acid to the imide functionality in **10** and the reaction proceeding through an s-cis conformer of the side chain accounts for the observed high regio- and diastereoselectivity in the formation of **14**−**16**. The preparation of benzyl copper or Grignards are often problematic owing to their relative instability and formation of dimeric compounds, and this in turn complicates their use in conjugate addition to activated enoates.[22] Thus, the present methodology using radical intermediates offers practical advantage in that one only requires the readily available benzylic bromides as starting materials.

Scheme 2



We have been interested in developing efficient and general methods for the preparation of lignan natural products with the caveat that a common precursor provides access to several targets (Scheme 2). A 2,3-disubstituted monosuccinate unit (structure **18**, Scheme 2) functions as one such intermediate that on selective functional group manipulations furnishes the target lignans.

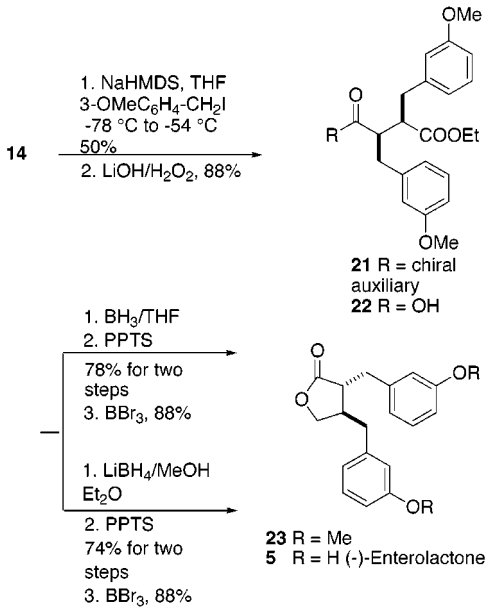
Having achieved the successful introduction of the remote benzyl substituent, we turned our attention to the introduction of the second benzylic group by an ionic process en route to the target natural products (Scheme 3). This was accomplished using the standard Evans protocol (base, −78 °C, alkylating agent).[23] Thus, treatment of **14** with 1.1 equiv of NaHMDS at −78 °C for 1.25 h followed by addition of 3-methoxybenzyl bromide gave the alkylated product **21** in moderate yield (<40%) and excellent diastereoselectivity. Improvement in chemical yield could be achieved by using the corresponding benzyl iodide as the alkylating agent (50%). The stereochemistry in the alkylation step is controlled by the chiral auxiliary resulting in the formation of the syn product (vide infra). The auxiliary could be cleaved readily using $LiOH/H_2O_2$/

(21) Perchyonok, V. T.; Schiesser, C. H. *Tetrahedron Lett.* **1998**, *39*, 5437.

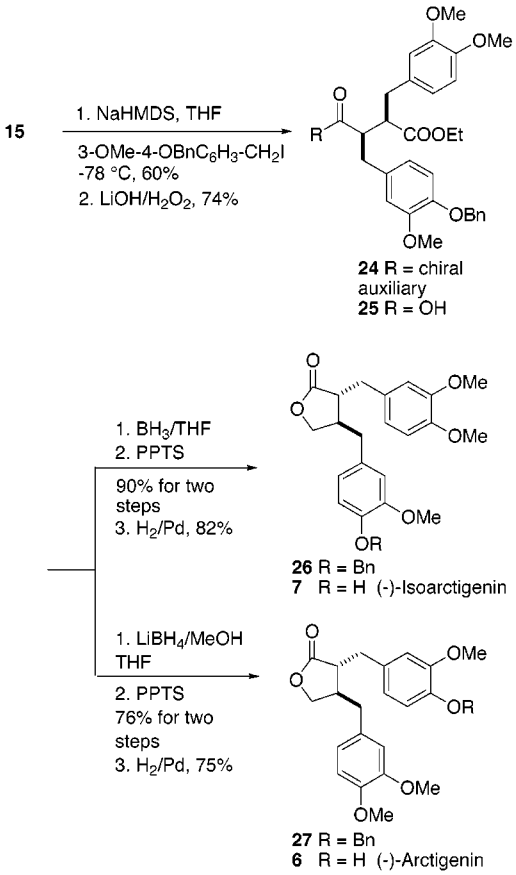
(22) For the preparation and reactions of benzyl organometallics, see: (a) Bernardon, C. J. *Organomet. Chem.* **1989**, *367*, 11. (b) van Heerden, P. S.; Bezuidenhoudt, B. C. B.; Steenkamp, J. A. *Tetrahedron Lett.* **1992**, *33*, 2383. (c) van Heerden, P. S.; Bezuidenhoudt, B. C. B.; Ferreira, D. *Tetrahedron* **1996**, *52*, 12313. (d) van Hereden, P. S.; Bezuidenhoudt, B. C. B.; Ferreira, D. *Tetrahedron Lett.* **1997**, *38*, 1821. (e) Jubert, C.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 5425. (f) For a recent discussion on benzyl organometallics, see: Kim, S.-H.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 2322.

(23) For selective alkylation of a similar C-4 unit, see: (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215. (c) Evans, D. A.; Bilodeau, M. T.; Somers, T. C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, *56*, 5750. (d) Oppolzer, W.; Cintas-Moreno, P.; Tamura, O. Cardinaux, F. *Helv. Chim. Acta* **1993**, *76*, 187.

Scheme 3



Scheme 4



THF in excellent yield providing the key intermediate **22**. The chiral auxiliary was recovered in >95% yield.

Two complimentary sequences were carried out to convert **22** to the target enterolactone. Selective reduction of the carboxyl group in **22** using borane gave the ester alcohol, which was cyclized using PPTS to furnish the lactone **23** in 78% yield over two steps. The spectral and analytical characteristics of lactone **23** were identical to that reported in the literature [$[\alpha]^{25}_D$ −38.8 (*c* 1.06, $CHCl_3$) for **23**; literature value: −39.2 (*c* 0.78, $CHCl_3$)].[8h] Demethylation of **23** using borontribromide provided (−)-enterolactone **5** in 88% yield. The overall yield for the natural product was 21% over six steps. We have exploited the inherent C_2 symmetry in the precursor molecule and carried out an alternate sequence of steps for the preparation of the lactone precursor **23**. Chemoselective reduction of the ester group in **22** using $LiBH_4$/MeOH in ether gave an alcohol that was lactonized using PPTS to provide **23**. The combined yield for the two steps was 74%. Boron tribromide mediated demethylation[8h] furnished the (−)-enterolactone **5** in excellent yield. The overall yield for **5** was 20%, which was similar to the sequence using borane reduction.

Compound **18** serves as a common intermediate for the synthesis of two different natural products depending on which of the two-carboxyl groups is selectively reduced. The preparation of isoarctigenin followed a similar reaction sequence as described above except for the final debenzylation reaction (Scheme 4). Thus, **15** was converted to disubstituted monosuccinate **25** in good chemical yield as a single diastereomer. Conversion of **25** to **26** involved selective carboxyl reduction followed by lactonization. Debenzylation under reductive conditions furnished (−)-isoarctigenin (**7**), whose spectral and analytical characteristics were identical to those reported in the literature.[10a,b] The overall yield for isoarctigenin was 26%. The synthesis of (−)-arctigenin (**6**) was achieved by the selective reduction of the ester functionality in **25** using $LiBH_4$/MeOH in THF followed by lactonization and debenzylation (20% overall) [$[\alpha]^{25}_D$ −28.9 (*c* 0.71, MeOH) for **6**; literature value −27.5 (*c* 4.5, MeOH)].[9a] Thus, a common precursor **25** provides access to two different natural products in a simple way. Compound **16** was converted to (−)-arctigenin (**6**) in overall higher chemical efficiency (24% overall) by alkylation with 3,4-dimethoxybenzyl iodide (64%) followed by hydrolysis (74%), borane reduction and lactonization (76% over two steps), and debenzylation (78%).

The synthesis of nephrosteranic and roccellaric acids required the addition of methyl radical to **10** followed by syn selective aldol reaction at the α-methylene to the chiral auxiliary carbonyl. Addition of methyl radical to **10** using methyl iodide and tributyl tin hydride gave mostly the starting material.[24] The successful installation of the methyl group was achieved in two steps (Scheme 5). Addition of chloromethyl radical to **10** ($ClCH_2I$/Bu_3SnH) in the presence of samarium triflate gave **28** as a single regio- and diastereomer in 91% chemical yield. Surprisingly, use of erbium triflate led to product with lower diastereoselectivity (10:1). Reduction of the chlorine substituent in **28** using freshly distilled Bu_3SnH gave **29**.[25] We have recently shown that differentially protected succinates undergo aldol reactions in a highly regio- and stereoselective manner.[26] Treatment of **29** with dibutylboron triflate and triethylamine[27] followed by quenching of the boron enolate with lauraldehyde and myristylaldehyde gave the lactones **30** and **31**, respectively. Both aldol reactions were >98% syn selective as evidenced by

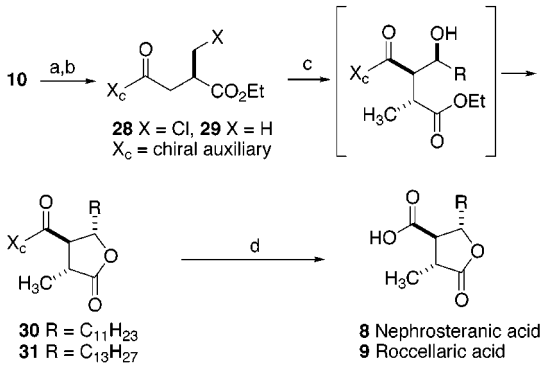
(24) A minor amount of ethyl radical addition (from triethylborane) was also observed.

(25) Aged tributyltin hydride led to some epimerization.

(26) Sibi, M. P.; Deshpande, P. K.; La Loggia, A. J. *Synlett* **1996**, 343.

(27) (a) Gage, J. R.; Evans, D. A. *Org. Synthesis* **1989**, *68*, 83. (b) Boger, D. L.; Colletti, S. L.; Honda, T.; Menezes, R. F. *J. Am. Chem. Soc.* **1994**, *116*, 5607.

Scheme 5[a]



[a] Key: (a) $Sm(OTf)_3$, $ClCH_2I$, Bu_3SnH, Et_3B/O_2, CH_2Cl_2/THF, 1 h, −78 °C, 91% (>100:1); (b) Bu_3SnH, AlBN, toluene, reflux, 12 h, 76%; (c) Bu_2BOTf, CH_2Cl_2, Et_3N, −78 to 0 °C, RCHO, 12 h, 84% for **30** and 65% for **31**; (d) LiOH, H_2O_2, THF/H_2O, rt, 92% for **8** and 94% for **9**.

crude NMR analysis. Selective removal of the chiral auxiliary from **30** gave nephrosteranic acid (**8**) in 92% yield, and a similar sequence starting with **31** gave roccellaric acid (**9**) in 94% yield.[28] The overall yield for nephrosteranic and roccellaric acid was 53% and 42%, respectively, over four synthetic steps from **10**.

Conclusions

In conclusion, we have described a highly regio- and stereoselective method for the addition of radicals to a desymmetrized fumarate. We have developed a novel methodology for the synthesis of lignan natural products from a common intermediate. The application of the addition methodology in the efficient total synthesis of paraconic acid natural products nephrosteranic and roccellaric acids has also been demonstrated. The present methodology alleviates some of the problems encountered in our alternate approach to these natural products.[29] Extension of the methodology to enantioselective radical additions, the synthesis of more complex natural products, and development of tandem addition protocols are underway in our laboratory.

Experimental Section

(4*R*)-4-(Diphenylmethyl)-3-[(3*R*)-3-(ethoxycarbonyl)-4-(3′-methoxyphenyl)]butanoyl-2-oxazolidinone (14). To a solution of chiral fumarate ester **10** (0.985 g, 2.6 mmol), $Sm(OTf)_3$ (1.55 g, 2.6 mmol), CH_2Cl_2 (60 mL), and THF (15 mL) at −78 °C under N_2 were added 3-methoxybenzyl bromide (1.82 mL, 13.0 mmol) and Bu_3SnH (2.08 mL, 7.8 mmol). Et_3B (1.0 M in hexane, 3.9 mL, 3.9 mmol) was then added. O_2 (20 mL) was added by syringe. After the mixture was stirred at −78 °C for 40 min, 3-methoxybenzyl bromide (0.91 mL, 6.5 mmol), Bu_3SnH (1.04 mL, 3.9 mmol), and Et_3B (1.0 M in hexane, 1.95 mL, 1.95 mmol) were added sequentially. O_2 (10 mL) was added by syringe. After another 40 min, 3-methoxybenzyl bromide (0.91 mL, 6.5 mmol), Bu_3SnH (1.04 mL, 3.9 mmol), and Et_3B (1.0 M in hexane, 1.95 mL, 1.95 mmol) were added sequentially. O_2 (10 mL) was added by syringe. The reaction mixture was stirred for 1 h and 40 min at −78 °C before dilution with Et_2O (300 mL). The mixture was washed with 2 M HCl (2 × 50 mL) and brine (2 × 50 mL). Silica gel 60 (230−400 mesh, 50 mL) was added. The solvent was removed under reduced pressure. The silica gel together with the compounds were loaded onto a fritted-filter funnel and washed with hexanes (700 mL) (to remove nonpolar tin). The receiving flask was changed, and the silica gel was washed with Et_2O (700 mL). The filtrate was then concentrated to provide the crude product. Flash column chromatography (20:80 ethyl acetate/hexanes as eluent) followed by crystallization (from ethyl acetate/hexanes) provided **14** (0.93 g, 71%): colorless solid; R_f 0.77 (50:50 ethyl acetate/hexanes); mp 120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, J = 7.0 Hz, 3H), 2.69 (dd, J = 13.3, 8.1 Hz, 1H), 2.79 (dd, J = 18.5, 3.6 Hz, 1H), 2.96−3.12 (m, 2H), 3.35 (dd, J = 18.5, 9.7 Hz, 1H), 3.82 (s, 3H), 4.10 (q, J = 7.0 Hz, 2H), 4.33−4.45 (m, 2H), 4.62 (d, J = 6.0 Hz, 1H), 5.26 (m, 1H), 6.73−6.82 (m, 3H), 7.03−7.09 (m, 4H), 7.22−7.29 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 171.5, 159.9, 153.5, 140.2, 139.6, 138.1, 129.7, 129.4, 129.1, 128.8, 128.6, 128.1, 127.3, 121.7, 114.7, 112.5, 65.6, 61.0, 56.6, 55.5, 51.2, 42.5, 38.1, 37.1, 14.4; $[\alpha]^{25}_D$ −79.3 (*c* 0.42, $CHCl_3$). Anal. Calcd for $C_{30}H_{31}NO_6$: C, 71.84; H, 6.23; N, 2.79. Found: C, 71.51; H, 6.24; N, 2.78.

(*R*)-4-(Diphenylmethyl)-3-[(2*R*,3*R*)-2-(3′-methoxyphenyl)methyl-3-(ethoxycarbonyl)-4-(3′-methoxyphenyl)]butanoyl-2-oxazolidinone (21). To a rapidly stirred mixture of **14** (0.47 g, 0.94 mmol) and THF (25 mL) at −78 °C was added NaHMDS (1.0 M in THF, 1.03 mL, 1.03 mmol) dropwise. The mixture was stirred at −78 °C for 1 h and 15 min. A solution of 3-methoxybenzyl iodide (0.373 g, 1.5 mmol) in THF (5 mL) was added dropwise. The reaction mixture was then warmed to −54 °C and stirred at this temperature for 26 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with Et_2O (3 × 60 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated. Flash column chromatography (15:85 ethyl acetate/hexanes) provided **21** (0.292 g, 50%): colorless amorphous solid; R_f 0.83 (50:50 ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (t, J = 7.3 Hz, 3H), 2.84−3.05 (m, 5H), 3.76 (s, 3H), 3.79 (s, 3H), 4.07−4.12 (m, 2H), 4.32−4.37 (m, 2H), 4.49−4.54 (m, 2H), 5.15 (m, 1H), 6.62−6.68 (m, 4H), 6.75 (dd, J = 8.4, 1.7 Hz, 1H), 6.82 (dd, J = 8.3, 1.7 Hz, 1H), 6.91 (m, 2H), 7.04 (d, J = 7.4 Hz, 2H), 7.15−7.32 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 173.9, 160.1, 159.8, 153.2, 140.7, 140.5, 140.0, 138.2, 129.8, 129.6, 129.5, 129.0, 128.6, 128.0, 127.3, 122.3, 121.7, 114.9, 114.7, 113.1, 112.4, 64.8, 61.0, 56.8, 55.4, 55.3, 50.8, 48.1, 46.1, 36.2, 35.7, 14.4; $[\alpha]^{25}_D$ −127.3 (*c* 2.63, $CHCl_3$). Anal. Calcd for $C_{38}H_{39}NO_7$: C, 73.41; H, 6.32; N, 2.25. Found: C, 73.69; H, 6.46; N, 2.18.

(2*R*,3*R*)-2,3-Bis-(3′-methoxybenzyl)succinic Acid 4-Ethyl Ester (22). To a rapidly stirred solution of **21** (0.387 g, 0.62 mmol), THF (4.5 mL), and H_2O (1.5 mL) at 0 °C was added a solution of $LiOH·H_2O$ (0.039 g, 0.93 mmol) in H_2O (0.85 mL) dropwise. After 2 min, H_2O_2 (30%, 0.255 mL, 2.48 mmol) was added. The mixture was stirred at 0 °C for 3 h, and aqueous Na_2SO_3 (10%, 5 mL) was then added. After the mixture was stirred at 0 °C for 10 min, THF was removed on a rotary evaporator (<35 °C). HCl (5 M) was used to achieve pH = 6. The mixture was made basic again using aqueous NaOH (2 M) to pH = 8−9. The organic layer was extracted with CH_2Cl_2 (60 mL). The organic layer was washed using aqueous NaOH (0.5 M, 2 × 20 mL) followed by brine, dried over $MgSO_4$, and concentrated to provided chiral auxiliary (0.15 g, 97%). The basic aqueous layers were combined and made acidic by HCl (5 M) to pH = 2−3. The organic compound was extracted with CH_2Cl_2 (3 × 50 mL) (each time of extraction, keep the pH = 2−3). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated. Flash column chromatography (40:60 ethyl acetate/hexanes as eluent) provided the acid **22** (0.21 g, 88%): colorless liquid; R_f 0.25 (50:50 ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (t, J = 7.0 Hz, 3H), 2.92−3.00 (m, 4H), 3.04−3.09 (m, 2H), 3.74 (s, 6H), 4.09 (q, J = 7.1 Hz, 2H), 6.61 (s, 2H), 6.67 (d, J = 7.3 Hz, 2H), 6.73−6.76 (m, 2H), 7.14−7.18 (m, 2H); acidic proton in baseline; ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.5, 173.5, 159.8, 159.8, 140.3, 140.1, 129.7, 129.6, 121.7, 121.6, 114.6, 114.6, 112.4, 112.4, 61.1, 55.3, 55.3, 47.4, 47.4, 35.8, 35.5, 14.3;

(28) The chiral auxiliary was recovered in 99% yield.

(29) Reference 26. The installation of the C-3 methyl group by enolate alkylation of the butyrolactone proceeds in low yields and is possible only with the carboxylic acid as the C-4 substituent.

$[\alpha]^{25}_D$ −41.6 (*c* 3.20, $CHCl_3$); HRMS (FAB$^+$) calcd for $C_{22}H_{26}O_6$ $(M + H)^+$ 387.1808, found 387.1800.

(3*R*,4*R*)-3,4-Bis[(3-methoxyphenyl)methyl]dihydro-2-(3*H*)-furanone (23). BH_3 reduction: To a rapidly stirred solution of acid **22** (173 mg, 0.447 mmol) and THF (15 mL) at −15 °C was added BH_3·THF (1.0 M, 0.67 mL, 0.67 mmol) slowly. After the mixture was stirred at this temperature for 18 h, MeOH (1 mL) was added dropwise to quench the reaction. The solvents were removed under reduced pressure. HCl (0.5 M, 5 mL) was added. The organic compound was extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated.

To the residue were added benzene (7 mL) and PTSA (2 mg). The reaction mixture was heated to reflux for 4 h and then cooled to room temperature. EtOAc was added. The mixture was sequentially washed with saturated aqueous $NaHCO_3$ (5 mL), water, and brine, dried over $MgSO_4$, and concentrated. Flash column chromatography (20:80 ethyl acetate/hexanes as eluent) provided **23** (100 mg, 78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43−2.62 (m, 4H), 2.90 (dd, J = 14.0, 7.2 Hz, 1H), 3.05 (dd, J = 14.0, 5.1 Hz, 1H), 3.76 (s, 3H), 3.77 (s, 3H), 3.83 (dd, J = 9.0, 7.3 Hz, 1H), 4.09 (dd, J = 9.0, 7.5 Hz, 1H), 6.53 (s, 1H), 6.59 (d, J = 7.6 Hz, 1H), 6.73−6.79 (m, 4H), 7.15−7.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 159.9, 159.9, 139.6, 139.4, 129.8, 129.7, 121.7, 121.0, 114.9, 114.6, 112.4, 111.9, 71.3, 55.2, 55.2, 46.4, 41.3, 38.6, 35.2; $[\alpha]^{25}_D$ −38.8 (*c* 1.06, $CHCl_3$) [lit.[8h] $[\alpha]^{23}_D$ −39.2 (*c* 0.78, $CHCl_3$)].

$LiBH_4$ reduction: To a rapidly stirred solution of **22** (200 mg, 0.52 mmol) in Et_2O (15 mL) were added $LiBH_4$ (2.0 M, 0.52 mL, 1.04 mmol) and dry MeOH (44 μL, 1.04 mmol) dropwise. After being stirred at room temperature for 24 h, the reaction mixture was cooled to 0 °C. HCl (2 M, 5 mL) was added. The mixture was extracted using EtOAc. The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated. Same lactonization procedure as BH_3 reduction provided 23 (126 mg, 74%).

(3*R*,4*R*)-3,4-Bis[(3-hydroxyphenyl)methyl]dihydro-2-(3*H*)-furanone (5). (−)-Enterolactone. Literature procedure as described in ref 8h was used for the synthesis of **5**: yield 88%; colorless solid; ^{1}H NMR (300 MHz, acetone-d_6) δ 2.46−3.00 (m, 6H), 3.06 (s, 1H), 3.85−4.06 (m, 2H), 6.59−6.78 (m, 6H), 7.06−7.16 (m, 2H), 8.29 (s, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 178.1, 157.6, 157.6, 140.5, 140.0, 129.7, 129.6, 120.7, 119.9, 116.3, 115.7, 113.7, 113.5, 70.8, 46.0, 41.3, 37.8, 34.5; $[\alpha]^{25}_D$ −38.3 (*c* 0.29, $CHCl_3$) [lit.[8h] $[\alpha]^{23}_D$ −38.4 (*c* 0.25, $CHCl_3$)].

(3*R*,4*R*)-3-[(3,4-Dimethoxyphenyl)methyl]-4-[(3-methoxy-4-hydroxyphenyl)methyl]dihydro-2(3*H*)-furanone-(7): (−)-Isoarctigenin. A H_2 balloon was placed over a rapidly stirred solution of **26** (0.069 g, 0.15 mmol), EtOAc (7 mL), AcOH (0.7 mL), and Pd/C (10%, 38 mg, 20 mol %). The reaction mixture was stirred under H_2 for 1.5 h. The reaction was quenched by the addition of EtOAc (15 mL) and H_2O (15 mL). The organic layer was separated, sequentially washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried over $MgSO_4$, and concentrated. Flash column chromatography (40:60 ethyl acetate/hexanes as eluent) provided **7** (0.046 g, 82%): colorless amorphous solid; R_f 0.28 (50:50 ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43−2.52 (m, 2H), 2.55−2.62 (m, 2H), 2.87−2.98 (m, 2H), 3.80 (s, 3H), 3.82 (s, 3H), 3.85−3.89 (m, 4H), 4.10−4.14 (m, 1H), 5.56 (broad, 1H), 6.42 (d, J = 1.3 Hz, 1H), 6.50−6.52 (m, 1H), 6.64−6.65 (m, 2H), 6.74−6.81 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 149.3, 148.1, 146.8, 144.6, 130.5, 130.0, 121.6, 121.5, 114.7, 112.6, 111.3, 111.2, 71.5, 56.1, 56.1, 56.0, 46.7, 41.3, 38.5, 34.7; $[\alpha]^{25}_D$ −27.6 (*c* 0.87, $CHCl_3$).

(3*R*,4*R*)-3-[(3-Methoxy-4-hydroxyphenyl)methyl]-4-[(3,4-dimethoxyphenyl)methyl]dihydro-2(3*H*)-furanone (6): (−)-Arctigenin. A procedure described for the preparation of **7** was used to prepare **6** from **27**: yield 75%; colorless amorphous solid; R_f 0.27 (50:50 ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.44−2.65 (m, 4H), 2.87−2.96 (m, 2H), 3.81 (s, 6H), 3.84 (s, 3H), 3.86−3.89 (m, 1H), 4.11−4.15 (m, 1H), 5.56 (broad, 1H), 6.46 (d, J = 1.7 Hz, 1H), 6.54 (dd, J = 8.1, 2.0 Hz, 1H), 6.60 (dd, J = 7.7, 1.7 Hz, 1H), 6.63 (d, J = 2.0 Hz, 1H), 6.74 (d, J = 8.1 Hz, 1H), 6.82 (d, J = 8.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 149.2, 148.1, 146.9, 144.8, 130.7, 129.7, 122.3, 120.8, 114.3, 112.0, 111.7, 111.5, 71.5, 56.1, 56.1, 56.0, 46.8, 41.1, 38.4, 34.7; $[\alpha]^{25}_D$ −28.9 (*c* 0.71, MeOH) [lit.[30] −27.5 (*c* 4.5, MeOH)].

(3*R*,4*R*,5*S*,4′*R*)-4-[Carboxyl-(4-diphenylmethyl-2-oxazolidin-3-onyl)]-3-methyl-5-undecyl-4,5-dihydro-2(3*H*)-furanone (30). To **29** (395.5 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was added Bu_2BOTf (freshly prepared, 1 M in CH_2Cl_2, 1.2 mL, 1.2 mmol) at 0 °C, followed by Et_3N (0.2 mL, 1.4 mmol). The yellow solution was stirred at 0 °C for 1 h. It was then cooled to −78 °C, and lauraldehyde (freshly distilled, 221 mg, 1.2 mmol, in 5 mL of CH_2Cl_2) was added over 10 min. The reaction was then gradually warmed to −10 °C and stirred at that temperature for 10 h. The reaction was quenched with MeOH−H_2O_2 (30%, 3:1, 4 mL). The mixture was then extracted with EtOAc (3 × 15 mL). The extracts were washed with brine (until pH = 7), dried over $MgSO_4$, and concentrated. Flash column chromatography (1:10 ethyl acetate/hexanes as eluent) purification provided **30** (450 mg, 84%): oil; R_f 0.55 (10:90 ethyl acetate/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 6.7 Hz, 3H), 1.05 (d, J = 7.2 Hz, 3H), 1.22−1.70 (m, 20H), 2.44 (dq, J = 10.2, 7.3 Hz, 1H), 4.20 (dd, J = 10.2, 8.6 Hz, 1H), 4.38 (m, 2H), 4.53 (dt, J = 8.6, 3.8 Hz, 1H), 4.64 (d, J = 7.5 Hz, 1H), 5.39 (dt, J = 7.2, 3.2 Hz, 1H), 7.15−7.38 (m, 10H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 176.9, 171.5, 153.2, 139.0, 137.9, 129.4, 129.0, 128.8, 128.6, 128.2, 127.6, 80.3, 65.8, 57.0, 52.1, 42.1, 34.9, 32.0, 29.7, 29.6, 29.5, 29.4, 29.3, 25.5, 22.8, 14.6, 14.2; $[\alpha]^{26}_D$ −68.3 (*c* 1.85, CH_2Cl_2). Anal. Calcd for $C_{33}H_{43}NO_5$: C, 74.26; H, 8.12; N, 2.62. Found: C, 74.03; H, 8.11; N, 2.24.

(3*R*,4*R*,5*S*,4′*R*)-4-[Carboxyl-(4-diphenylmethyl-2-oxazolidin-3-oyl)]-3-methyl-5-tridecyl-4,5-dihydro-2(3*H*)-furanone (31). A procedure similar to that for the preparation of **30** was used to prepare **31** from **29** and myristylaldehyde: yield 65%; oil; R_f 0.55 (10:90 ethyl acetate/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 6.7 Hz, 3H), 1.05 (d, J = 7.2 Hz, 3H), 1.22−1.70 (m, 24H), 2.43 (dq, J = 10.2, 7.2 Hz, 1H), 4.20 (dd, J = 10.2, 8.3 Hz, 1H), 4.39 (m, 2H), 4.53 (dt, J = 8.3, 4.6 Hz, 1H), 4.64 (d, J = 7.5 Hz, 1H), 5.39 (dt, J = 7.0, 3.8 Hz, 1H), 7.15−7.38 (m, 10H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 176.9, 171.4, 153.2, 139.0, 137.9, 129.4, 129.0, 128.8, 128.6, 128.2, 127.6, 80.4, 65.8, 57.0, 52.1, 51.1, 42.1, 34.9, 32.0, 29.8, 29.7, 29.7, 29.6, 29.5, 29.5, 29.3, 25.5, 22.8, 14.6, 14.2; $[\alpha]^{26}_D$ −53.3 (*c* 1.82, CH_2Cl_2). Anal. Calcd for $C_{35}H_{47}NO_5$: C, 74.83; H, 8.43; N, 2.49. Found: C, 74.54; H, 8.52; N, 2.41.

(3*R*,4*R*,5*S*)-4-Carboxy-3-Methyl-5-undecyl-4,5-dihydro-2(3*H*)-furanone (8): (−)-Nephrosteranic Acid. To a solution of **30** (320 mg, 0.6 mmol) in THF (4 mL) and H_2O (1 mL) were added H_2O_2 (30%) (0.27 mL, 2.4 mmol) and LiOH·H_2O (37 mg, 0.9 mmol) at 0 °C. The reaction was stirred for 1 h at 0 °C. The reaction was monitored by TLC. After completion, excess H_2O_2 was quenched with NaS_2O_3 solution (10%). Most of the THF was removed under reduced pressure at room temperature. The residue (pH = 12) was then extracted with EtOAc (3 × 10 mL) (recovery of chiral auxiliary, 150 mg, 99%). The aqueous solution was then acidified with HCl (10%) (until pH = 1) and extracted with EtOAc (5 × 10 mL). The extracts were washed with brine (2 × 5 mL), dried over $MgSO_4$, and concentrated. The white solid was recrystallized (from hexanes) to provide **8** (155 mg, 92%): mp 105−107 °C [lit.[11a] mp: 96−98 °C ((+)-**8**)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, J = 6.3 Hz, 3H), 1.24 (m, 17H), 1.36 (d, J = 7.1 Hz, 3H), 1.40 (m, 1H), 1.65−1.85 (m, 2H), 2.68 (dd, J = 11.3 Hz, 9.4, 1H), 2.96 (dq, J = 11.6, 7.0 Hz, 1H), 4.47 (dt, J = 9.1, 4.0 Hz, 1H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 177.2, 176.8, 79.4, 53.8, 39.6, 34.7, 31.7, 29.4, 29.5, 29.1, 29.1, 29.0, 25.1, 22.4, 14.2, 13.8; $[\alpha]^{26}_D$ −28.1 (*c* 1.02, $CHCl_3$) [lit.[11a] $[\alpha]^{26}_D$: +27.2 (*c* 1.45, $CHCl_3$) ((+)-**8**)].

(3*R*,4*R*,5*S*)-4-Carboxy-3-methyl-5-tridecyl-4,5-dihydro-2(3*H*)-furanone (9): (−)-Roccellaric Acid. A procedure

(30) Rahman, M. M. A.; Dewick, P. M.; Jackson, D. E.; Lucas, J. A. *Phytochemistry* **1990**, *29*, 1971.

described for the preparation of **8** from **30** was used to prepare **9** from **31**: Yield: 94%; mp 110−111 °C (lit.[12a] mp 108 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 6.4 Hz, 3H), 1.36 (d, J = 6.9 Hz, 3H), 1.25 (m, 21H), 1.50 (m, 1H), 1.70 (m, 1H), 1.80 (m, 1H), 2.69 (dd, J = 11.4, 9.4 Hz, 1H), 2.96 (dq, J = 11.8, 7.0 Hz, 1H), 4.46 (dt, J = 9.1, 4.3 Hz, 1H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 176.7, 176.2, 79.4, 54.0, 39.9, 35.0, 32.0, 29.8, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 25.4, 22.8, 14.6, 14.2; $[\alpha]^{26}_D$ −26.3 (*c* 1.24, $CHCl_3$) [lit.[12a] $[\alpha]^{26}_D$ −26 (*c* 1.93, $CHCl_3$)].

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Supporting Information Available: General experimental details, procedures for the preparation of **10**, **11**, **13**, **15**−**17**, and **24**−**29** and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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