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Kinetically Controlled Diastereoselective Synthesis of CPS124, a Carnitine Monothiophosphate

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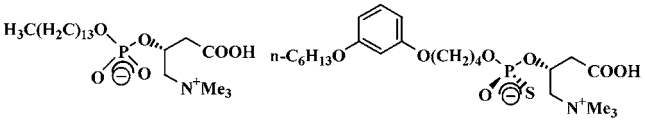
Abstract:

An expedient synthesis of CPS124 (1) is described using the diastereoselective reaction of the in situ generated dichlorophosphite 6 with L-carnitine tetrafluoroborate salt 7 under kinetic control as the key step. Alkylations of resorcinol 2 and its benzoate 13 are discussed. The use of α-cellulose as a support for solids that are difficult to filter or low melting is presented.

The therapeutic potential of fatty acid oxidation inhibitors in the treatment of noninsulin dependent diabetes mellitus (NIDDM) has been well documented and forms the basis for the advancement of our first generation of reversible and competitive inhibitors of carnitine palmitoyltransferase I (CPT-1), represented by CPI975.[1] The amphiphilic nature of the first generation of CPT-1 inhibitors and the concern that they could lead to gastrointestinal irritation and low absorption prompted us to look for the second generation of this class of compounds, and CPS124 (**1**) was selected for further development from 400 analogues that were screened.[2]



CPI975 **CPS124 (1)**

The original synthesis of **1** used by the medicinal chemists is outlined in Scheme 1. Several issues associated with scale-up in the pilot plant (nonselective alkylation of resorcinol, multiple chromatographies, distillative purification of dichlorophosphite intermediate **6**, and nonselective formation of thiophosphates) were noted and possible solutions are presented.

Results and Discussion

Monoalkylation of 2. In the original synthesis, the monoalkylation of **2** was nonselective although two equivalents were employed. Chromatographic purification was used for the isolation of the product **3**, and this had to be eliminated to make the synthesis practical. At the outset, different alkylating conditions were tried using equimolar amounts of **2** and 1-bromohexane, and the results are listed in Table 1. These results revealed the nonselective nature of the alkylation process, which is not very surprising if one considers the similar acidities of resorcinol and its monoether (pK_a is about 0.1 units apart). The use of the phase-transfer catalyst tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1), a nontoxic crown ether substitute, clearly helped the alkylation.

The results from further work carried out using TDA-1 as the catalyst are shown in Table 2. The conditions in the entry 4 were best. Thus, to a refluxing solution of **2** in acetonitrile containing 10% of TDA-1 and 0.6 equiv of potassium carbonate was slowly added 1 equiv of 1-bromohexane over a period of 2 h. The mixture was further refluxed for an additional 3 h before aqueous workup. The isolated yield of the monoalkylated product was in the range of 50−55%. The product isolation was conceived on the basis of the expected solubility differences of the starting resorcinol, monoalkylated product, and bisalkylated product in different solvents. The solvent acetonitrile was first removed from the reaction mixture. The bisalkylated byproduct was then extracted into the organic phase by partitioning the slurry between heptane and NaOH solution. After acidification, the product was extracted into heptane, which was further washed with water and $NaHCO_3$ solution to remove trace amounts of resorcinol. The product isolated this way routinely had a purity of >90% and met the criteria for the next step.

Preparation of Alcohol 5. Ethyl 4-bromobutyrate was used as the alkylating agent with **3**. This necessitated the reduction of the ester group in **4** with $LiAlH_4$ to give **5**. We felt that by choosing the alkylating agent with the correct oxidation state, the reduction step of **4** to **5** could be avoided. Therefore, the alternative synthesis shown in Scheme 2 was designed. The hydroxyl group in chlorobutanol was protected as a mixed ketal group as it is stable under basic conditions and can be removed easily under acidic conditions.

In the protection of chlorobutanol, significant amounts of free HCl in the commercial chlorobutanol had to be neutralized before the reaction, otherwise a complicated mixture resulted. In the present process, the commercial chlorobutanol was first neutralized with sodium bicarbonate. Among various acid catalysts ($POCl_3$, PPTS, and Amberlyst-15) tried for the preparation of **10**, PPTS was the most satisfactory. The reaction took place even at −78 °C. A small increase in byproduct formation, especially the dimeric product was observed by GC analysis at higher temperatures (e.g., rt). As a compromise between operational convenience and product purity, the reaction was carried out at −15 °C. The reaction was run neat, and the workup involved dilution with heptane, filtration, and evaporation. The colorless oil

(1) Anderson, R. C. *Curr. Pharm. Des.* **1998**, *4*, 1−15.

(2) Fraser, J. D.; Anderson, R. C.; Fillers, W. S.; Villhauer, E. B. *Abstracts of Papers*, 214th National Meeting of the American Chemical Society, Las Vegas, NV, September 6−11, 1997; American Chemical Society: Washington, DC, 2001; ORGA 327.

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Scheme 1. **Original synthesis of 1**

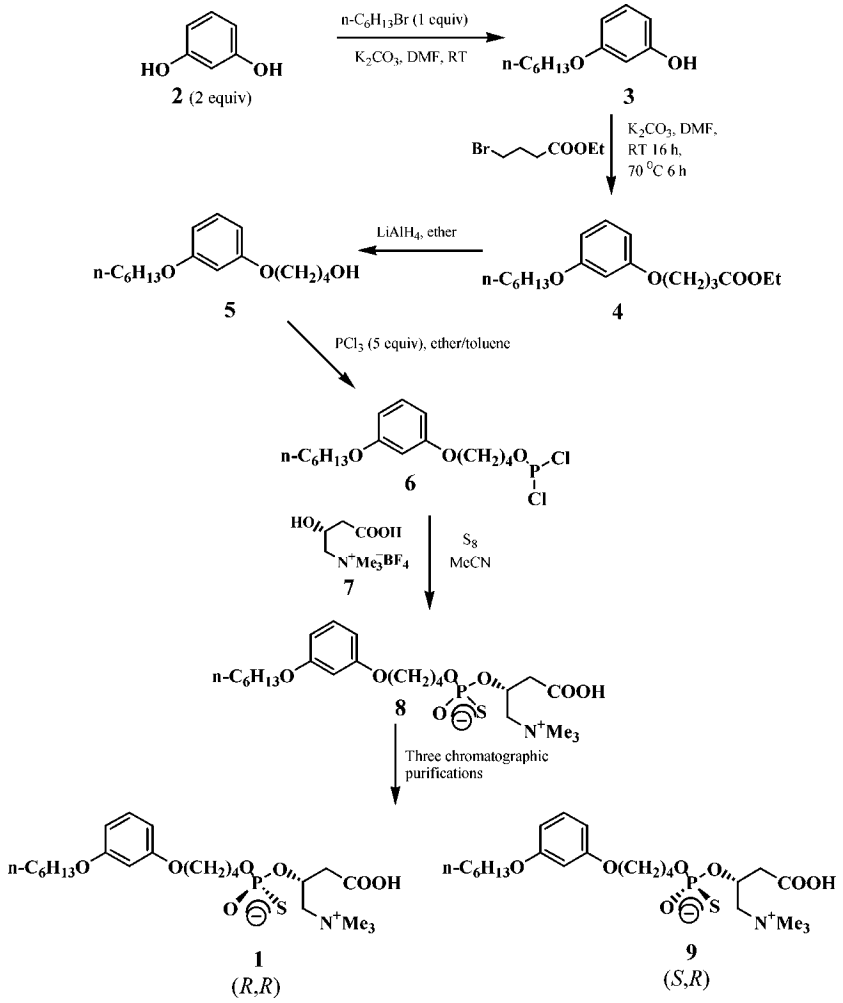


Table 1. **Alkylation of resorcinol**

entry	conditions	results
1	Na_2CO_3, acetone, reflux, 15 h	only ~5% conversion, no selectivity
2	K_2CO_3, water, rt, 2 d	no reaction
3	1 equiv of NaOH (5 N), toluene, 45 °C, 3 h	no reaction
4	1 equiv NaH, i-PrOH, reflux 3 h	**2**/**3**/bis- ~1:1:1 (from GC)
5	K_2CO_3, MeCN, 5% TDA-1, reflux, 15 h	**2**/**3**/bis- ~1:3:3 (from GC); 38% yield of monoalkylated product

Table 2. **Alkylation of Resorcinol using TDA-1 as a Catalyst**

entry	conditions	results
1	2 equiv $NaHCO_3$, 10% NaI, 20% TDA-1, acetone, 40 °C, 2 d	<10% conversion
2	1 equiv NaOH (2 N), 10%TDA-1, PhMe, reflux, 2 h	<10% conversion
3	1 equiv Na_2CO_3, 20% TDA-1, 10% NaI, MeCN, 70 °C, 16 h, reflux, 4 h	**2**/**3**/bis- ~6:4:1 (from GC), 12% isolated yield of **3**
4	0.5 equiv K_2CO_3, 10% TDA-1, MeCN, reflux 5 h, slow add′n of the bromide	53% isolated yield of **3**

thus contained about 10% of the byproduct but was used successfully in the next step (the dimeric byproduct functions the same way as the chloroacetal in the alkylation).

Among the factors studied for the optimization of the alkylation of **3** with 1.1 equiv of **10** were solvents, base, and catalysts. These results are summarized in Table 3. It is clear from these studies that generally longer reaction times and higher temperatures are needed to drive the reaction to completion using K_2CO_3 or Na_2CO_3 as bases under anhydrous conditions. The alkylation goes faster when NaH was used in combination with tetrabutylammonium iodide (entry 6) and also worked well when NaH/NaI/TDA-1 combination was used (entry 8). As conditions mentioned in the entry 9 (aqueous NaOH with tetrabutylammonium bromide) were simpler and superior, these conditions were chosen for the first scale-up of the process. On large scale, the product was isolated in 60−70% yield.

Further Modification to the Synthesis of 5. The method described was successfully applied for a kilogram-scale synthesis of CPS124. After completing the first campaign, we returned to the process to improve it even further. Through the earlier work we noted that the first alkylation was nonselective, the aqueous workup was too involved, and the oily intermediate **3** was prone to air-oxidation that produced dark unknown impurities affecting the product

Scheme 2. **Modified synthesis of 5**

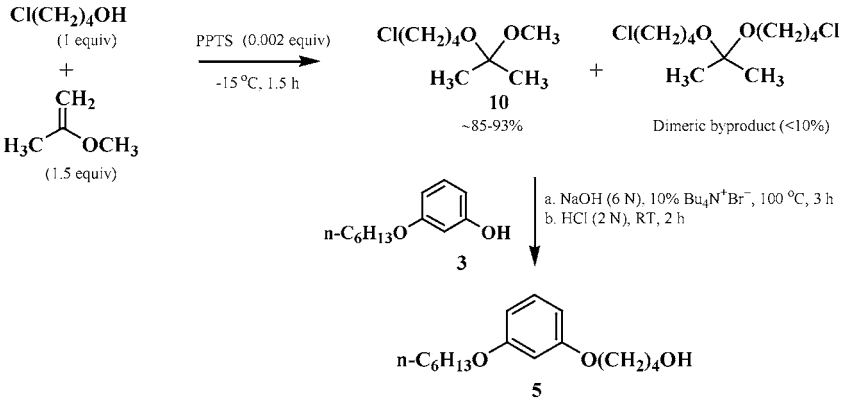


Table 3. **Alkylation of 3 using acetals**

entry	conditions	results
1	5% NaI, 10% TDA-1, Na_2CO_3, MeCN, reflux, 36 h	44%, rxn not complete
2	20% NaI, 20% TDA-1, K_2CO_3, MeCN, reflux, 24 h	61%, rxn not complete
3	20% NaI, 25% TDA-1, K_2CO_3, PhMe, reflux, 24 h	78% (not pure)
4	20% Bu_4NI, K_2CO_3, MeCN, reflux, 20 h	65%
5	20% Bu_4NI, K_2CO_3, no solvent, 100 °C, 10 h	trace product, mainly SM
6	20% Bu_4NI, NaH, PhMe, reflux, 6 h	63%
7	5% Bu_4NI, NaH, PhMe, reflux, 14 h	39%, rxn not complete
8	20% NaI, 25% TDA-1, NaH, PhMe, reflux, 8 h	73%
9	10% Bu_4NBr, 6 N NaOH, 100 °C, 2−3 h	71%

Table 4. **Alkylation of resorcinol monobenzoate**

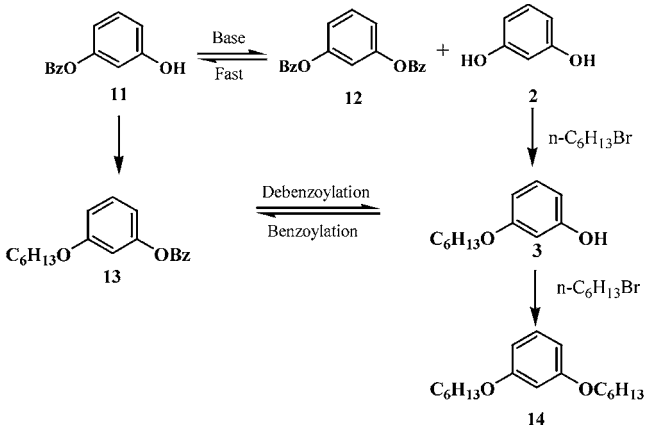
entry	conditions [equiv]	ratio[a] of **11**:**13**:**12**
1	1.2 RBr,[b] 1.2 K_2CO_3, 0.1 TDA-1, heptane, ↑↓, 24 h	1:1.5:3
2	1.2 RBr, 1.2 K_2CO_3, 0.1 TDA-1, MeCN, ↑↓ 5 h	trace:1:6
3	1.2 RBr, 1.2 K_2CO_3, 1 NaI, acetone, ↑↓, 2 h	1:1:1
4	1.2 RBr, 1.2 K_2CO_3, 0.1 TDA-1, PhMe, 110 °C, 6 h	trace:1:7
5	1.5 RBr, 1.5 K_2CO_3, 0.1 TDA-1, EtOAc, ↑↓, 1 h	2:0.8:1
	1.5 RBr, 1.5 K_2CO_3, 0.1 TDA-1, EtOAc, ↑↓, 18 h	0:6:1
6	1.5 RBr, 1.5 K_2CO_3, 0.1 TDA-1, PhMe, ↑↓, 6 h	0:17:1

[a] The ratio was taken from integration of peak areas of the HPLC trace of the reaction mixture without normalization. [b] RBr and RCl refer to 1-bromohexane and 1-chlorohexane, respectively.

quality. While looking for alternate isolation methods for **3**, we found that the corresponding benzoyl derivative **13** was a solid crystallizable from hexane. We envisioned that **13** could conceptually be obtained directly from the commercially available resorcinol monobenzoate **11**.[3] The only concern was whether the second alkylation could be carried out with **13** directly without resorting to an extra hydrolysis step. The strong aqueous basic condition employed for the second alkylation assured us that the deprotection could be achieved in situ.

Initially this alkylation was found to be more complicated than was originally thought. Besides the expected product and starting material, two new products appeared, identified as **12** and **14**. The results in Table 4 demonstrate that higher temperatures and longer reaction times were needed for good conversion and an improved ratio in favor of the desired product. The exact amounts of **14** were not determined due to its overlap with the reaction solvent (toluene) in our HPLC, but they could be estimated from the TLC. The reaction was speculated to follow through an initially established equilibrium between **11**, **12**, and **2**, and the alkylation eventually

Scheme 3



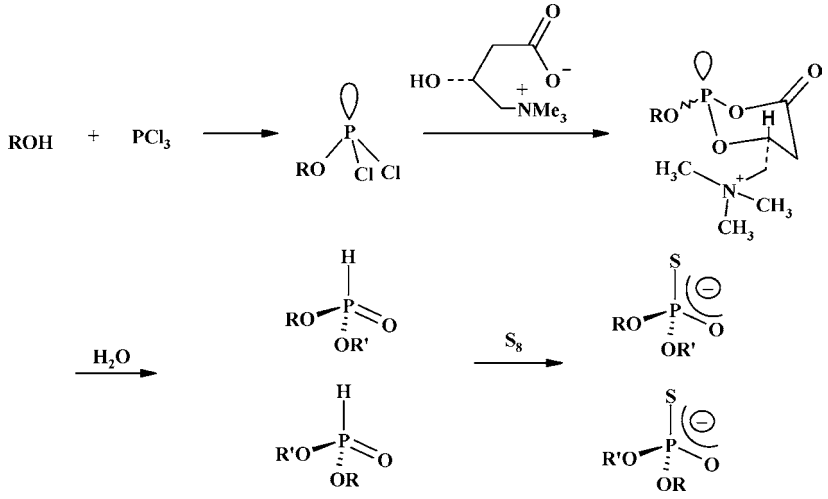
drove the equilibrium towards the desired product **13** and some bisalkylated product **14** (Scheme 3).

Since the alkylation involved an equilibrium among different reactive species, the process required higher temperatures and longer reaction times. Thus, the procedure chosen for the alkylation of **11** was entry 6, and **13** was isolated in 69% yield as a low-melting solid (mp 33.5−35.5 °C).

On scale-up we found that the filtration of this material was very slow and resulted in the isolation of a low-melting gummy paste rather than a free-flowing solid and partial

(3) During the preparation of this manuscript an inresting publication (ref. Boxhall, J. Y.; Page, P. C. B.; Chan, Y.; Hayman, C. M.; Heaney, H.; McGrath, M. J. *Synlett* **2003**, 997−1001) appeared on desymmetrization of resorcinol using Mitsunobu reaction conditions.

Scheme 4. **Alkylation of resorcinol monobenzoate**



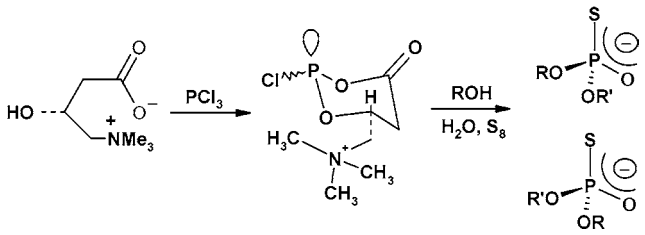
dissolution of the product in the solvent heptane. Attention was therefore turned toward improving this filtration. Our efforts focused on the addition of α-cellulose (Sigma) to the suspension of crude product prior to filtration. We expected that the presence of cellulose would increase the speed of the filtration and act as a support, thus improving the quality of the solid. The proportion of cellulose was judiciously varied, and the optimal amount was found to be 5% (w/w), based on the amount of expected product (or 21 g/ 1.9 mol of **13**). The best crystallization conditions in the laboratory were found to be methanol, with 5% (w/w) cellulose, at −10 °C. The product was a stable, free-flowing solid. The cellulose added for the precipitation of **13** is removed during the following step after the coupling and before the acid-deprotection of the alcohol function.

The hydrolysis of the benzoate **13**, as anticipated, was a very facile process under the alkylation conditions. Therefore, the conditions used for the alkylation of **3** were adapted for the alkylation of **13**. The synthesis of **5** described in this section consisted of the alkylation of **11** and the in situ hydrolysis−akylation of the intermediate **13** and was the method of choice.

Diastereoselective Thiophosphate Formation. Conversion of **5** to the drug substance was rather complicated. Coupling of **5** with PCl_3 afforded the dichlorophosphite **6**, which was purified by distillation and reacted with L-carnitine tetrafluoroborate salt (**7**), followed by hydrolysis and oxidation with sulfur to give a mixture of diastereomeric thiophosphates **1** and **9**. The two diastereomers were separated as gelatinous materials by multiple chromatographic purifications. The major stumbling block was the formation of thiophosphate diastereoisomers in a 1:1 ratio with no apparent selectivity.

Our key objective thus became defining the chirality at the phosphorus center and making the present approach viable for the preparation of the desired *R,R*-diastereoisomer **1**. At the outset of this work it was not obvious when the stereochemistry at the phosphorus atom was established. The thiophosphate product formation itself involved several steps, i.e. coupling of $PC1_3$ with the alcohol and L-carnitine, hydrolysis, and oxidation **(**Scheme 4). In our earlier work

Scheme 5



on CPI975, the cyclic phosphite[4] was proposed, and later confirmed to be the initial product of L-carnitine coupling with the dichlorophosphite. We believe the phosphorus thus first becomes chiral at this cyclic anhydride stage. The oxidation of H-phosphonate to thiophosphate is known[5,6] to be highly stereoselective. Thus, to be successful, we had to find conditions that would give the desired selectivity during the cyclic phosphite formation.

On the basis of the above analysis, our first approach was to switch the sequence of the coupling. Phosphorus trichloride was reacted with L-carnitine followed by the addition of **5**. It was hoped that the asymmetric induction from the L-carnitine to the phosphorus would be maximized in an intramolecular mode (Scheme 5). However, this reaction was very messy and gave no product. The reaction of $PC1_3$ with L-carnitine seemed to work (one principal spot on TLC), but the coupling with alcohol led to a complicated mixture.

After many unsuccessful trials and some brief experimentation with $P(S)C1_3$, we took a closer look at the diastereoselectivity in the normal reaction sequence. We were delighted to find a rather good intrinsic diastereoselectivity in the cyclic phosphite formation starting from **6** and L-carnitine. The selectivity was found to be dependent on the coupling temperature and the "aging" of the cyclic phosphite intermediate.

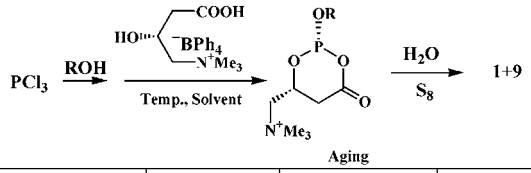
Different parameters such as L-carnitine coupling, hydrolysis, and sulfur oxidation (Scheme 5) were probed for

(4) Prashad, M.; Amedio, J. C.; Ciszewski, L.; Lee, G.; Villa, C.; Chen, K.-M.; Prasad, K.; Repič, O. *Org. Process Res. Dev.* **2002**, *6*, 773−776.
(5) Battistini, C.; Fustinoni, S.; Brasca, M. G.; Borghi, D. *Tetrahedron* **1993**, *49*, 1115−1132.
(6) Seela, F.; Kretschmer, U. *J. Chem. Soc., Chem. Commun*. **1990**, 1154−1159.

Table 5. **Coupling temperature effect on selectivity**

coupling temperature (°C)	**1**/**9**
20	1.8−2.2
0	2.6−3.2
−20	3.4−3.9

Scheme 6. **Aging effect**



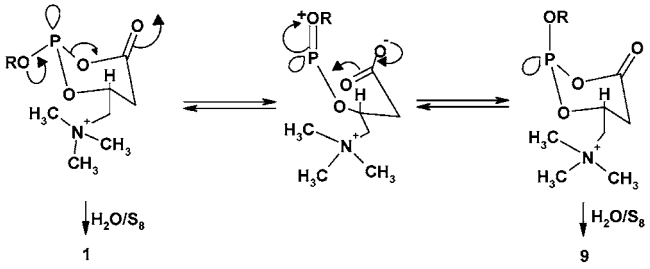
Coupling Temp.	Solvent	Aging time	**1**:**9** ratio
−20 °C	THF	None	3.8:1
		RT, 6 d	1.2:1
RT	Toluene	None	3.5:1
		80 °C, 3 h	1:11

their potential influence on the final selectivity as measured by the combination of HPLC and NMR data. A nice linear correlation between the L-carnitine coupling temperature and the diastereomer ratio of **1**/**9** was found, i.e. with higher selectivity at lower coupling temperatures (Table 5). Results below −20 °C were erratic and not included in the table as we believe the coupling in these runs actually occurred during warm-up.

The base and solvent used in the coupling step were also briefly investigated. Most selectivity studies were done initially with collidine as the base. Switching from collidine to the much cheaper tributylamine was found to have no apparent effect on the selectivity. Thus, tributylamine was used in the later work. Besides the commonly used THF, toluene was also tried. With toluene as the solvent, the coupling reaction did not proceed at 0 °C but went to completion at room temperature in 2 h. The selectivity was found to be slightly higher than in THF (**1**/**9** = 3.5 vs 1.8−2.2) at the same temperature. However, THF was chosen as the solvent as it could be incorporated better into the overall reaction sequence. The diastereoselectivity of the reaction is dramatically altered upon "aging" of the cyclic phosphite (Scheme 6).

The cyclic phosphite that leads to the desired **1** is clearly the kinetic product[7] of the coupling step, and it should be immediately hydrolyzed to minimize the undesired isomerization. The hydrolysis conditions did not show much effect on the final selectivity. The hydrolysis was studied at temperatures ranging from −20 to 25 °C. The methods of hydrolysis included the normal addition of water to the reaction mixture, and the inverse addition of the reaction mixture into water. The acidity of the quenching water was adjusted to pH 0 (1 N HC1), pH = 7 (phosphate buffer), and pH 14 (1 N NaOH). Both the basic and the acidic quenchings were found to be unacceptable as they did not give the drug substance upon oxidation with sulfur. The oxidation with sulfur was very slow due to the limited solubility of elemental sulfur in the reaction medium. It normally took 6 h at room temperature for completion.

We believe that the selectivity on the phosphorus atom is decided in the first reaction of L-carnitine with dichlorophosphite, since apparently both subsequent reactions, the hydrolysis and the sulphurization, proceed with retention of stereochemistry on phosphorus. The product is apparently kinetically controlled: If the cyclic phosphite is aged, the ratio of diastereomers drops, and if it is heated, the other isomer predominates. This occurs presumably through ring opening and closing. A probable mechanism is shown below. Ring-opening and -closing reactions initiated by Cl^- or amine nucleophiles are not ruled out.



Product Isolation and Purification. While studying selectivity, an important advance in simplifying the product isolation was also made. As the drug substance **1** and its diastereomer **9** have a carboxyl group and a fairly large lipophilic side chain, we envisioned that the compound could be partially purified by an acid−base aqueous workup. Thus, the polarity of the crude reaction mixture was carefully adjusted with ethyl acetate and heptane, and the thiophosphates were extracted into aqueous NaOH solution. After acidification of the aqueous extract with HCl, they were extracted back into ethyl acetate. This operation was found to be very effective, and the material loss during extractions was found to be minimal. The ratios of the two diastereomeric thiophospates were then determined by analyzing the ethyl acetate extracts. This partial purification method was critical in developing the new isolation/purification process for the drug substance.

Attempts to isolate the desired drug substance from the crude organic extract were initially frustrating. Many different solvents and combinations were tried before it was found that the drug substance slowly (over a period of several days) precipitates from its ethyl acetate solution as thin silky solid. The precipitated particles were too small to be filtered. The material was collected by centrifugation and was pleasantly found to be predominately the desired isomer **1**. The isolation was further improved by the addition of some more polar additives to the ethyl acetate solution (Table 6). The crude residue from the ethyl acetate extract obtained after acidic workup gave a filterable precipitate on redissolving in ethyl acetate containing 10% of deionized water. It was later realized that **1** could be crystallized from the original crude ethyl acetate extract containing just the right amount of water. The product thus isolated by this direct crystallization normally had a chemical purity of >96% and a diastereomeric purity in the range of 92−95%. The material recovery was also very good: The two diastereomers were usually

(7) Gordon, N. J.; Evans, S. A. *J. Org. Chem.* **1993**, *58*, 5295−5297 and references therein.

Table 6. **Polar additive effect on the crystallization**

additive	result
5% MeOH	flaky crystals, low recovery
5−20% EtOH	no precipitate
5% water	silky precipitate, nonfilterable solid
10% water	amorphous and filterable solid good material recovery
crude extract	flaky crystals, good material recovery

present in the starting crude extract in an approximately 3:1 ratio, favoring **1**. The mother liquor obtained after crystallization normally had a diastereomeric ratio of ∼1:2.5, indicating 70% of the desired **1** in the original crude extract was collected by this crystallization.

The material obtained was further purified by a recrystallization from hot water (50 °C). The recrystallized product had a chemical purity of over 99% and a diastereomeric purity of >98%. However, this aqueous crystallization was somewhat slow (24 h). Later we found that the drug substance could be better crystallized from EtOH at 0 °C.

In the pilot-plant runs, the crude CPS124 obtained from ethyl acetate was found to be a wet glue, similar to the one initially obtained with **13**. The opportunity to use α-cellulose as a filter aid presented itself again. The process was optimized by adding α-cellulose into the suspension of crystallized **1** in ethyl acetate at −15 °C, prior to filtration. When this procedure was followed, the collected **1**/cellulose mixture was free-flowing and kept its form indefinitely at room temperature.

Now that the drug substance could be obtained cleanly from ethyl acetate, the cellulose had to be removed during the second (ethanol) crystallization. In practice, the **1**/cellulose filter cake was suspended in ethanol, warmed to 50 °C to dissolve the product, stirred vigorously for 30 min, and filtered. The cellulose cake was washed with hot ethanol to remove the final traces of **1**. The ethanol filtrate on concentration, followed by cooling, gave **1** routinely with ∼96−97% chemical purity and contained 0.6−0.8% of the undesired diastereomer. To further increase the purity of the product, we included an additional recrystallization from ethanol. This last recrystallization gave drug substance of 99.1−99.8% purity, with 0.0−0.2% of the diastereomer.

Conclusions

In summary, an expedient synthesis of **1** has been developed starting from **13** and **7**. Highlights of this synthesis include alkylation of resorcinol monobenzoate **13** with bromohexane, in situ hydrolysis of the benzoate group followed by alkylation with a masked chlorobutanol to afford **5**, and the formation of cyclic phosphite under kinetic control to afford **1** selectively after hydrolysis and oxidation with sulfur. Isolation/filtration problems involving both **13** and hydrated **1** were solved by using α-cellulose as a bulking agent/filter aid, and simple methods were devised for the removal of cellulose at the appropriate times.

Experimental Section

All reagents were of commercial grade and were used without further purification. Melting points were measured with a capillary apparatus and are uncorrected. Purities of products were determined by HPLC and area normalization.

***m*-Hexyloxyphenyl Benzoate (13).** A 5-L, four-necked, round-bottomed flask equipped with a mechanical stirrer, a temperature monitor/controller, a condenser, and heating mantle was flushed with N_2 for 10 min and charged with 0.4 L of heptane, 64.7 g (0.2 mol) of TDA-1, 428.4 g (1.9 mol) of resorcinol monobenzoate, 414 g (3.0 mol) of potassium carbonate, and 429.2 g (2.6 mol) of 1-bromohexane and heated to 110 °C. The heating was continued at 110 °C until the proportion of bis-benzoate side-product was ≤5% (10 h). The heating was stopped, and the mixture was allowed to cool to room temperature. About 1 L of deionized water and 1 L of heptane were added to the reaction mixture and stirred for 15 min. The organic layer was separated and washed first with 0.5 L of I N NaOH aqueous solution and then with 0.5-L portions of deionized water. The volatiles were removed at 50 °C and 40 mbar pressure. About 200 mL of methanol was added to the residue, and the volatiles were removed again at 50 °C and 40 mbar pressure. About 200 mL of methanol was added to the residue, and the volatiles were removed once more at 50 °C and 40 mbar pressure. Methanol (1.5 L) was added to the distillation residue. The solution was warmed to 30 °C with stirring until homogeneous. α-Cellulose (21 g) was added, cooled to −10 °C (external temperature), and stirred at −10 °C for 2 h. The product was collected by filtration. The filter cake was washed with 25 mL of chilled methanol (−5 °C) and again with 15 mL of chilled methanol (−5 °C). The product was allowed to stand on the filter under vacuum for 1 h. Then the filter cake was dried in a vacuum oven (25 °C, 40 mbar) for 48 h to give 490.0 g of the *m*-hexyloxylphenyl benzoate with cellulose as an off-white solid. HPLC purity 71.58%; (62% yield); mp of the pure product 33.5−35.5 °C.

1-Chloro-4-(1-methoxy-1-methylethoxy)butane (10). A 500-mL, three-necked flask, equipped with a mechanical stirrer, a powder addition funnel and a gas outlet, was charged with 250 g of 4-chlorobutanol. Sodium bicarbonate (50 g) was added in portions over a period of 30 min and stirred at room temperature for 2 h. An aliquot of the filtrate (217 g) was used directly for the following reaction. A 1-L, four-necked, round-bottomed flask, equipped with a mechanical stirrer, nitrogen inlet−outlet, thermometer/temperature controller, addition funnel, and cooling bath (−20 °C) was flushed with nitrogen for 10 min and charged with 287 mL (3.0 mol) of 2-methoxypropene and 0.5 g (0,002 mol) of pyridinium *p*-toluenesulfonate. The above pretreated 4-chloro-l-butanol (217 g, 2.0 mol) was added to the cooled solution over a period of 1 h while maintaining an internal temperature of −15 °C. The mixture was stirred at −15 °C for an additional 30 min. Heptane (300 mL) and 0.5 mL of diisopropylethylamine were added to the mixture. The suspension was filtered through a K_2CO_3 (50 g) on a polyethylene filter, and the flask and the filter cake were rinsed with 50 mL of heptane. Volatile solvents were distilled off (30 °C, 30 mbar). The clear oil was further dried under the same vacuum (30 °C, 30 mbar) for 8 h to give 302.4 g of the product as a clear, colorless oil; crude yield: ∼100%.

The material was carried to the next step without purification.

4-(3-Hexyloxyphenoxy)-1-butanol (5). A 5-L, four-necked, round-bottomed flask, equipped with a mechanical stirrer, addition funnel, thermometer/temperature controller, nitrogen inlet/outlet, condenser, and heating mantle, was flushed with nitrogen for 10 min and charged with 120 g (3.0 mol) of sodium hydroxide pellets, 0.5 L of deionized water, 32.2 g (0.1 mol) of tetrabutylammonium bromide, and 314.0 g (0.75 mol) of 3-hexyloxyphenyl benzoate (containing α-cellulose). The mixture was heated to 100 °C under nitrogen, and 234.9 g (1.3 mol) of **10** was added over a period of 1 h, heated at 100 °C for 5 h, and cooled to 50 °C. Heptane (0.4 L) and 1.0 L of deionized water were added, and the mixture was stirred at 25 °C for 15 min and filtered. The cellulose residue was washed with 0. 1 L of heptane. The layers were separated, and the organic layer was washed twice with 0.5 L of deionized water. To the organic layer were added 0.2 L of 6 N HCI solution and 100 mL of deionized water, and the mixture was stirred vigorously at 25 °C for 1 h. The layers were separated, and the organic layer was diluted with 0.4 L of heptane and 0. 1 L of ethyl acetate, washed with 0.5 L of deionized water, and cooled to −15 °C. After 2 h at −15 °C, the product was collected by filtration. The filter cake was washed twice with 0.05 L of cold heptane (∼−15 °C). The product was dried in a vacuum oven (25 °C, 30 mbar) for 24 h to give 179.3 g of **2** (89.4% yield) as white, flaky crystals; mp 35.0−36.5 °C.

(***R,R*)-3-Carboxy-2-[[[[4-[(3-hexyloxy)phenoxy]butoxy]-mercapto]phosphinyl]oxy]-*N,N,N*-trimethyl-propanaminium Inner Salt (1).** A 5-L, four-necked, round-bottomed flask, equipped with a mechanical stirrer, thermometer, addition funnel, nitrogen inlet/outlet, and cooling bath was charged with 200 mL of dry and peroxide-free THF and cooled to −15 °C. $PC1_3$ (45.8 mL, 0.525 mol) was added over a period of 10 min, followed by a solution of 133 g (0.492 mol) of **2** in 300 mL of THF over a period of 30−40 min, while maintaining an internal temperature of −15 °C. The mixture was stirred at the same temperature for 10 min, and 150 mL of tributylamine was added over a period of 30 min (very exothermic!) at −15 °C. An additional 327 mL of tributylamine was added at the same temperature over 15 min. The reaction mixture was warmed to 3 °C over 10 min, and a solution of 252.0 g (0.525 mol) of L-carnitine tetraphenylborate salt dissolved in 500 mL of THF was added over a period of 30 min, while maintaining the internal temperature at 0 °C. The mixture was stirred at the same temperature for 1 h. Deionized water (250 mL) was added slowly over a period of 30 min at a temperature of 0−10 °C. To the reaction mixture was added 77 g (2.4 mol) of sulfur, and the mixture was warmed to 20 °C over 30 min and stirred for 16 h. The suspension was diluted with 500 mL of ethyl acetate, filtered through a polypropylene filter pad, and rinsed with 100 mL of ethyl acetate. The filtrate was diluted with 300 mL of heptane and cooled to 10 °C. The mixture was stirred rapidly, and ∼1000 mL of 2 N NaOH aqueous solution was added to adjust the pH of the stirred suspension to 8. (*The actual amount of base varies. It is important to bring the pH to the specified value.*) The layers were separated, the lower aqueous layer was cooled to 10 °C, and ∼130 mL of 6 N HCI aqueous solution was added to adjust the pH to 2 (*it is important to bring the pH to the specified value*). Ethyl acetate (1 L) was added, the mixture was stirred for 5 min, and the layers were separated. The upper organic extract was cooled to −15 °C (external) for 2.5 h; seed crystals were added to the solution. α-Cellulose (67 g) was added to the suspension and stirred vigorously for 15 min. The precipitate was filtered through a polypropylene filter, and the filter cake was washed twice with 20 mL of cold ethyl acetate (−10 °C). The filter cake was transferred to a 3-L, three-necked flask, 120 mL of ethanol was added, and the mixture was warmed to 60 °C. The suspension was filtered through a polypropylene filter pad; the cellulose residue was washed with an additional 400 mL of ethanol preheated to 50 °C, and again with 100 mL of ethanol preheated to 50 °C. The combined filtrates were concentrated under vacuum (40 °C, 60 mbar) to remove a total of 900 mL of ethanol and stirred at 0 °C over a period of 3.5 h. The suspension was filtered through a polypropylene filter, and the filter cake was transferred the to a 3-L, three-necked flask and dissolved in 800 mL of ethanol by heating to 60 °C. The solution was cooled to 0 °C and stirred for 2 h, and the product was collected by filtration through a polypropylene filter followed by washing with 25 mL of cold ethanol (10 °C). The white solid was dried at 45 °C, 60 mbar for 16 h to give 70.9 g of **1**; (28% yield); mp 140.6−141.1 °C; ^{1}H NMR (CD_3OD) δ 0.92 (t, 3H, J = 7.0 Hz), 1.27−1.42 (m, 4H), 1.42−1.55 (m, 2H), 1.70−1.82 (m, 2H), 1.82−1.95 (m, 4H), 2.70 (d,d, 1H, J = 15.5, 9 Hz), 3.20 (d,d, 1H, J = 15.5, 2 Hz), 3.27 (s, 9H), 3.51−3.72 (m, 2H), 3.91−4.15 (m, 6H), 5.16−5.30 (m, 1H), 6.42−6.53 (m, 3H), 7.13 (t, 1H); ^{13}C NMR (CD_3OD) δ 14.41, 23.70, 26.91, 26.95, 28.19, 28.31, 32.44, 32.81, 39.57, 55.06, 66.84, 66.91, 68.20, 68.26, 68.58, 70.91, 102.59, 107.82, 107.85, 130.87, 161.78, 161.85, 173.91; ^{31}P NMR (CD_3OD) δ 57.74; OR: $[\alpha]^{25}$ −21.98° (c = 0.95, MeOH).

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