cooling, the phases were separated, and the organic phase was diluted with methylene chloride, washed with water, dried, and evaporated to dryness. Purification of the crude product by preparative silica gel TLC (hexane/ethyl acetate, 3:2) yielded 0.264 g (88%) with mp 184–185 °C after recrystallization from methylene chloride–hexane. In addition 0.010 g of 3-(phenylsulfinyl)indole was recovered.

*N*-Benzyl-3-(methylsulfinyl)indole (**10f**), prepared from 3-(methylsulfinyl)indole and benzyl bromide, had mp 110–111 °C (methylene chloride–hexane): IR ($CHCl_3$) 1050 $cm^{-1}$; NMR 7.95 (m, 1 H), 7.53 (s, 1 H), 7.45–7.05 (m, 8 H), 5.30 (s, 2 H), 3.00 (s, 3 H); MS, *m/e* 269 ($M^+$). Anal. Calcd for $C_{16}H_{15}NOS$ (269.351): C, 71.34; H, 5.61; N, 5.20. Found: C, 71.35; H, 5.66; N, 5.17.

**The Chlorination of 3-(Phenylthio)indole with Sulfuryl Chloride.** To a solution of 3-(phenylthio)indole[16] (0.20 g) in anhydrous methylene chloride, maintained at 0 °C, was added dropwise sulfuryl chloride (0.071 mL), via microsyringe. The reaction was stirred at 0 °C for (1 h) and then washed with saturated sodium bicarbonate solution. The organic phase was dried and evaporated to dryness. The crude mixture, composed of several compounds, was separated on preparative silica gel TLC, by eluting with hexane–ethyl acetate (7:3), and the band corresponding to the previously characterized 2-chloro-3-(phenylthio)indole (**11a**) was isolated. The product weighed 0.046 g (20%) and had mp 98–99 °C after recrystallization from methylene chloride–pentane.

**Acknowledgment.** We express our appreciation to Dr. Joseph Muchowski, Syntex Research, Palo Alto, CA, for his support and encouragement of this work, as well as useful discussion.

**Registry No.** **5a**, 75421-89-5; **5b**, 75421-91-9; **5c**, 113976-52-6; **6a**, 98207-68-2; **6b**, 113976-53-7; **6c**, 113976-54-8; **7a**, 113976-55-9; **7b**, 113976-56-0; **8a**, 113976-57-1; **8b**, 113976-58-2; **8c**, 113976-59-3; **10a**, 98508-67-9; **10b**, 108698-57-3; **10c**, 98508-70-4; **10d**, 113976-64-0; **10e**, 113976-65-1; **10f**, 108698-58-4; **11a**, 98508-68-0; **11b**, 108698-59-5; **11c**, 98508-72-6; **11d**, 113976-60-6; **11e**, 113997-01-6; **11f**, 108726-69-8; **12c**, 108698-77-7; **12d**, 113976-61-7; **13a**, 98508-69-1; **13c**, 98508-74-8; **13d**, 113976-62-8; **13e**, 113976-63-9; **13f**, 108698-64-2; 3-(phenylthio)indole, 54491-43-9; 3-(methylthio)indole, 40015-10-9; 3-(methylsulfinyl)indole, 86925-06-6.

## Enzymes in Organic Synthesis. 43.[1] Investigation of the Preferred Orientations of Ester Groups in Pig Liver Esterase Catalyzed Hydrolyses Using Conformationally Rigid Substrates[2]

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Of the many enzymes that are useful in asymmetric synthesis,[3] pig liver esterase (PLE, EC 3.1.1.1) is one that has already proven of great value[3] and for which there remains considerable potential, as reflected by the degree of current interest in its synthetic applications.[4] One of the active-site models[5] for PLE has been proposed by the group of Tamm.[5a] In this, the preferred orientation for hydrolysis of an ester group at the active site was postulated to be equatorial when attached to a cyclohexane ring. This assumption, a key one for all PLE active-site model formulations, has now been verified in a study of the PLE-catalyzed hydrolyses of the conformationally rigid *tert*-butylcyclohexanecarboxylic acid esters **1a–4a**.

**Table I. Relative Rates of PLE-Catalyzed Hydrolyses of 1a–4a**[a]

| substrate | rel rate |
|---|---|
| ethyl butyrate | 100 |
| **1** | 29 |
| **2** | 127 |
| (±)-**3** | 57 |
| (±)-**4** | 8 |

[a] Determined at 23 °C. [S] = 0.5 nM in 0.1 M KCl (pH 7) containing 5% MeOH.

**Table II. Preparative-Scale PLE-Catalyzed Hydrolyses of (±)-3a and (±)-4a**[a]

| substrate | product acid (% yield, % ee) | recovd ester (% yield, % ee) |
|---|---|---|
| (±)-**3a** | (−)-(1*R*,3*S*)-**3b** (quant, 5) | (+)-(1*S*,3*R*)-**3a** (85, 6) |
| (±)-**4a** | (+)-(1*S*,3*S*)-**4b** (93, 4) | (−)-(1*R*,3*R*)-**4a** (80, 5) |

[a] At pH 7, 20 °C. Reactions terminated after 50% of hydrolysis.

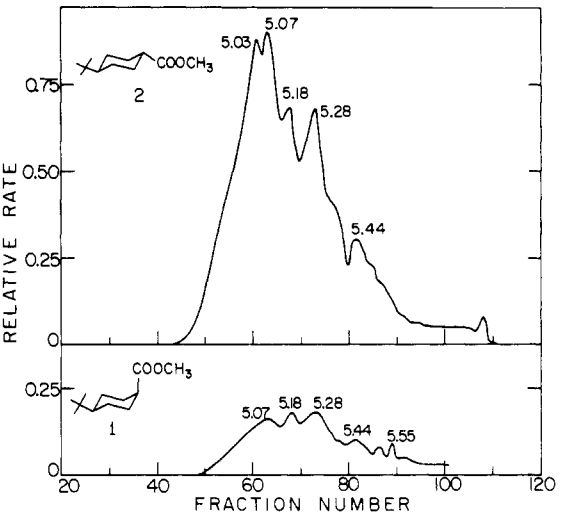


**Figure 1.** PLE-isozyme activity toward the equatorially and axially oriented ester groups of **2a** and **1a**, respectively, determined at pH 7 in 5% aqueous MeOH at 25 °C. The rates are relative to ethyl butyrate = 100. The fraction numbers are those from the isoelectric focusing separation. The numbers at the peaks are the p*I* values of the major isozyme fractions.

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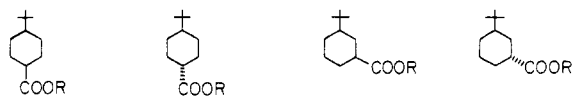


1 2 (±)-3 (±)-4

a, R = Me ; b, R = H

## Results

Esters **1a–4a** were prepared by combinations of literature methods. Their rates of PLE-catalyzed hydrolyses were then measured, using ethyl butyrate as the reference standard. The results are summarized in Table I. Esters **2a** and (±)-**3a**, with equatorially oriented –COOMe groups, are clearly much favored over **1a** and (±)-**4a**, for which the –COOMe orientations are axial. The preference for **2a** over **1a** was also confirmed for the different isozymes of PLE, as shown in Figure 1.

Since the relative hydrolysis rates of Table I for the racemates (+)-**3a** and **4a** might have been distorted by differences in the enantiomeric specificity of PLE toward the two substrates, preparative-scale reactions were carried out to the 50%-of-hydrolysis points in order to establish the degrees of enantiomeric selectivity involved. The results, summarized in Table II, showed marginal enantiomeric selectivity only in both cases.

The ee's of the chiral product acids **3b** and **4b** of Table II were determined, after KOH-mediated epimerization in the case of the trans acid **4b**, on their (*S*)-1-phenethylamides[6] by $^1$H NMR analysis of the *tert*-butyl proton resonances, using the corresponding racemic compounds as reference standards, and by GLC analyses. The ee's of the recovered esters **3a** and **4a** were established similarly after their KOH-mediated hydrolyses, and with epimerization to the trans series in the case of **4a**, to the corresponding cis acids **3b**.

The absolute configuration assignments were made by correlations with the known (–)-(1*R*,3*S*)-**3b** and (+)-(1*S*,3*R*)-**3b**[7], again after epimerization in the cases of the trans acid (+)-**4b** and trans ester (–)-**4a**.

## Discussion

The data in Table I show that, within the **1a–4a** substrate series, PLE-catalyzed hydrolyses of the equatorially oriented carboxymethyl groups are favored over those with axial –COOMe configurations by a factor of four- to seven-fold. This situation also applies to the individual isozymes composing commercial PLE (Figure 1). Differences in enantiomeric specificity toward the 3-*tert*-butyl substrates **3a** and **4a** do not affect the conclusion since PLE exhibits little stereoselectivity in its hydrolyses of these racemic esters (Table II). The ee's of (+)- and (–)-**3a,b** and –**4a,b** were determinable by either the NMR or GLC methods, with the latter, with its wide peak separation, being the more accurate. Despite the low optical rotations observed and the vigorous conditions required to hydrolyze and epimerize the trans compounds (+)-**4b** and (–)-**4a** to the known cis acids (+)- and (–)-**3b**, respectively, the absolute configuration assignments were made without difficulty. The results in Table II show that for both the *cis*- and *trans*-3-*tert*-butyl substrates **3a** and **4a**, PLE shows marginal selectivity for the 3*S* enantiomers.

The equatorial –COOMe preference of PLE observed for these conformationally rigid ester substrates confirms the key assumption made in this regard by Tamm and co-workers in their active-site model proposal.[5a]

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## Experimental Section

The instrumentation and general purification and analytical methods used were as described previously.[8] PLE (EC 3.1.1.1) was Sigma Chemical Co. Type II (lot 123F-0240). Unless otherwise noted, NMR's and $[\alpha]_D$'s were determined in $CDCl_3$ and $CHCl_3$, respectively, and IR's on KBr disks.

**Preparation of Substrates. Methyl *cis*- and *trans*-4-*tert*-Butylcyclohexanecarboxylate (1a and 2a).** Hydrogenation of *tert*-butylbenzoic acid, followed by separation of the cis- and trans-acid product via thiourea complexes as described by Krapcho and Dundulis[9] gave *cis*-4-*tert*-butylcyclohexanecarboxylic acid (**1b**, 48% yield), mp 117–118 °C (lit.[9] mp 116–118 °C), and *trans*-4-*tert*-butylcyclohexanecarboxylic acid (**2b**, 38% yield), mp 174–175.5 °C (lit.[9] mp 173.5–175 °C).

These acids were individually treated with ethereal diazomethane to give methyl *cis*-4-*tert*-butylcyclohexanecarboxylate (**1a**, 99% yield) [recrystallized from MeOH at –78 °C: mp 25.5–26.5 °C (lit.[10] mp 26.1–26.7 °C); IR 1736 cm$^{-1}$; $^1$H NMR $\delta$ 0.85 (9 H, s), 0.93–2.47 (9 H, m), 2.47–2.77 (1 H, m, $w_{1/2}$ = 9 Hz), 3.68 (3 H, s); $^{13}$C NMR $\delta$ 23.74, 27.30, 27.88, 32.32, 38.83, 47.90, 51.13, 175.49] and methyl *trans*-4-*tert*-butylcyclohexanecarboxylate (**2a**, 99% yield) [bp 84–85 °C (0.9 mmHg) (lit.[10] bp 84 °C (0.9 mmHg); IR 1736 cm$^{-1}$; $^1$H NMR $\delta$ 0.87 (9 H, s), 0.93–2.53 (10 H, m), 3.67 (3 H, s); $^{13}$C NMR $\delta$ 26.46, 27.30, 29.34, 32.22, 43.35, 47.30, 51.16, 176.45.

**Methyl *cis*- and *trans*-3-*tert*-Butylcyclohexanecarboxylate ((+)-3a and (+)-4a).** By the method of Whitham et al.[11] 4-*tert*-butylcyclohexane[12] (from *cis*- and *trans*-4-*tert*-butylcyclohexanol (Aldrich)) was converted into methyl *cis*-3-*tert*-butylcyclohexanecarboxylate ((±)-**3a**, 41% overall yield) [bp 88–90 °C (5 mmHg) (lit.[11b] bp 100 °C (bath) (10 mmHg); IR (film) 1738 cm$^{-1}$; $^1$H NMR $\delta$ 0.88 (9 H, s), 0.93–2.50 (10 H, m), 3.67 (3 H, s)] and methyl *trans*-3-*tert*-butylcyclohexanecarboxylate ((±)-**4a**, 39% overall yield) [bp 92–94 °C (5 mmHg) (lit.[11b] bp 100 °C (bath) (10 mmHg)); IR (film) 1736 cm$^{-1}$; $^1$H NMR $\delta$ 0.87 (9 H, s), 0.90–1.90 (7 H, m), 1.90–2.50 (2 H, m), 2.50–2.90 (1 H, m, $w_{1/2}$ = 10 Hz), 3.70 (3 H, s).

**Relative Rates of PLE-Catalyzed Hydrolyses of 1a–4a.** These were determined in the usual way.[13] The results for commercial PLE are recorded in Table I. PLE was resolved into its isozymes by isoelectric focusing as described previously.[1] The relative rate of hydrolyses of **1a** and **2a** catalyzed by the different isozyme fractions are shown in Figure 1.

**Preparative-Scale PLE-Catalyzed Hydrolyses of (+)-3a and (+)-4a.** These hydrolyses were carried out at pH 7, 20 °C by the standard procedure for racemic substrates,[13] with the reactions being terminated after 50% of hydrolysis. The results (summarized in Table II) were as follows:

Methyl *cis*-3-*tert*-butylcyclohexanecarboxylate ((±)-**3a**, 339 mg, 1.7 mmol) with PLE (240 units; 6h) gave methyl (1*S*,3*R*)-*cis*-3-*tert*-butylcyclohexanecarboxylate ((+)-**3a**, 144 mg, 43% yield, 6% ee) [bp 90–92 °C (5 mmHg) (lit.[11b] bp (for (±)-**3a**) 100 °C (bath) (10 mmHg)); $[\alpha]^{25}_D$ +1.5° (*c* 0.4); IR and NMR as for (+)-**3a** above] and (1*R*,3*S*)-*cis*-3-*tert*-butylcyclohexanecarboxylic acid ((–)-**3b**, 160 mg, 49% yield, 5% ee) [mp 92–93 °C (lit.[14] mp (for (±)-**3a**) 94.5–95 °C); $[\alpha]^{25}_D$ –0.71° (*c* 4.0) (lit.[7] $[\alpha]^{25}_D$ –19.1° (*c* 1.6)); IR 3300–2590, 1690 cm$^{-1}$; $^1$H NMR $\delta$ 0.88 (9 H, s), 0.90–2.50 (10 H, m), 11.0 (1 H, br s)]. Methyl *trans*-3-*tert*-butylcyclohexanecarboxylate ((±)-**4a**, 140 mg, 0.71 mmol) with PLE (120 units; 15 h) gave methyl (1*R*,3*R*)-*trans*-3-*tert*-butylcyclohexanecarboxylate ((–)-**4a**, 56 mg, 40% yield, 5% ee) [bp 91–94 °C (5

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mmHg) (lit.[11b] bp (for (±)-**4a**) 100 °C (bath) (10 mmHg)); $[\alpha]^{25}_D$ −0.42° (*c* 1.9); IR and NMR as for (±)-**4a** above] and (1*S*,3*S*)-*trans*-3-*tert*-butylcyclohexanecarboxylic acid ((+)-**4b**, 30 mg, 46% yield, 4% ee) [mp 117–118 °C (lit.[15] mp (for (+)-**4a**) 119–120 °C); $[\alpha]^{25}_D$ +0.33° (*c* 4.0); IR 3300–2570, 1697 $cm^{-1}$; $^1H$ NMR δ 0.88 (9 H, s), 0.90–2.46 (9 H, m), 2.63–2.97 (1 H, m), 9.27 (1 H, br s)].

**Absolute Configuration Determinations.** All correlations were to (+)-(1*S*,3*R*)- and (−)-(1*R*,3*S*)-**3b**.[7] Methyl *cis*-3-*tert*-butylcyclohexanecarboxylate ((+)-**3a**, 80 mg, 0.40 mmol) was hydrolyzed with KOH to give (+)-(1*S*,3*R*)-*cis*-3-*tert*-butylcyclohexanecarboxylic acid (**3b**, 52 mg, 70% yield): mp 90–92 °C (lit.[14] mp (for (±)-**3b**) 94.5–95 °C); $[\alpha]^{25}_D$ +1.0° (*c* 4.0) (lit.[7] $[\alpha]^{25}_D$ +21.1° (*c* 1.6).

*trans*-3-*tert*-Butylcyclohexanecarboxylic acid ((+)-**4b**, 60 mg, 0.3 mmol) in ethylene glycol (10 mL) was epimerized with KOH (1.0 g, 17.9 mmol) under reflux for 14 h. Workup with diethyl ether extraction of the acidified mixture gave (−)-(1*R*,3*S*)-**3b** (50 mg, 83% yield): mp 89–91 °C; $[\alpha]^{25}_D$ −0.29° (*c* 3.8) (lit.[7] $[\alpha]^{25}_D$ −19.1° (*c* 1.6).

Methyl *trans*-*tert*-butylcyclohexanecarboxylate ((−)-**4a**, 20 mg, 0.1 mmol) was hydrolyzed and epimerized as for (+)-**4b** above to give (+)-(1*S*,3*R*)-**3b** (15 mg, 80% yield): mp 90–93 °C; $[\alpha]^{25}_D$ +0.54° (*c* 1.3).

**Enantiomeric Excess Determinations.** These were performed on the (*S*)-1-phenylethanamides of the trans acids (+)- and (−)-**3b** obtained directly from the enzyme reactions or from the absolute configuration determinations. The ee's (Table II) were determined from integrations of the diastereomeric *tert*-butyl proton peaks or, better, from GLC analysis, using the amide from (+)-**3b** as the reference standard, and are accurate to ≤±2%. The reference amide (1*R*/*S*,3*S*/*R*,1′*S*)-*N*-(1′-phenylethyl)-*cis*-3-*tert*-butylcyclohexancarboxamide, prepared by the method of Heathcock and co-workers[6] in quantitative yield, had the following properties: mp 126–128 °C; IR 3270, 1637 $cm^{-1}$; $^1H$ NMR (200 MHz) δ 0.84 and 0.85 (9 H, two s, 1:1), 0.93, 2.27 (10 H, m), 1.46 (3 H, d, *J* = 6.9 Hz), 5.06–5.21 (1 H, m), 5.66–5.70 (1 H, br s), 7.07–7.33 (5 H, m); GLC (DB wax capillary column, 220 °C) retention times 26.11 (49.02%), 26.91 (50.98%) min.

**Acknowledgment.** The support of the Natural Sciences and Engineering Research Council of Canada and the awards (to L.K.P.L.) of a Gollop Memorial and a University of Toronto Open Scholarship are gratefully acknowledged.

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## Direct Synthesis of Spiro[5.5]undeca-1,4,7-trienones from Phenols via a Quinone Methide Intermediate

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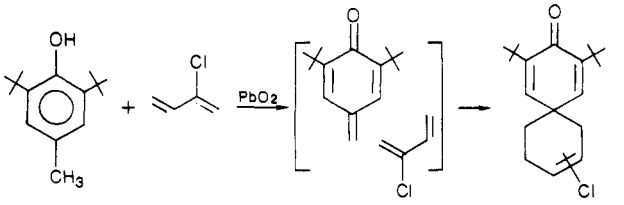
Spiro ketones, such as 2,4-dialkylspiro[5.5]undeca-1,4,7-trien-3-ones, are rather unusual compounds which are reported only infrequently in the literature. An intriguing feature of these molecules is their ability to undergo a dienone–phenol rearrangement and thereby yield a fused ring system. Reported herein is a significant improvement in the synthesis of dienones, specifically spiroundecatrienones.

In 1958 Hatchard[1a] synthesized 2,4-di-*tert*-butyl-8(or 9)-chlorospiro[5.5]undeca-1,4,7-trien-3-one (**1**) by treating 4-methyl-2,6-di-*tert*-butylphenol with lead dioxide in the presence of chloroprene. Hatchard suggested a radical mechanism for the formation of spiro ketone **1**. It was not until McClure's report[1b] in 1962 that this reaction was recognized as proceeding via entrapment of a quinone methide intermediate to give a [4 + 2] cycloadduct. McClure prepared compounds **1**, **2a**, and **2b** in yields of 93%, 10%, and 44%, respectively. Subsequently, only

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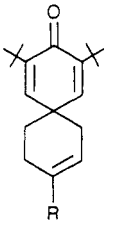
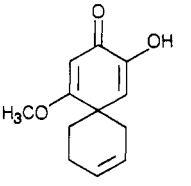



**2a**, R = H
**b**, R = $CH_3$

a few isolated reports[1c-g] of spiroundecatrienone synthesis via cycloaddition have appeared in the literature. These reports include an unexpected spiro ketone synthesis discovered by Danishefsky[1e,f] while studying Diels–Alder reactions of *o*-benzoquinones. Under certain circumstances, spiroundecatrienone **3** was formed and not the expected fused ring product **4**. All the references cited

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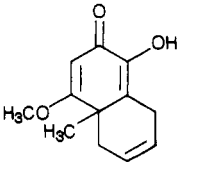


4

herein rely upon a *p*-alkyl-substituted phenol as starting substrate. Generally, these para-alkylated phenols require a labile benzyl substituent in order to generate a reactive quinone methide dienophile. This paper reports a synthetic method which avoids this requirement by utilizing phenols as starting substrates for spiroundecatrienone synthesis.

### Results and Discussion

A series of observations lead to the conclusion that spiroundecatrienones could be prepared directly from 2,6-dialkylphenols and thereby avoid the necessity of first preparing and then isolating a para-substituted phenol possessing a leaving group at the benzylic position. Initially spiro ketone **6a** was prepared by treating **5a** with methyl iodide to give (4-hydroxy-3,5-di-*tert*-butylbenzyl)trimethylammonium iodide. Heating this quater-

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