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Synthesis of a Peroxime Proliferator Activated Receptor (PPAR) α/γ Agonist via Stereocontrolled Williamson Ether Synthesis and Stereospecific S_N2 Reaction of *S*-2-Chloro Propionic Acid with Phenoxides

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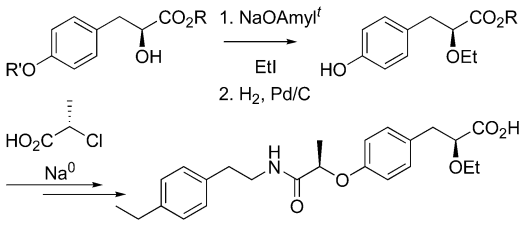
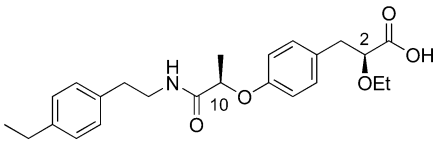


The stereospecific synthesis of the PPAR α/γ agonist **1** was accomplished via ethylation of the optically pure trihydroxy derivative **6**, itself derived via an enzymatic resolution. The ethylation can be accomplished without epimerization only under strict control of the reaction conditions and the choice of base (sodium *tert*-amylate), temperature (−30 °C), order of addition, and solvent (DMF). The key diastereospecific S_N2 reaction of the phenol **4** with *S*-2-chloropropionic acid is best achieved via the sodium phenoxide of **4** derived from Na^0 as the reagent of choice. The structure elucidation and key purification protocols to achieve pharmaceutical purity will also be described

Introduction

Non-insulin-dependent diabetes mellitus (type 2 diabetes) is a serious disease that affects tens of millions of people in the developed world. It is estimated that 120 million people worldwide suffer from this condition that can affect the eyes, kidneys, and periferal nervous system. In addition to the hyperglycemia that characterizes the disease, there is frequently dyslipidemia associated with this condition, which accelerates coronary arteriosclerosis and is thus linked to increased mortality of these patients.[1] Recent reports have identified that selective agonists of a nuclear receptor family, the peroxime proliferator activated receptors (PPAR) α, γ, and δ, can concurrently normalize glucose levels and lower lipid levels, thus making such agonists attractive targets for the treatment of type 2 diabetes.[2] Significant attention has also been paid to *dual agonists* in an attempt to balance clinical benefits by the simultaneous activation of two of the above receptors.

In this paper, we would like to describe the total synthesis of **1**, the pharmacophore of our PPAR α/γ dual agonist that is potentially useful for the treatment of type 2 diabetes and dyslipidemia.[3]



1

The initial goal of our synthetic strategy aimed to install, stereospecifically, the two stereogenic centers, at C-2 and C-10, in a way that avoids resolution or chiral chromatography. Indeed initial syntheses of the molecule

(1) (a) Porte, D., Jr.; Schwartz, M. W. *Science* **1996**, *27*, 699. (b) Cobb, J.; Dukes, I. *Annu. Rep. Med. Chem*. **1998**, *33*, 213. (c) Goldberg I. J. *J. Clin. Endocrinol. Metab*. **2001**, *86*, 965 (d) Grag, A. *Am. J. Cardiol*. **1998**, *81*, 47 B.

(2) (a) Lehman, J. M.; Moore, L. B.; Smith-Oliver, T. A.; Wilkinson, W. O.; Willson, T. M.; Kliewer, S. A. *J. Biol. Chem.* **1995**, *270*, 12953. (b) Staels, B.; Dallongeville, J.; Auwerx, J.; Schoonjans, K.; Leitersdorf, E.; Fruchart, J.-C. *Circulation* **1998**, *41*, 5020. (c) Oliver, M. F.; Heady, J. A.; Morris, J. N.; Cooper, J. *Lancet* **1984**, *2*, 600.

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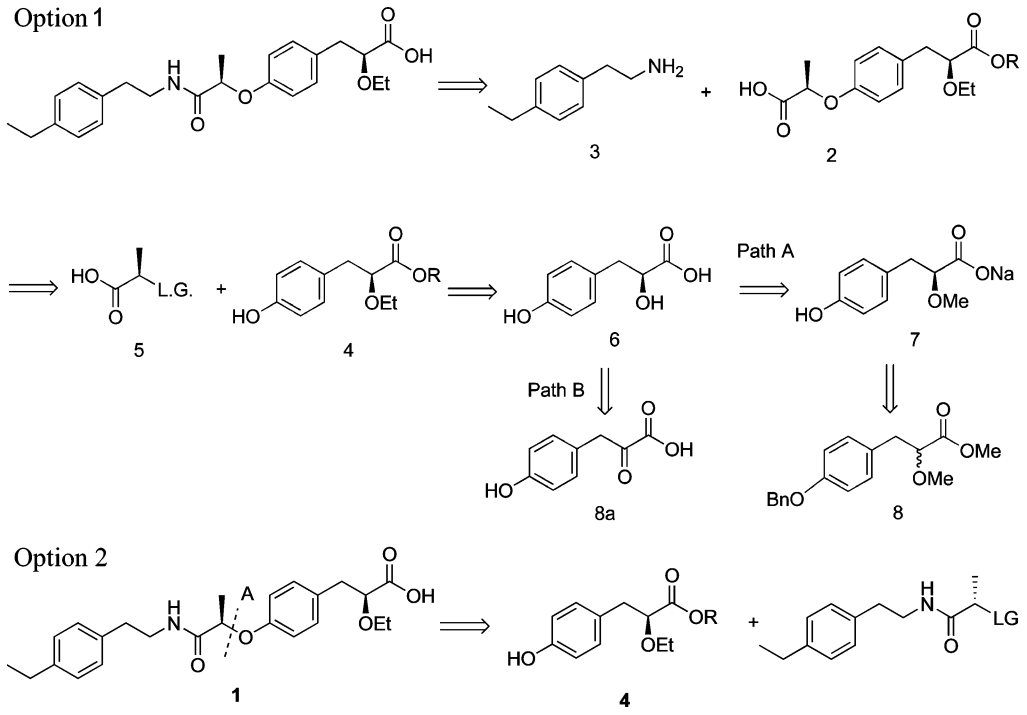
SCHEME 1. Retrosynthetic Options



relied on such techniques for the isolation of the desired 2-*R*,10-*S* diastereomer.[4]

In addition, it was necessary to develop a process that preserved the enantiomeric purity of the readily epimerizable stereogenic centers in subsequent reactions. Furthermore, convenient purification points had to be established to avoid chromatographic purifications that are inconsistent with large-scale synthesis. This latter task was not trivial because of the lipophilic nature of this molecule and the absence of heteroaromatic rings.[5] Herein we report the details of our synthetic and development work that succeeded in meeting all of the above goals.

Retrosynthetic Analysis. Two retrosynthetic strategies were considered for the synthesis of **1** (Scheme 1 options 1 and 2).

Disconnection of bond A (Scheme 1, option 2) would lead to a convergent approach to **1**; however, that would place the key transformation, setting the C-10 stereocenter, at the last step of the synthesis. Consequently, although on first principles convergent syntheses are sought, in our case the strategy shown in option 1 is more consistent with scale-up principles. For example, intermediate **2** could provide an excellent purification point especially if perfect stereocontrol could not be achieved in the earlier transformations. Consequently this stepwise approach was selected for the synthesis of **1** and is detailed below.

The key transform in this strategy (Scheme 1, option 1) involves a stereocontrolled displacement transformation to yield the activated lactic acid derivative **5** and the phenol **4**. The challenge to effect this transformation, in the synthetic direction, would lie in effecting complete control of the inversion or retention of the stereogenic center in **5** (eventually C-10) under conditions that do not induce epimerization of the chiral center in **4** (eventually C-2).

The coupling partner, **4**, could be derived from **7**, which was readily available in our laboratories via an enzymatic kinetic resolution of the racemic methyl ether, methyl ester **8**.[6]

An alternative approach to **6** could be also envisioned (option 1, path B) via an asymmetric reduction of the commercially available 4-hydroxyphenyl pyruvic acid derivative **8a**.

Despite the advantages derived from the availability of **7** in multikilo quantities, triggering the S-goal retrosynthetic approach described above,[7] considerable effort was expended in the implementation of this strategy. The problem lay in the fact that any base-mediated ethylation reaction, on the way to **4**, could potentially involve significant risk of epimerization at C-2.

In the next section we describe a variety of solutions that permit the use of **6**. Recently, and in order to

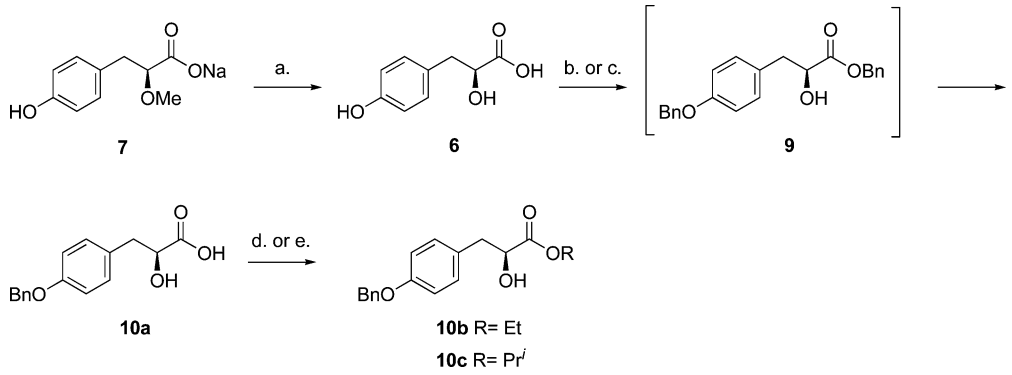
(3) A number of excellent reports for the action of PPAR agonists have recently appeared in the literature. Further details on the biological significance of these receptors can be found therein: (a) Haigh, D.; Birrell, H. C.; Cantello, B. C. C.; Eggleston, D. S.; Haltiwanger, R. C.; Hindley, R. M.; Ramaswamy, A.; Stevens, N. C. *Tetrahedron: Asymmetry* **1999**, *10*, 1353. (b) Liu, K. G.; Smith, J. S.; Ayscue, A. H.; Henke, B. R.; Lambert, M. H.; Leesnitzer, L. M.; Plunket, K. D.; Willson, T. M.; Sternbach, D. D. *Bioorg. Med. Chem. J*. **2001**, *11*, 2385. (c) Sauerberg, P.; Pettersson, I.; Jeppeses, L.; Bury, P. S.; Mogensen, J. P.; Wassermann, K.; Brand, C. L.; Sturis, J.; Woeldike, H. F.; Fleckner, J.; Andersen, A.-S. T.; Mortesen, S. B.; Svensson, L. A.; Rasmussen, H. B.; Lehmann, S. V.; Polivka, Z.; Sindelar, K.; Panajotova, V.; Ynddal, L.; Wulff. E. M. *J. Med. Chem*. **2002**, *45*, 789.

(4) Potlapally, R. K.; Siripragada, M. R.; Kotra, N. M.; Sirisilla, R.; Mamillapalli, R. S.; Gaddam, O. R. PTC WO 02/24625 A2, 2002.

(5) Initial attempts to identify suitable pharmaceutical and/or "technical" salts for **1**, **2c**, and **4a** met with limited success. Significant experimentation was required to crystallize the salts mentioned herein.

(6) Rizzo, J.; Zhang, T. Personal communication. Deusen, H.-J.; Zundel, M.; Valdois, M.; Lehmann, S. V.; Weil, V.; Hjort, C. M.; Ostergaard, P. R.; Marcussen, E.; Ebdrup, S. *Org. Process Res. Dev.* **2003**, *7*, 82.

SCHEME 2. Synthesis of Intermediate 10a−c[a]



[a] (a) (1) NaI (1.2 equiv), 12 M HCl, reflux; (2) filtration at ambient temperature. (b) (1) K_2CO_3, EtOH, reflux; (2) removal of EtOH then NaOH, H_2O; (3) acidification and filteration. (c) K_2CO_3, EtOH, H_2O for in situ conversion to **10a**. (d) EtOH, H_2S0_4 (cat.) for **10b**. (e) *i*PrOH, H_2S0_4 (cat.) for **10c**.

overcome the shortcomings of this synthetic strategy, a totally different approach to **4** was discovered and will be detailed elsewhere.[8]

Results and Discussion

Synthesis of Ethoxy Cinnamate Derivative 4. The intense interest in PPAR agonists and the presence of the α-alkoxy dihydrocinnamate pharmacophore in a number of these drug candidates have spurred significant research activity to discover an efficient and scaleable synthesis of these molecules. The need for convenient syntheses of these molecules is augmented by recent reports that these pharmacophores could be useful for the treatment of inflammatory disease.[9]

The initial focus on the synthesis of these α-*alkoxy* esters was centered on the preparation of α-*hydroxy* esters followed by alkylation, and so both enzymatic and chemical methods have been designed to give the phenol, monoprotected, C-2 hydroxy derivatives, e.g., **10b** or **10c**, with high enantiomeric excess.[10] These compounds can be prepared via chem-enzymatic methodology developed by Deng and co-workers, and a number of these derivatives have become commercially available.[11]

In our laboratories, the synthesis of **4** commenced from **7** (Scheme 2), which was in turn synthesized from **8** via a sequence developed in the Lilly Research Laboratories involving (a) an enzymatic hydrolysis of **rac-8**, (b) debenzylation via catalytic hydrogenation, and (c) hydrolysis and crystallization of the sodium salt to afford enantiomerically pure **7**. This key intermediate was added slowly to a solution of concentrated HCl in water, containing NaI, and the mixture was heated to 100 °C for 16 h. The product was easily obtained in 85−95% yield by filtration at ambient temperature. On a small scale, where heating times are short, significant frothing was observed, presumably due to rapid evolution of CH_3Cl/CH_3I. On a large scale this problem was easily avoided by controlling the rate of heating and ensuring rigorous stirring of the reaction mixture. On a 6 kg scale the results were reproducible; however, care was required in the isolation of **6** as the volume of solvent used for the wash of the crude crystals and the temperature during the wash needed to be controlled to minimize losses in the mother liquors.

It is noteworthy that even under these relatively harsh reaction conditions no epimerization was observed at C-2, as shown by chiral HPLC analysis of the product. It is indeed true, in all the cases we have investigated, that the C-2 center is not prone to epimerization under acidic conditions.

Selective protection of the phenol could be accomplished smoothly, in ca. 82% yield, by reacting **6** with benzyl chloride in ethanol in the presence of K_2CO_3 at reflux for ca. 24 h. The resulting bis-benzyl derivative **9** was not isolated; rather, the ethanol was evaporated in vacuo and the mixture was treated with aqueous NaOH to effect hydrolysis of the benzyl ester. Acidification of the reaction mixture induced precipitation of the product, which was isolated by filtration. Interestingly the transformation of **6** to **10** can be accomplished directly by performing the benzylation in aqueous EtOH. Under these conditions **9**, which is still formed as indicated by HPLC, hydrolyzed in situ to afford **10a**. The enantiomeric purity of the product was established to be identical to the starting material by chiral HPLC analysis.

Alternatively, following the literature procedure[12] (eq 1) to produce enantiomerically enriched **10a**, *p*-hydroxyphenyl pyruvic acid was reduced with (+)-DIP-Cl to afford **6** in 90% ee and 92% chemical yield. Upgrade of the enantiomeric purity can be performed after monobenzylation (as described above) by a single recrystallization

(7) Corey, E. J.; Cheng X.-M. *The Logic of Chemical Synthesis*; John Wiley & Sons: New York, 1989.

(8) Alt, C.; Haurez, M.; Forst, M.; Houpis, I. N.; Patterson, L.; Rizzo, J.; Zhang, T. *Org. Lett*. **2005**, in press.

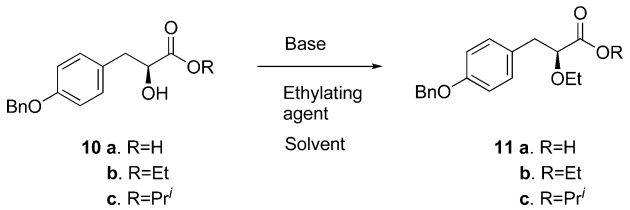
(9) See ref 3 and Storz, T.; Dittmar, P. *Org. Process Res. Dev*. **2003**, *7*, 559

(10) (a) Wong, H. N. C.; Xu, Z. L.; Chang, H. M.; Lee, C. M. *Synthesis* **1992**, 793 (b) Camps, P.; Perez, F.; Soldevilla, N. *Tetrahedron: Asymmetry* **1997**, *8*, 1877 (c) Jeppesen, L.; Bury, P. s.; Sauerberg, P. PCT WO 00/23415 A1, 2000. (d) Ebdrup, S.; Deusen, H.-J. W.; Zundel, M. PCT WO 01/11072 A1, 2001. (e) Boije, M. Horvath, K. Inghardt, T. PCT WO 01/40171 A1, 2001. (f) Nemoto, T.; Kakei, H.; Gnanadesikan, V.; Tosaki, S.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc*. **2002**, *124*, 14544. (g) Linderberg, M. T.; Moge, M.; Sivadasan, S. *Org. Process Res. Dev*. **2004**, *8*, 838.

(11) Liang, T.; Deng, L. *J. Am. Chem. Soc*. **2002**, *124*, 2870. This technology has been licensed to the Diacel corporation, which has made these derivatives commercially available.

(12) Wang, Z.; La, B.; Fortunak, J. M.; Meng, X.-J.; Kabalka, W. *Tetrahedron Lett*. **1998**, *39*, 5501.

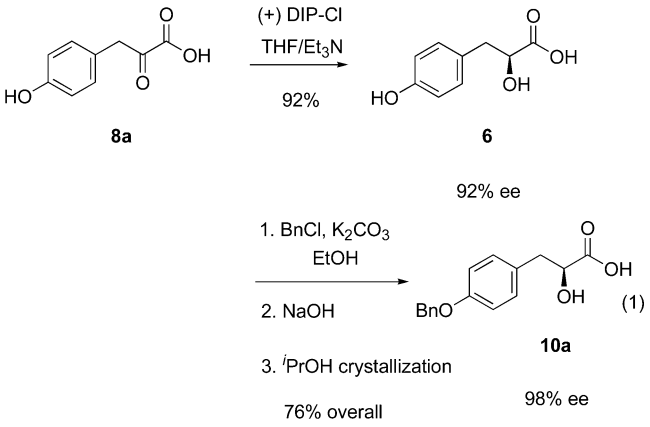
TABLE 1. Attempts at Alkylation of 10a−c



entry	starting material	product	solvent mixture	base	alkylation agent[a]	temp (°C)	conversion (yield, %)	*S*:*R* ratio[b]
1	**10b**	**11b**	DMF	NaH, 1.05 equiv	EtI	−30	0	
2	**10b**	**11b**	DMF	NaH, 2 equiv	EtI	0	70−80	82:18
3	**10b**	**11b**	DMF	NaHMDS	EtOTs	0	55	
4	**10b**	**11b**	THF/DMF	NaHMDS	EtI	0	80	80:20[c]
6	**10b**	**11b**	THF/DMF	NaHMDS	EtI	−30	80−90	97:3[d]
5	**10b**	**11b**	$PhCH_3$/DMF	KHMDS	EtI	0	85	70:30
7	**10b**	**11b**	$PhCH_3$	K_2CO_3	EtI	95	0	
8	**10b**	**11b**	$PhCH_3$/DMF	NaO^{t}Amyl, 1.4 equiv	EtI	−30	99 (70)[e]	96:4

[a] Routinely 5 equiv of alkylating agent was used. [b] Ratio by HPLC area % at 220 nm. [c] EtI added last to the mixture of the base and hydroxy ester at −30 °C. [d] The base was added slowly to a mixture of the hydroxy ester and EtI. [e] Material balance is due to hydrolysis of the product to give **11a**.

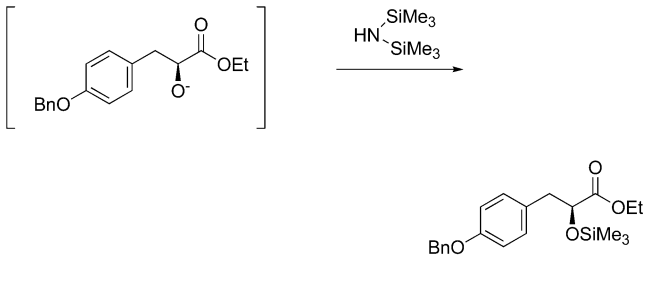
from *i*PrOH to afford the desired product (**10a**) in 98% ee and 76% overall yield.[13]



Formation of Ethyl Ether 11. Contrary to the plethora of synthetic approaches to the α-hydroxy ester function, the ether formation at C-2 is considerably more challenging. Despite intense research, significant epimerization has been observed with a number of the alkylation procedures described, and naturally, heavy reliance on resolution or chiral chromatography protocols was necessary for several of the syntheses. We have also been successful in developing an efficient resolution by formation of the D-alaninol salt of **11a** (**11d**); however, we endeavored to effect this reaction with minimal epimerization, to be able to productively use our optically pure starting material **10**.

Initial attempts to effect simultaneously alkylation of both the alcohol and carboxylate functions were met with modest success. Specifically, in our hands procedures from the patent literature[14] describing high yields and enantiomeric excess for the transformation **10a** → **11b** ($PhCH_3$, K_2CO_3 EtI reflux) failed to produce any of the desired product. Several other procedures were investigated that afforded mixtures of **10a**, **11a**, and **11b**. Furthermore the chiral assays of the **11b** thus formed indicated that up to 10% epimerization of the ethoxy center had occurred.[15] Although our downstream purification protocols could cope with the undesired enantiomer (up to 11%), a greater issue was that the results seemed to depend on the quality of NaH used. Both the enantiomeric excess and conversion varied with different lots of NaH, whereas in some cases, when incomplete reaction was observed, further addition of NaH resulted in extensive epimerization (≥20%). To avoid the complexity of effecting both transformations concurrently, the ethyl and isopropyl esters were formed (see Scheme 2) by acid-catalyzed esterification. In this manner, **10b** and **10c** can be conveniently prepared without racemization. Alkylation attempts on those substrates are shown in Table 1.

Our screen initially revealed that the best conditions involed NaHMDS in THF and EtI as the alkylating agent at −30 °C, affording **11b** in ca. 60% isolated yield and >94% ee (Table 1, entry 6). However closer examination of the reaction mixture indicated that competing silylation of the alkoxide occurred even at −30 °C to afford the silyl ether **12** in 20−30% yield.[16]



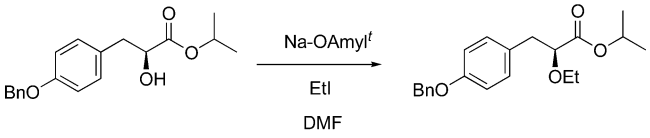
Fortunately, further screening of bases identified that sodium *tert*-amylate (1 M $PhCH_3$ solution) effected com-

(13) We thank Dr. Vincent Mancuso and his team for the execution of the transformation and discovery of the crystallization protocol.

(14) Potlapally, R. K.; Sipirpagada, M. R.; Kotra, N. M.; Sirisilla, R.; Mamillapalli, R. S.; Gaddam, O. R. PTC WO 02/24625 A2, 2002.

(15) Alkylation screens for the conversion of **10a** to **11b** were performed using the following combinations of components. Bases: Na, K and Cs_2CO_3, Li, Na, K-HMDS, KOH, NaOH with or without phase transfer catalysts, and NaH. Solvents: THF, $PhCH_3$, DMF, NMP, CH_2Cl_2. Alkylating agents: EtI, Et_2SO_4.

TABLE 2. Optimization Screen for the Synthesis of 11c



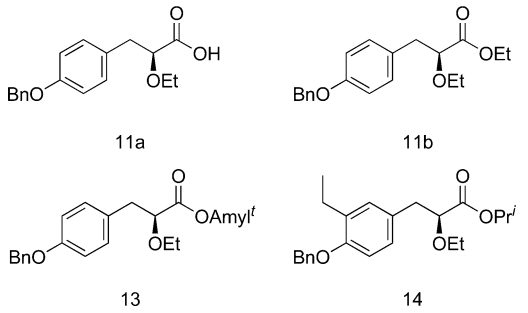
10c 11c

entry	equiv of base	equiv of EtI	temp (°C)	rate of addition (min)	% H_2O in DMF	yield (%)	*S*:*R* ratio
1	1.4	5	−30	60	0.14	91	96:4
2	**1.5**	**5**	**−30**	**60**	**0.52**	**87**	**98:2**
3	1.2	5	−10	45	0.05		90:10
4	1.2	2	−30	60	0.05		85:15
5	1.2	5	−30	170	0.05	95	93:7

plete conversion to the desired product, although initially with modest yield (Table 1, entry 8). Not surprisingly, control experiments indicated that **11b** epimerizes under the reaction conditions, albeit at a slower rate than the alkylation reaction. A short optimization study was undertaken (Table 2) that allowed us to arrive at the following conclusions: (a) The ethyl ester (**10b**) was sensitive to both hydrolysis (to give **10a**) and epimerization, and thus the isopropyl ester **10c** was chosen for this reaction. (b) Five equivalents of EtI are required for optimal reaction rate and enantiomeric excess. (c) It is crucial to ensure that the base is consumed as rapidly as possible to avoid epimerization of the product. Consequently the EtI and **10c** or **10b** are premixed at −30 °C, followed by slow addition of the base while maintaining the temperature of the reaction at ≤−30 °C to avoid epimerization. This slow addition of the solution of *tert*-amylate was particularly important toward the end of the reaction where solid (NaI) precipitation caused a sudden increase in the internal reaction temperature. The amount of water in the reaction medium was also monitored, as extensive hydrolysis was observed with increasing amounts of water. Gratifyingly, this effect was less severe when the isopropyl ester **10c** was utilized. Ironically, the selectivity of the reaction *increased* with increasing amounts of H_2O as less "live" sodium *tert*-amylate was present in the medium. It is noteworthy that the anhydrous NaOH generated during the reaction by the presence of adventitious water does not seem to cause epimerization of the product **11c** (or **11b**). At this point, we cannot exclude the possibility that the H_2O or resulting NaOH played a different beneficial role in this transformation.

Thus the optimal conditions for the reaction involve addition of sodium *tert*-amylate in toluene to a mixture of **10c** and EtI at −30 °C over 60 min, followed by quench with AcOH and extractive workup. The product is isolated in 86−88% yield with 96−98% ee.[17] Several side products were identified by mass spectrometry and correlation to known compounds and are shown in Scheme 3. In addition to the starting material **10c** and the hydrolysis byproduct **11a**, **11b** was also detected, presumably from ethylation of **11a**, as well as the transesterification product **13**. The latter two compounds are anticipated to afford the desired final product.

SCHEME 3. Impurities Produced in the Ethylation Step



Remarkably the orthometalation/alkylation product **14** was also detected, albeit in small amounts (<0.5%).

On a larger scale, the reaction performed with some variability. Indeed some initial reactions, on the 1 kg scale, were performed by addition of solid NaO^{t}Amyl to the reaction mixture instead of a toluene solution. Three different batches were run to give **11c** with enantiomeric excess between 99.5% and 89%. It was speculated that the variability was due to uncontrolled local warming as the base dissolved in DMF, and consequently a solution of NaO^{t}Amyl in toluene was used, to afford a more consistent 95−97% ee (5 batches, 700 g scale). Although under strict control of the reaction conditions we obtained useful ee's of **11c**, we developed a crystallization procedure that could accommodate the ca. 89% ee values observed under less rigorous reaction control. Specifically, **11c** was hydrolyzed in EtOH and NaOH solution at ambient temperature back to **11a** followed by salt formation with D-alaninol in 2-propanol. In this manner, material of 88% ee can be upgraded to 98% ee. Resubjecting the salt to H_2SO_4 in 2-propanol reforms **11c** without loss of enantiomeric purity. The D-alaninol salt, **11d**, gave crystals suitable for X-ray crystallographic analysis, and thus structural proof and the absolute configuration of these intermediates was established via X-ray crystallography.[18]

This variability along with the difficulties in using reactive alkylating agents (EtI) prompted the search for alternative approaches to the synthesis of **11b** or **11c**. We chose a reductive alkylation method in which a silyl ether is reacted with an aldehyde in the presence of $BiBr_3$ and Et_3SiH to afford the corresponding alkylation product (eq 2). The mechanistic considerations and interesting applications of this reaction have appeared recently.[19]

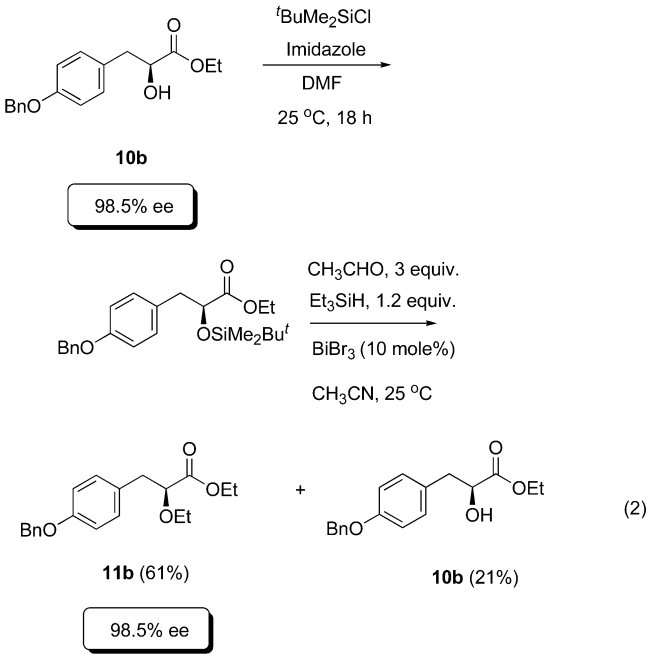
In our hands this reaction proceeded to afford useful yields of the product **11b** only when the hindered *t*BuMe$_2$-Si ether was used. With the less hindered Me$_3$Si and Et$_3$-Si derivatives, the yield was ca. 15% and 30%, respectively, with **10b** comprising the remainder of the material

(16) In addition to the significant yield loss, all downstream purification protocols developed could not remove **10b** or **10c** derived byproducts from the final drug substance.

(17) The enantiomeric excess was determined by chiral electrophoresis analysis.

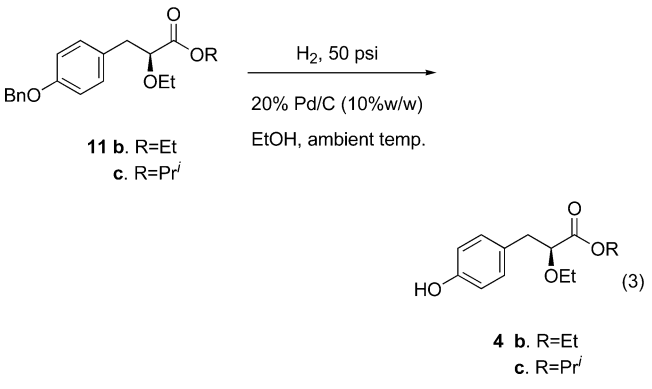
(18) Chiral analysis of **11d** was established with chiral HPLC. X-ray crystallographic data can be found in Supporting Information.

(19) We thank Prof. P. A. Evans for pointing out to us the reactivity trends of the silyl ether derivatives in this reaction. (a) Bajwa, J. S.; Jiang, X.; Slade, J.; Prasad, K.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **2002**, *43*, 6709 (b) Evans, P. A.; Cui, J.; Gharpure, J. *Org. Lett.* **2003**, *5*, 3883. (c) Evans, P. A.; Cui, J.; Gharpure, J.; Hinkle, R. J. *J. Am. Chem. Soc.* **2003**, *125*, 11456. (d) Evans, P. A.; Cui, J.; Gharpure, J.; Polosukhin, A.; Zhang, H.-R. *J. Am. Chem. Soc.* **2003**, *125*, 14702 and references therein.

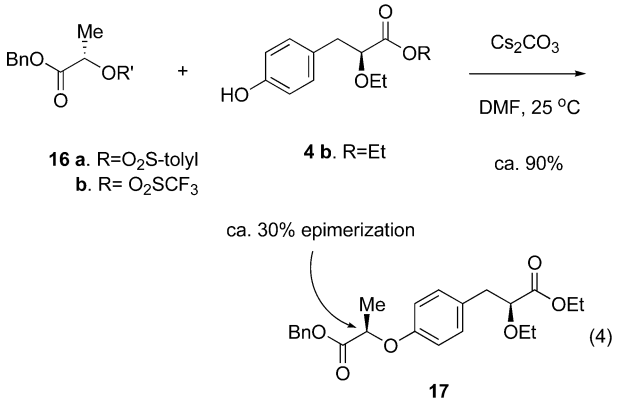


balance. Nonetheless, in all three cases, the optical purity at the C-2 center in **10b** is perfectly preserved in **11b**. Although the chemical yield is relatively low, with some significant hydrolysis of the silyl ether during the reaction, this method provided an attractive alternative to the base-mediated alkylation reaction and is being explored further.

Debenzylation of 11c. Facile debenzylation of **11b** or **11c** can be effected by heterogeneous catalytic hydrogenation (eq 3) with 20 wt % of 10% Pd/C at 50 psi at ambient temperature to afford the product in nearly quantitative yield at the multikilo scale (eq 3).

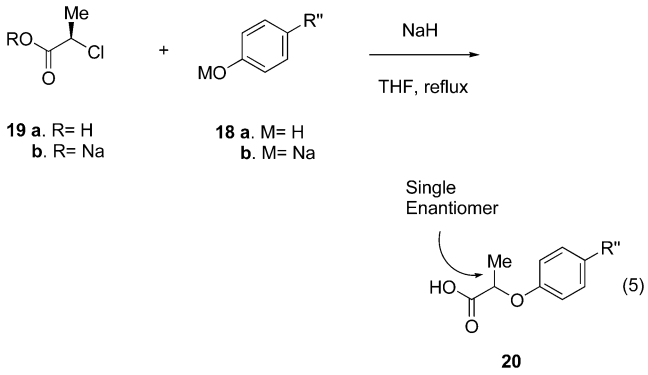


Coupling of 4c with Activated Lactic Acid Derivatives. Our initial attempts for the synthesis of **2** in a diastereoselective manner involved the coupling of the phenoxide of **11c** with readily available lactic acid derivatives, which would be appropriately activated for the substitution reaction. Although initially this appeared to be a fairly straightforward approach with literature precedence,[20] several technical problems needed consideration. For example, one would need to avoid epimerization or elimination reaction of the activated lactic acid derivative **16** (eq 4) or epimerization of **4** under the basic coupling conditions. The product, of course, is also susceptible to epimerization. Indeed in preliminary work, reaction of **16a** or **16b** with phenol **4b** in the presence of Cs_2CO_3 in DMF at ambient temperature resulted in partial epimerization at C-10 as determined by chiral HPLC analysis (eq 4).



To determine what species was responsible for this epimerization several control experiments were performed that showed that **16a** or **17** do not readily epimerize under the reaction conditions, so it is assumed that the cesium phenoxide acted as the base responsible for the observed loss of optical purity. This reaction was not investigated further, as a more effective solution was discovered.

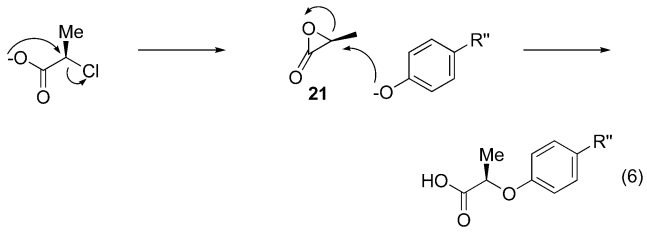
In a related project in our laboratories, aimed at the synthesis of arylated lactic acid derivatives, it was discovered that coupling of phenol **18a** (eq 5) with *R*-chloropropionic acid (**19a**) in the presence of 2 equiv of NaH afforded **20** in good yield. Furthermore the product was shown to be a single enantiomer based on chiral HPLC analysis.



Unfortunately we were, initially, unable to determine the absolute stereochemistry of the product (**20**), as most of the derivatives studied at the time failed to afford crystalline chiral salts appropriate for single-crystal X-ray crystallographic analysis. Nonetheless, we were

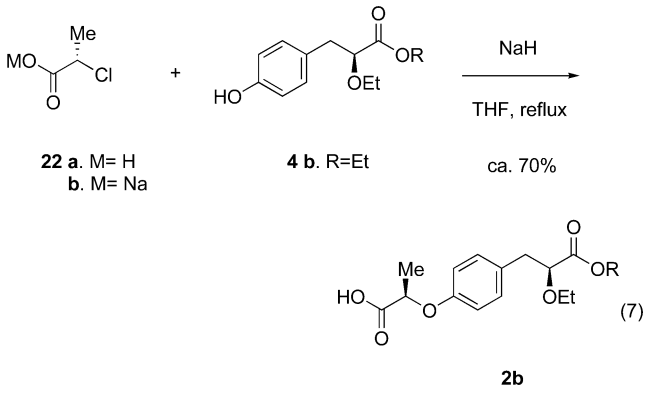
(20) Significant research has been devoted to the stereospecific substitution of activated lactic acid derivatives with carbon, nitrogen, oxygen. or sulfur nucleophiles. Some select examples are: (a) Effenberger, F.; Burkard, U.; Willfahrt, J. *Angew. Chem*. **1983**, *95*, 50. (b) Burkard, U.; Effenberger, F. *Chem. Ber*. **1986**, *119*, 1594. (c) Sato, T.; Otera, J. *J. Org. Chem.* **1995**, *60*, 2627 and references therein. (d) Otera, J.; Nakazawa, K.; Sekoguchi, K.; Orita, A. *Tetrahedron* **1997**, *53*, 13633. (e) Larcheveque, M.; Petit, Y. *Synthesis* **1991**, 162. (f) Nestler, H. J.; Hoerlein, G.; Handte, R.; Bieringer, H.; Schwerdtle, F.; Langelueddeke, P.; Frisch, P. U.S. Patent US005712226A, 1998 and references therein

gratified and intrigued by such complete control of stereochemistry and excellent yield at refluxing THF (no elimination of epimerization of **19a** or **20**) and postulated, as have others, that formation of **21** followed by opening of the α-lactone by the phenolate was responsible for the control of the stereochemistry and stabilization of the reactive intermediate (eq 6). Naturally, if such a mechanism were in effect, overall retention of the stereochemistry of the chloropropionic acid stereogenic center would have been observed. An S_N2 mechanism would, of course, give inversion at that center.[21]



Despite the fact that the stereochemistry was unknown, since a single product was obtained from the reaction we felt that we could successfully incorporate this chemistry into our synthetic strategy. If the reaction proceeded with retention of configuration, the *R*-chloropropionic acid would be used, whereas inversion would require the *S*-isomer. Both isomers of chloropropionic acid are commercially available.[22]

Consequently, according to our original procedure, phenol **4b** was dissolved in THF and treated with 2.1 equiv of NaH, and the resulting phenoxide was in turn treated with 1.2 equiv of *S*-chloropropionic acid (**22a**). A thick suspension (presumably **22b**) was formed, which was heated to 75 °C to form the product **2b** (R = Et) in ca. 70% yield (eq 7).



To our delight, once more a single diastereomer (**2b**) was formed. Thus, it has been established that the reaction proceeded with complete inversion of stereochemistry at the chloropropionic acid stereogenic center. This clearly established that formation of α-lactone **21** does not occur to any significant degree. This fact was further established by React IR experiments, in which the expected α-lactone resonance at 1800 cm^{-1} was not observed.

TABLE 3. Reaction of Phenol 4b−c with *S*-2-Chloropropionic Acid under Basic Conditions[a]

entry	starting material	base	temp (°C)	solvent	2a (%)	4 (%)	24 (%)
1	**4b**	^{t}BuONa	65	THF/$PhCH_3$	38	14	38
2	**4b**	^{t}BuOK	65	THF/$PhCH_3$	34	23	16
3	**4c**	^{t}BuOK	65	THF	18		
4	**4b**	K_2CO_3	65	THF	*b*		
5	**4b**	LDA	65	THF/$PhCH_3$	*b*		
6	**4b**	Cs_2CO_3	65	DMF	tr	>90	
7	**4c**	NaH	65	THF	68	10	18
8	**4c**	Na^0	50	THF	94	1.7	2.5
9	**4c**	Na^0	rt → 50	THF	89	4.5	2.5

[a] All results in this screen are given in HPLC area % at 210 nm. [b] No reaction was observed under these reaction conditions, although some hydrolysis of the starting material due to adventitious water was observed. [c] The chloropropionic acid was added to a solution of the preformed phenoxide **23**.

Unfortunately, the stereochemistry of the C-2 and C-10 centers could not be established directly as none of the salts of the final product **2b** or **2c** produced X-ray quality crystals. The stereochemistry was thus established at the final product in an indirect way as discussed later.

Alternative Coupling Agents. Despite the success in the stereochemical outcome of the coupling reaction, there was a significant yield loss due to hydrolysis of the ester function during the course of the reaction. This significant side reaction was not due to adventitious water in the medium but, once more, due to the presence of NaOH on the surface of the NaH.

To avoid these yield losses, we investigated alternative bases for this coupling. Once more the choices of reagents were limited by the presence of the epimerizable chiral centers; however, our previous experience in the ethylation reaction guided our experimental design (Table 3).

As seen in the table, Na^0 offered significant advantages over NaH and was chosen as an interim solution for our development work (Scheme 4).

Phenol **4c** in THF was added to Na^0 cubes in THF and stirred for 1 h until **23** was produced as judged by the cessation of the H_2 evolution. The solution was heated to 50 °C, and **22a** was added slowly to form a thin, easily stirred suspension. After overnight reaction (98−99% conversion) the mixture was quenched with acetic acid to ensure destruction of Na^0, followed by normal aqueous workup.

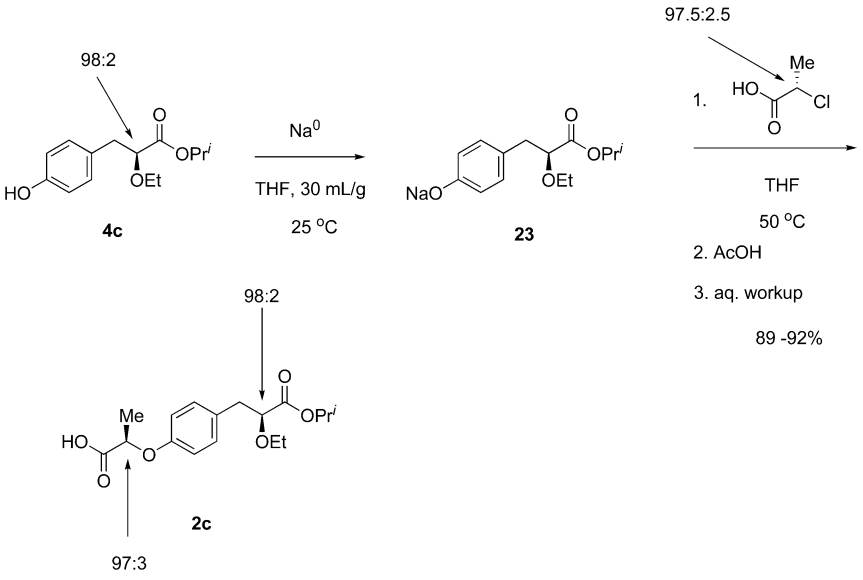
The resulting product had sufficient chemical and diastereomeric purity (≥97%) to be carried forward crude; however, crystallization as the *R*-naphthylethylamine salt considerably enhanced its diastereomeric purity. For instance, material produced in some of our earlier batches with significant amounts of the wrong C-2 isomer (7.4%, from the NaH ethylation reaction) could be successfully upgraded to pharmaceutically acceptable levels via the *R*-naphthylethylamine salt **2d** as shown in Scheme 5.

Next, we examined the parameters that influenced the robustness of this key transformation. Not surprisingly, the water content of the reaction solvent and starting material had to be controlled in order to avoid the formation of diacid **24**. Although this impurity did not impact the purity of the final product, its formation diminished the overall yield.

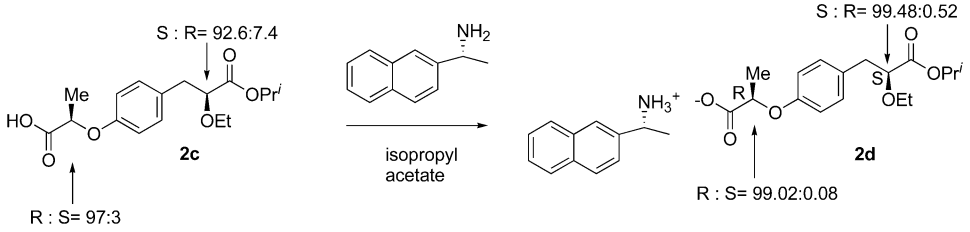
(21) Formation of transient α-lactones has been accomplished via photochemical means: Chapman, O. L.; Wojtkowski, P. W.; Adam, W.; Rodriquez, O.; Rucktaeschel, R. *J. Am. Chem. Soc.* **1972**, *94*, 1365. They have also been postulated in solvolysis reactions of α-bromo propionates: Grunwald, E.; Winstein, S. *J. Am. Chem. Soc.* **1948**, *70*, 841.

(22) Both *R*-(+)- and *S*-(−)-2-chloropropionic acid are available from Sigma-Aldrich Co. On a production scale the *S*-derivative is available at ca. $100/kg and 96% ee.

SCHEME 4. Diastereoselective Coupling of 4c with *S*-2-chloropropionic Acid



SCHEME 5. Diastereomeric Excess Upgrade of 2c

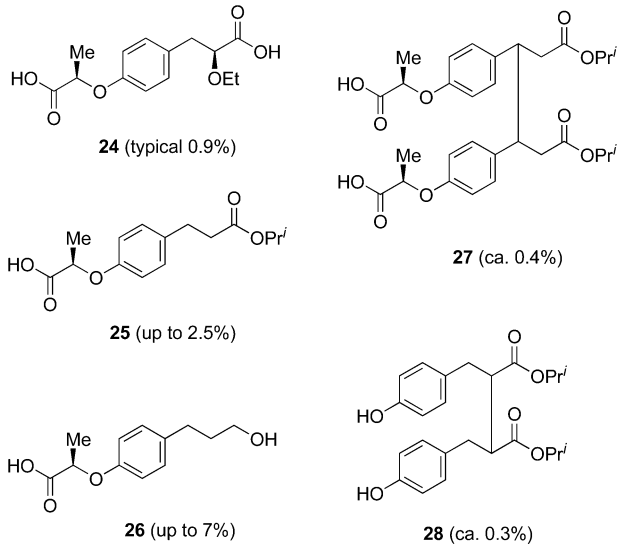


It is noteworthy that the temperature of the reaction and the temperature of addition of **22a** have no impact to the chemical or diastereomeric purity, although the rate and operational convenience are indeed affected. For example, addition of the chloropropionic acid to the solution of **23** at ambient temperature resulted in a thick suspension, which covered the surface of the Na^0, causing some variable reaction rates depending on the rate of agitation and vessel configuration. These problems were avoided by slow addition of the acid at the reaction temperature (50 °C), affording reproducible results (rate and yield) in the laboratory as well as kilogram scale (3 kg scale).

Remarkably the concentration of the reaction had a significant effect on product purity. The optimal reaction conditions, described in Scheme 4, required fairly dilute conditions at ca. 30 mL of THF per gram of **4c**. Under these conditions the des-ethoxy impurity **25** (Scheme 6) was formed at a manageable level of 2−2.5%, presumably via a single election transfer (SET) mechanism. However, when the reaction was attempted in a concentration of 20 mL per gram, not only **25** but also the over-reduced alcohol **26** was produced in substantial amounts (≥10%). The dimeric products **27** and **28** were also detected at ca. 0.3% and 0.4%, although they were not observed under our standard protocol (30 mL per gram).

Despite the fact that the level of these impurities was not significant at this stage, their existence raised concerns about the manufacturability of this reaction. In particular the quality of Na^0 (and its K^0 content) could enhance the degree of the SET component, leading to

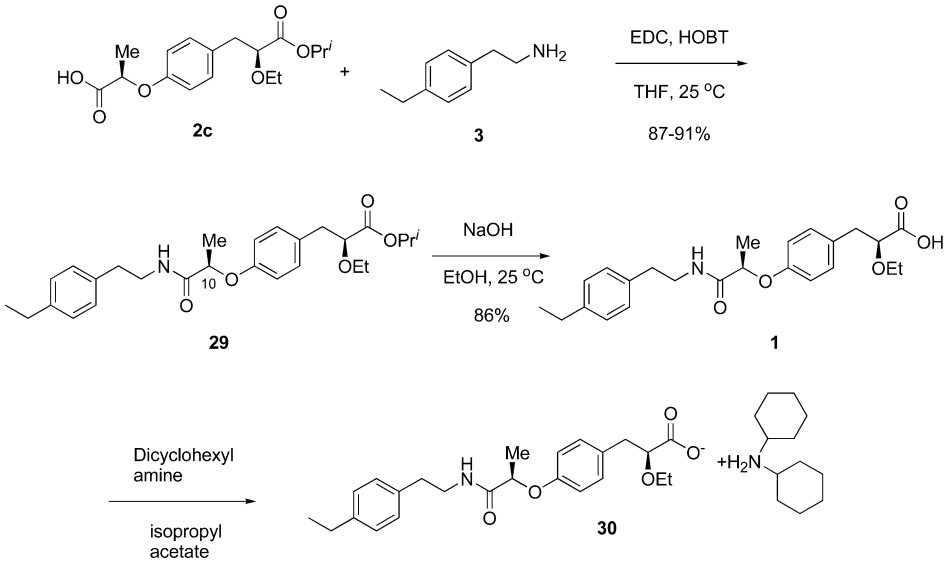
SCHEME 6. Impurities in the Sodium-Induced Coupling of 4c with *S*-2-Chloropropionic Acid



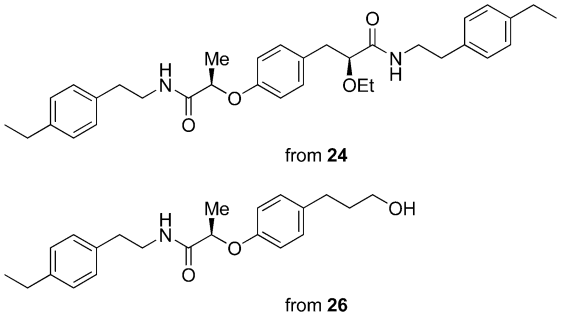
higher amounts of these impurities. Preliminary results in our laboratories showed that the use of $(CH_3)_3SiONa$ in THF was capable of effecting the transformation with complete inversion of configuration. These results will be reported elsewhere upon further development.

The Final Sequence. Formation of the amide bond proceeded in good yield, with no epimerization at C-10. Although the reaction proceeded smoothly, care had to be taken to add the EDC slowly or in portions in a

SCHEME 7. Final Reaction Sequence



SCHEME 8. Impurities Identified in the Final Product



mixture of **2c**, **3**, and HOBT in order to avoid the heavy precipitate that resulted when the addition was done all at once.

An extractive workup afforded the product (**29**), which was taken directly to the next step. The isopropyl ester moiety was readily hydrolyzed with 1 NaOH in EtOH to give **1** in quantitative yield. No epimerization was observed at C-2 or C-10, and indeed performing the hydrolysis at 70 °C also gave no epimerization of our stereogenic centers.

It is noteworthy that impurities resulting from **24** and **26** can readily be removed during workup via base and acid extractions (Scheme 8)

Finally, purification of **1** to afford purity consistent with API requirements can be effected by formation of the dicyclohexylammonium salt (**30**).

Structure Determination. Unfortunately, we were unable to establish directly the absolute stereochemistry of the final product, so an indirect method was used. First the center at C-2 was firmly established by X-ray crystallography as discussed above. Next both possible diastereomers (10-*R*, desired, and 10-*S*) of **1** were prepared by separate reaction of **4c** with *S*- and *R*-chloropropionic acid, respectively (Scheme 5), and the resulting **2c** was carried forward to the final product (Scheme 8). The undesired 10-*S*,2-*S* diastereomer *did* give X-ray quality crystals, and its stereochemistry was unequivocally established. Thus by exclusion our compound is the required 2-*S*,10-*R*, biologically active compound.[23]

Alternative Coupling Results. Finally, some preliminary investigation was conducted to evaluate the convergent approach outlined in Scheme 1. We were particularly interested to examine whether in this reaction the intermediacy of an α-lactam[24] could be observed, in contrast to the absence of the α-lactone with chloropropionic acid.

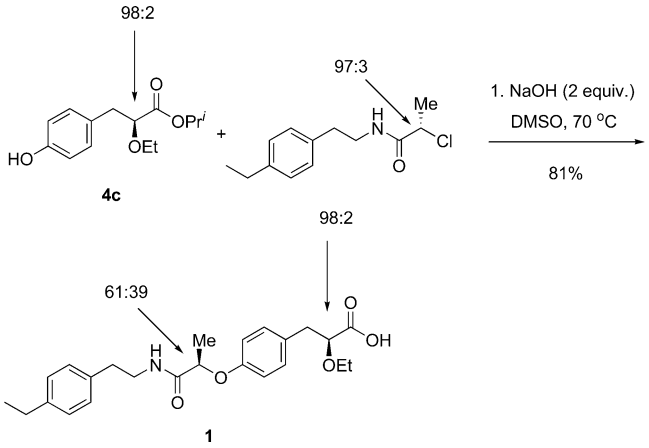
Formation of the amide took place smoothly under our standard coupling conditions to produce the desired *S*-chloropropionic acetamide in high yield and with complete preservation of optical purity. Unfortunately coupling attempts under our established conditions did not give the superior results realized with the propionic acid itself. Both Na^0 and NaH afforded a mixture of the coupling product **29** and its hydrolysis product **1** in modest yields. More disappointing was the fact that significant erosion of the enantiomeric excess was observed. Alternative bases and solvents such as NaOH in DMSO (Scheme 9) improved the overall yield of the coupling reaction, unfortunately at the expense of selectivity. React IR experiments failed to reveal the intermediacy of the α-lactam, and so it is assumed that the reaction did not proceed exclusively via S_N2 displacement or that the chloropropionamide racemizes under the reaction conditions. This approach was not considered further for both technical and strategic reasons discussed before, as with this approach the purification opportunity of the intermediate **2c** is no longer possible and thus a valuable control point has been eliminated.

In conclusion, we have devised a number of synthetic strategies for the synthesis of **1** with control of the absolute and relative stereochemistry without the need for resolution or chiral chromatography. Purification of all intermediates was accomplished without the need for column chromatography. Both stepwise and convergent

(23) The X-ray structure determination and chiral separation of all four possible diastereomers of **1** are shown in Supporting Information.

(24) A thorough discussion with extensive references on the formation and reactivity of α-lactams is described: Tantilla, D. J.; Houk, N. K.; Hoffman, R. V.; Tao, J. *J. Org. Chem*. **1999**, *64*, 3830.

SCHEME 9. Attempts at a Convergent Synthesis of 1



approaches were evaluated, the former proving superior in terms of overall selectivity and purity control.

The selective synthesis of **4** without the need for the sensitive alkylation step is under investigation in our laboratories and will be reported shortly.

Experimental Section

Preparation of 2-Hydroxy-3-(4-hydroxyphenyl)-propionic Acid (6). Solid sodium salt **7** (204 g, 0.94 mol) and sodium iodide (375 g, 2.5 mol) were dissolved in 1 L of concentrated hydrochloric acid, at ambient temperature, in an inerted reaction vessel equipped with a caustic scrubber. The solution was heated gently to 110 °C for 24 h. Upon completion of the reaction, as judged by HPLC analysis, the mixture was cooled in an ice−water bath for 2 h. The slurry was filtered, and the filter cake was washed with 300 mL of cold water. The white solid was collected and dried in a vacuum oven at 60 °C with nitrogen purge to provide 178.7 g of crude solid. The crude solid, which contains some NaI, can be used as-is in the next step. Further purification could be effected by washing the filter cake with further amounts of cold water, with slight yield losses. Average yield at 5 kg scale (2 batches): 91%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.66 (dd, J = 13.77, 7.96 Hz, 1H), 2.83 (dd, J = 13.77, 4.42 Hz, 1H), 4.05 (dd, J = 7.71, 4.67 Hz, 1H), 5.20 (s, 1H), 6.64 (d, J = 8.08 Hz, 2H), 7.00 (d, J = 8.34 Hz, 2H), 9.12, s, 1H), 12.35 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 71.4, 114.8, 128.1, 130.2, 155.7, 175.2.

Preparation of 3-(4-Benzyloxyphenyl)-2-hydroxy-propionic Acid (10a). A solution of **6** (43.32 g, 0.238 mol) in absolute ethanol (950 mL) was treated with K_2CO_3 (65.73 g, 0.476 mol) and benzyl chloride (55 mL, 0.476 mol), and the suspension was refluxed for 12−24 h. Upon completion of the reaction (note: the phenol benzyl ether, benzyl ester compound was formed at this stage), the ethanol was removed by vacuum distillation (65% of the total volume). Water (1 L) and sodium hydroxide (44 mL) were added (pH = 13−14) in order to hydrolyze the benzyl ester formed during the reaction. The hydrolysis was complete after 2 h at ambient temperature. The remainder of the ethanol was removed followed by the addition of water (500 mL) and MTBE (1000 mL) before acidification by dropwise addition of HCl 37% (88 mL). Carbon dioxide evolution was accompanied by the precipitation of the product as an off-yellow solid. The solid was filtered, rinsed with water (500 mL), and dried overnight under reduced pressure and nitrogen purge at 50 °C to give **10a** as an off-white solid (60.81 g, 94%). At the kilo scale, 5 batches, lower yields (ca 82%) were obtained as a result of higher losses in the mother liquors. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.73 (dd, J = 13.77, 8.21 Hz, 1H), 2.90 (dd, J = 13.77, 4.42 Hz, 1H), 4.10 (dd, J = 7.83, 4.55 Hz, 1H) 5.06 (s, 2H), 5.30 (s, 1H) 6.91 (d, J = 8.34 Hz, 2H), 7.14 (d, J = 8.34 Hz, 2H) 7.33 (d, J = 7.07 Hz, 1H), 7.38 (t, J = 7.33 Hz, 2H), 7.42−7.46 (m, 2H), 12.42 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 69.1, 71.2, 114.3, 127.5, 128.4, 130.2, 130.3, 137.3, 156.8, 175.1. HRMS: calcd 273.1127, found 273.1118

Preparation of 2-Hydroxy-3-(4-benzyloxyphenyl)-propionic Acid Isopropyl Ester (10c). The solid **10a** (20 g, 73.5 mmol) was suspended in 400 mL of 2-propanol, and 2.2 mL of H_2SO_4 (41.3 mmol) was added. After 1 h of stirring at ambient temperature, the mixture was heated at 45 °C overnight. The HPLC showed <4% (HPLC area) of remaining starting material. The product can be isolated in two different ways. The first is an extractive workup with addition of toluene (300 mL) and $NaHCO_3$ (200 mL, saturated solution) to remove the traces of unreacted starting material. The layers are separated, and the organic layer is dried by azeotropic distillation followed by a clarifying filtration. The dried solution can be used as-is in the next step after a switch of solvent to DMF. Quantitative assay by HPLC indicated 21.5 g of product **10c** (93%). Alternatively, the material can be isolated as a low melting solid by precipitation from the reaction mixture by the addition of water at pH 8.5 (0.35 g of K_2CO_3, 2.1 g of $NaHCO_3$), again to remove traces of starting material. Ratio of 2-propanol to aqueous = 1:3. Average yield at the kilo scale: 95% (5 batches). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.15−1.31 (m, 6H), 2.54 (s, 1H), 2.90 (dd, J = 14.02, 6.44 Hz, 1H), 2.98−3.13 (m, 1H) 4.35, t, J = 5.56 Hz, 1H), 4.99−5.10 (m, 3H), 6.90 (d, J = 8.34 Hz, 2H), 7.15 (d, J = 8.34 Hz, 2H), 7.28−7.35 (m, 1H), 7.37 (t, J = 7.33 Hz, 2H), 7.40−7.44 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 21.8, 39.6, 69.6, 70.0, 71.3, 114.7, 127.41, 127.9, 128.5, 130.6, 137.1, 157.8, 173.7. HRMS: calcd 315.1596, found 315.1603.

Preparation of 2-Ethoxy-3-(4-benzyloxyphenyl)-propionic Acid Isopropyl Ester (11c). The isolated **10c** (105 g, 0.334 mol) was placed in an inerted 6 L reactor and dissolved in anhydrous DMF (1 L, <200 ppm H_2O). The resulting solution was cooled to −30 °C and treated with ethyl iodide (261 g, 1.674 mol). This homogeneous mixture was subsequently treated with a solution of sodium *tert*-amylate in toluene (420 mL, 0.42 mol, 1 M solution) at such a rate that the temperature was maintained between −27 to −30 °C. After addition of approximately three-fourths of the total charge of base, a precipitate formed that caused an increase in the internal temperature, requiring a decrease in the addition rate to maintain the prescribed temperature. After 1.5 h of stirring at −30 °C, an in-process assay indicated 6% of **10c** still remained. An additional portion of 1 M sodium *tert*-amylate (30 mL, 0.03 mol) was added, and the reaction mixture was stirred for an additional l h. Acetic acid (32.5 g, 1.54 mol) was added dropwise, and the mixture was warmed to ca. 10 °C. Toluene (2 L) was added followed by water (1 L), added at 10 °C (exothermic dissolution of the solids caused a temperature increase up to 22 °C). The organic layer was separated, and the aqueous layer was diluted with an additional 0.5 L of water and re-extracted by 0.5 L toluene. The combined organic layers are washed twice with 0.5 L of water followed by 15% NaCl solution (0.5 L). The toluene was evaporated under reduced pressure to afford crude **11c** (ca 130 g). The crude material was then purified on silica gel (330 g) using cyclohexane/ethyl acetate (90/10 v/v) as the eluent. Purified **11c** was isolated as a pale yellow oil in 90% yield (122.8 g, 0.3 mol). Enantiomeric purity data for two different runs: run 1 = 1.2% of wrong isomer; run 2 = 2.2% of the wrong isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.11−1.2 (m, 6H), 1.23 (d, J = 6.32 Hz, 3H), 2.94 (d, J = 6.57 Hz, 2H), 3.30−3.42 (m, 1H), 3.53−3.65 (m, 1H), 3.94 (t J = 6.69 Hz, 1H), 4.96−5.09 (m, 2H), 6.89 (d, J = 8.59 Hz, 2H), 7.16 (d, J = 8.59, 2H), 7.31 (t, J = 7.07 Hz, 1H), 7.37 (t, J = 7.33 Hz, 2H), 7.40−7.45 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 15.1, 21.7, 21.8, 38.4, 66.0, 68.2, 70.0, 80.4, 114.6, 127.41, 127.9, 128.5, 129.6, 130.4, 137.2, 157.6, 172.0. HRMS: calcd 343.1909, found 343.1942

Preparation of 2-Ethoxy-3-(4-hydroxyphenyl)-propionic Acid Isopropyl Ester (4c). A dry and inerted 2 L

Parr hydrogenator was charged with Pd/C 10% (anhydrous, 8 g) and **11c** (80 g, 0.232 mol) dissolved in 800 mL of absolute ethanol. The vessel was purged five times with 1.5 bar nitrogen and set under 40 psi H_2 pressure keeping the temperature under 27 °C. When no more hydrogen consumption was observed and HPLC analysis confirmed consumption of starting material, the mixture was filtered through 20 g of Celite. The filter cake was rinsed twice with 50 mL of ethanol, and the combined solutions were concentrated under reduced pressure. Toluene (200 mL) was added to the residue, and distillation was continued at ca. 80 mbar at about 40 °C in order to remove any residual ethanol. The volatiles were concentrated at 50 °C at 10 mbar pressure. The product **4c** was isolated as a yellow oil (59.7 g, 0.236 mol, 100% yield) and stored under nitrogen, protected from light. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.08,−1.21 (m, 6H), 1.22 (d, J = 6,0.32 Hz, 3H), 2.92 (d, J = 6.57 Hz, 2H), 3.28−3.43 (m, 1H), 3.50−3.65 (m, 1H), 3.95 (t, J = 6.57 Hz, 1H), 4.93−5.11 (m, 1H), 6.71 (d, J = 8.34 Hz, 2H), 7.07 (d, J = 8.08 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 15.0, 21.6, 21.8, 38.4, 66.1, 68.6, 80.5, 115.2, 128.7, 130.5, 154.6, 172.4. HRMS: calcd 253.1440, found 253.1444

Preparation of *S*-2-Ethoxy-3-[4-(*R*-1-carboxy-ethoxy)-phenyl]-propionic Acid Isopropyl Ester (2c). A 500 mL dry and inerted vessel was charged with freshly cut pieces of Na^0 (24.1 g, 1.04 mol, 2.65 equiv) in THF (1 L). The starting material **4c** (99.84 g, 395.7 mmol, 1.0 equiv) was azeotropically dried from toluene and added as a solution in anhydrous THF (2 L). Controlled gas evolution was observed on the surface of the metal. The brownish red mixture was stirred at ambient temperature for 1 h. The surface of the sodium turned black. The resulting phenoxide was heated to 50 °C and was treated with chloropropionic acid (36 mL, 414.7 mmol, 1.05 equiv added neat) added dropwise over 10 min. The sodium surface cleaned again and precipitation of an easily stirred solid was observed. It is worth noting that addition of the chloropropionic acid at ambient temperature resulted in the formation of a gel that may present stirring problems at larger scales.

After 6 h at ca. 50 °C, HPLC analysis indicated that the reaction was 95% complete, while <2% of the diacid **24** could be observed. The mixture was cooled to ambient temperature and transferred into 2.5 L of a 5% aqueous solution of NaH_2PO_4 (pH = 4.2). The pH after the quench is 5.8 (which avoids ester hydrolysis). Toluene was added (1.5 L), and the pH of the aqueous layer was adjusted to 2.4 with 6 N HCl (ca. 110 mL). The layers are separated, and the organic layer was extracted twice with $NaHCO_3$ (2.2 L, saturated aqueous solution) to remove unreacted starting material. The aqueous layers (containing the desired product) were combined, fresh toluene (4.4 L) was added, and the mixture was acidified with HCl (6 N) to pH = 2.4. The desired compound is quantified in the different layers by HPLC against a standard. The yield in the organic layer was thus estimated at 109 g, 86%, with the following impurity profile: 1.2% (area% at 220 nm) of starting material, 1.0% of the diacid impurity **24**, and 92.9% of the desired compound **2c**. This solution was used directly in the next reaction. Alternatively, the toluene was removed by vacuum distillation and replaced with isopropyl acetate (1.1 L) followed by *R*-naphthylethylamine (58 g, 340 mmol), and the mixture was stirred overnight. Filtration and washing of the salt with isopropyl acetate afforded **2d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.02−1.15 (m, 9H), 1.19 (d, J = 6.32 Hz, 3H), 1.46 (d, J = 6.06 Hz, 3H), 2.63−2.83 (m, 2H), 3.15−3.29 (m, 1H), 3.45−3.51 (m, 1H), 3.68−3.77 (m, 1H), 4.14−4.23 (m, 1H), 4.94−4.99 (m, 2H), 6.47 (d, J = 8.08 Hz, 2H), 6.82 (d, J = 8.08 Hz, 2H), 7.34 (t, J = 7.58 Hz, 1H), 7.42−7.52 (m, 2H), 7.69−7.81 (m, 3H), 7.85 (m, 1H), 7.90 (br s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 15.0, 18.5, 21.5, 21.8, 38.2, 46.6, 65.9, 68.2, 74.5, 80.3, 115.0, 122.2, 122.6, 125.80, 126.6, 128.5, 129.0, 129.2, 130.1, 135.9, 156.8, 172.0, 178.7. HRMS: calcd 325.1651, found 325.1644.

Preparation of *S*-2-Ethoxy-3-(4-{*R*-1-[2-(4-ethyl-phenyl)-ethylcarbamoyl]-ethoxy}-phenyl)-propionic Acid Isopropyl Ester (29). Anhydrous THF (2.75 L), ethylphenethylamine (118.6 g), HOBT (127 g), and EDCI (90.2 g) were added to the toluene solution of **2c** (above) between 20 and 30 °C. After 15 min, a second portion of EDCI (90.2 g) was added, and the reaction mixture was stirred at room temperature for 2 h. H_2O (1.15 L) and HCl 37% (8.2 g) were added to a pH of ca. 2. The layers were separated, and the organic layer was washed with an aqueous solution of NaCl (10% solution, 250 mL), an aqueous solution of Na_2CO_3 (20% solution, 780 mL), and finally with a second aqueous solution of NaCl (10% solution, 250 mL). The organic layer was partially distilled (2.2 L) under reduced pressure. Ethanol (820 mL) was added, and a second distillation was performed (430 g of distillate) under reduced pressure Finally the ethanol volume was adjusted to 25 mL per gram of **29** (determined by quantitative HPLC analysis), and the solution was used directly in the next step.

Preparation of *S*-2-Ethoxy-3-(4-{*R*-1-[2-(4-ethyl-phenyl)-ethylcarbamoyl]-ethoxy}-phenyl)- propionic Acid (1). The solution of **29** above was treated with aqueous NaOH solution (84 g of NaOH/2.1 L of H_2O), and the reaction mixture was strirred at 30 °C for 5 h. The weight of the reaction mixture was 8.5 kg (3.29% w/w = 279.5 g of **1**). The ethanol was partially distilled (direct aqueous workup did not succeed because of the large volume of ethanol present), and H_2O (3.80 L) and MTBE (2.70 L) were added to the residue. The aqueous phase was acidified with HCl 37% (ca. 200 mL) to pH = 2 and extracted with MTBE (2 × 2.8 L). The MTBE was partially evaporated under reduced pressure to give 5336 g of a solution of **1** (4.636% w/w = 247.3 g of **1**). The MTBE was removed in vacuo and replaced with isopropyl acetate (2.5 L, ca. 10 mL/g). The resulting homogeneous solution was treated with neat dicycloexylamine (109 g, 1.02 equiv) at ambient temperature overnight. The resulting slurry was filtered, and the filter cake was washed with isopropyl acetate (300 mL) and dried in vacuo at 40 °C to afford **1** as the DCHA salt (326 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.09−1.35 (m, 12 H), 1.44−1.61 (m, 7H), 1.69 (d, J = 10.86 Hz, 2H), 1.83 (d, J = 12.13 Hz, 4H), 2.07 (d, J = 11.12 Hz, 4H), 2.60−2.76 (m, 3H), 2.77−2.86 (m, 1H), 2.91 (dd, J = 13.26, 9.73 Hz, 1H), 2.96−3.12 (m, 3H), 3.26−3.41 (m, 1H), 3.47−3.54 (m, 1H), 3.57−3.63 (m, 1H), 3.66−3.72 (m, 1H), 3.86 (d, J = 7.33 Hz, 1H), 4.57−4.7 (m, 1H), 6.54 (t, J = 5.18 Hz, 1H), 6.78 (d, J = 7.33 Hz, 2H), 7.02 (d, J = 6.82 Hz, 2H), 7.12 (d, J = 7.07 Hz, 2H), 7.25−7.32 (m, 2H), 8.50 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 15.2, 15.5, 18.9, 24.8, 25.3, 28.4, 29.3, 29.4, 35.3, 39.0, 40.1, 52.6, 65.2, 75.1, 82.5, 114.9, 128.0, 128.7, 130.5, 133.4, 135.7, 142.4, 155.3, 172.2, 177.6. HRMS: calcd 414.2280, found 414.2254

Supporting Information Available: NMR and high resolution mass spectral data for all new isolated compounds; HPLC and chiral HPLC data for the key intermediates; X-ray data in CIF format for the determination of the absolute configuration of **4** and support of the absolute stereochemistry of the final product. This material is available free of charge via the Internet at http://pubs.acs.org.

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