gave $\Delta G^{\ddagger} = 9.6$ kcal/mol. The assumption that $\Delta\nu$ at −97 °C represents maximum peak separation introduces some uncertainty in this value, but a significantly increased value of $\Delta\nu$ would lower $\Delta G^{\ddagger}$ by only as much as several tenths of 1 kcal.

X-ray Crystallographic Analyses of 20 and 25. Crystal data are provided in ref 13. Nonhydrogen atom fractional coordinates are recorded in Table IV. Thermal parameters are available as supplementary material.

Registry No. 4, 2819-48-9; **5**, 65482-10-2; **6**, 80754-56-9; **7**, 65482-11-3; **8**, 80754-57-0; **9**, isomer I, 80754-58-1; **10**, 54290-41-4; **11**, 70179-64-5; **12**, 70179-63-4; **13**, 70179-65-6; **14**, 75401-33-1; **15**, 75401-34-2; **16**, 75401-35-3; **17**, isomer I, 80754-59-2; **17**, isomer II, 80794-93-0; **18**, 55781-96-9; **19**, 74078-07-2; **20**, 65114-88-7; **21**, 80754-60-5; **22**, 65114-89-8; **23**, isomer I, 80754-61-6; **23**, isomer II, 80794-94-1; **24**, 75401-36-4; **25**, 75531-99-6; **26**, 80461-86-5; **27**, isomer I, 80794-95-2; **27**, isomer II, 80794-96-3; **28**, 74078-08-3; **40**, 33383-70-9; **40** diamide, 80754-62-7; **40** diamine, 80754-63-8; methylphosphonous dichloride, 676-83-5; phenylphosphonous dibromide, 1073-47-8; phosphorus tribromide, 7789-60-8; 2,3-diphenylbutadiene, 2548-47-2; **9**, isomer II, 80794-97-4.

Supplementary Material Available: Tables of anisotropic thermal parameters for **20** and **25**, hydrogen atom fractional coordinates and isotropic thermal parameters for **20**, hydrogen atom fractional coordinates for **25**, and elemental analyses for compounds **5–7**, **11–13**, and **20–28** (5 pages). Ordering information is given on any current masthead page.

Synthesis of Aromatic Carbonyl Compounds via Thallation–Carbonylation of Arenes

Richard C. Larock* and Constance A. Fellows

Contribution from the Department of Chemistry, Iowa State University, Ames, Iowa 50011. *Received December 1, 1980*

Abstract: Simple arenes, substituted benzylic and β-phenethyl alcohols, benzoic acid, phenylacetic acid, benzamide, acetanilide, phenylurea, and benzophenone have been thallated under a variety of reaction conditions with thallium(III) trifluoroacetate and subsequently carbonylated with 10% $PdCl_2$, 2 equiv of LiCl, and MgO in either methanol or tetrahydrofuran under 1 atm of carbon monoxide to give aromatic esters, substituted phthalides and 3,4-dihydroisocoumarins, phthalic and homophthalic anhydride, phthalimide, and the ortho-substituted methyl esters of acetanilide, phenylurea, and benzophenone, respectively. The scope and limitations of this approach to aromatic carbonyl compounds are examined.

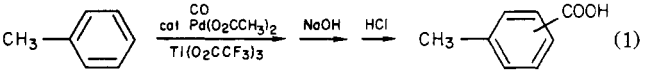
Organothallium compounds have recently proven to be valuable intermediates in organic synthesis.[1-3] The highly regiospecific electrophilic thallation of arenes[4,5] and many novel methods by which the thallium moiety can be substituted by a variety of functional groups of great importance to the organic chemist have provided a number of important new routes to substituted arenes. Our own interests in the carbonylation of organomercurials[6-8] have encouraged us to look at similar applications of the closely related organothallium compounds. We herein report that the successful thallation and subsequent carbonylation of a variety of substituted arenes provides a highly convenient new route to simple aromatic esters, phthalides, 3,4-dihydroisocoumarins, anhydrides, and imides.[9]

While the direct carbonylation of arylthallium compounds has been studied, it requires high temperatures and pressures, and the yields are generally poor.[10] Since organomercurial carbonylation reactions are greatly facilitated by addition of palladium salts,[6,7] we have examined the possibility that arylthallium compounds might be carbonylated at room temperature and atmospheric pressure by addition of palladium chloride. The transmetalation of arylthallium compounds by palladium chloride has previously been communicated.[11,12] During our investigations, Van Venrooy patented a similar approach to aromatic carboxylic acids using excess benzene or toluene, thallium trifluoroacetate (TTFA), 0.1–10% palladium acetate, and 4–7 atm of carbon monoxide (eq 1).[13] Good yields of carboxylic acids were obtained based on thallium reagent, but in order to be useful the aromatic starting material must either be cheap or recyclable. The elevated pressures and product mixtures further detract from the procedure. Our own work has concentrated on developing a simple atmospheric-pressure, room-temperature method of catalytically carbonylating arenes which provides excellent yields of the carbonyl product without using an excess of starting arene and which takes advantage of the high regioselectivity of electrophilic aromatic

Table I. Carbonylation of Phenylthallium Bis(trifluoroacetate)[a]

entry	added salt(s), equiv	% yield of methyl benzoate (% biphenyl)[b] −78 °C → 25 °C	0 °C	25 °C
1	$PdCl_2$, 1	28 (11)	53	13 (24)
2	$PdCl_2$, 1; LiCl, 2	57	39 (3)	54
3	$PdCl_2$, 1; LiCl, 2; MgO, 1			57
4	$PdCl_2$, 0.1			13 (9)
5	$PdCl_2$, 0.1; LiCl, 2	25 (7)	34 (6)	57
6	$PdCl_2$, 0.1; LiCl, 2; MgO, 1	44 (7)	57	

[a] 1 mmol of $PhTl(O_2CCF_3)_2$ in 10 mL of CH_3OH. [b] GLC analysis with tetradecane as an internal standard.



(1)

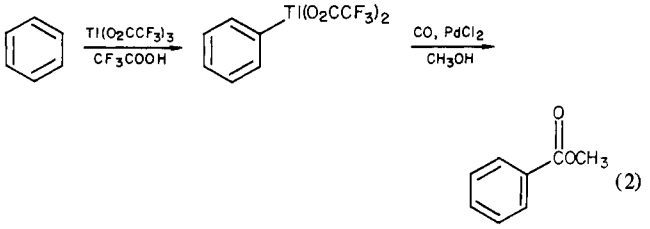
(1) Taylor, E. C.; McKillop, A. *Acc. Chem. Res.* **1970**, *3*, 338–46.
(2) McKillop, A.; Taylor, E. C. *Chem. Br.* **1973**, *9*, 4–11.
(3) McKillop, A.; Taylor, E. C. *Adv. Organomet. Chem.* **1973**, *11*, 147–206.
(4) McKillop, A.; Hunt, J. D.; Zelesko, M. J.; Fowler, J. S.; Taylor, E. C.; McGillivray, G.; Kienzle, F. *J. Am. Chem. Soc.* **1971**, *93*, 4841–4.
(5) Taylor, E. C.; Kienzle, F.; Robey, R. L.; McKillop, A.; Hunt, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 4845–50.
(6) Larock, R. C. *J. Org. Chem.* **1975**, *40*, 3237–42.
(7) Larock, R. C.; Riefling, B.; Fellows, C. A. *J. Org. Chem.* **1978**, *43*, 131–7.
(8) Larock, R. C.; Hershberger, S. S. *J. Org. Chem.* **1980**, *45*, 3840–6.
(9) Preliminary communication: Larock, R. C.; Fellows, C. A. *J. Org. Chem.* **1980**, *45*, 363–5.
(10) Davidson, J. M.; Dyer, G. *J. Chem. Soc. A* **1968**, 1616–7.
(11) Uemura, S.; Ikeda, Y.; Ichikawa, K. *J. Chem. Soc., Chem. Commun.* **1971**, 390–1.
(12) Spencer, T.; Thorpe, F. G. *J. Organomet. Chem.* **1975**, *99*, C8-10.
(13) Van Venrooy, J. J. U.S. Patent 4 093 647, 1978; *Chem. Abstr.* **1978**, *89*, P163274u.

0002-7863/82/1504-1900$01.25/0

thallation to provide a single regioisomeric carbonyl product.

Results and Discussion

Aromatic Esters. A convenient carbonylation procedure was developed using the conversion of benzene to methyl benzoate as a model system (eq 2). Isolated phenylthallium bis(trifluoro-



(2)

acetate)[4] was used to study the effect of each of the following reaction conditions on the yield of methyl benzoate: reaction temperature and presence or absence of lithium chloride (2 equiv) and/or magnesium oxide. Previous experience with carbonylation reactions and organopalladium chemistry has pointed out the importance of these variables. The results are summarized in Table I.

The most important finding is that only catalytic amounts of palladium chloride are required in these reactions. This greatly increases the potential synthetic utility of this reaction sequence. It is not necessary to add cupric chloride to reoxidize the palladium, as reported by Spencer and Thorpe for the palladium chloride–catalyzed olefination of arylthallium compounds.[12] Apparently, the thallium(III) salt generated upon transmetalation with the palladium(II) salt is a sufficiently strong oxidant that it continually reoxidizes the palladium metal formed upon carbonylation and esterification (eq 3–6).

$$ArTlX_2 + PdX_4^{2-} \rightarrow ArPdX_3^{2-} + TlX_3 \quad (3)$$

$$ArPdX_3^{2-} + CO \rightarrow ArC(=O)PdX_3^{2-} \quad (4)$$

$$ArC(=O)PdX_3^{2-} + ROH \rightarrow ArC(=O)OR + HX + Pd + 2X^- \quad (5)$$

$$Pd + TlX_3 \rightarrow PdX_2 + TlX \quad (6)$$

For the most part, the carbonylation reactions were quite clean, with only one major side product, biphenyl. Undoubtedly, biphenyl arises from palladium-promoted coupling of phenylthallium bis(trifluoroacetate).[11] Addition of lithium chloride and magnesium oxide appeared to suppress biphenyl formation at room temperature. Based on the results of Table I, which indicated that the highest yields of methyl benzoate could be obtained at room temperature in the presence of lithium chloride and magnesium oxide, subsequent carbonylation reactions were run with 0.1 equiv of palladium chloride and 2 equiv of lithium chloride and magnesium oxide at room temperature.

Due to the difficulties inherent in attempting to isolate and purify toxic arylthallium intermediates, we next chose to examine the "direct" thallation and carbonylation of benzene. Benzene was thallated with TTFA in trifluoroacetic acid (TFA),[4] excess TFA was evaporated from the reaction, and the crude material was subsequently dissolved in methanol and added to a stirred mixture of palladium chloride, methanol, and other salts under 1 atm of carbon monoxide. Changing the proportions of benzene to TTFA in the thallation reaction had a pronounced effect on the overall yield as shown in Table II. Excess thallium reagent proved detrimental, while excess benzene gave high yields. Commercial TTFA generally afforded somewhat lower yields of carbonylation product than reagent prepared ourselves.

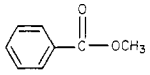
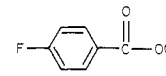
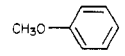
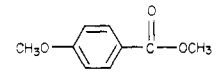
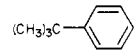
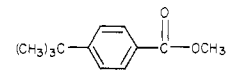
Several simple monosubstituted benzenes have also been carbonylated with 1 equiv of TTFA and our best carbonylation conditions. Fair to good yields of essentially isomerically pure methyl esters were obtained (Table III). With *tert*-butylbenzene less than 2% of the ortho-substituted ester was observed. Anisole afforded approximately 2–9% of a side product presumed to be the *o*-methoxy ester.

Table II. Effect of Stoichiometry on the Thallation–Carbonylation of Benzene

entry	benzene: $Tl(O_2CCF_3)_3$	% yield of $PhCO_2CH_3$[a]
1	1:0.9	44[b]
2	1:1	48,[b] 47[c]
3	1:1.2	55,[b] 45[c]
4	1:2	20[b]
5	5:1	73[c,d]

[a] GLC yield based on 1 mmol of benzene. Carbonylation conditions: 0.1 mmol $PdCl_2$, 2 mmol of LiCl, 1 mmol of MgO, 10 mL of CH_3OH under 1 atm of CO at room temperature for 24 h. [b] Prepared thallium trifluoroacetate. [c] Commercial thallium trifluoroacetate. [d] GLC yield based on 1 mmol of thallium trifluoroacetate.

Table III. Synthesis of Aryl Esters via Thallation–Carbonylation

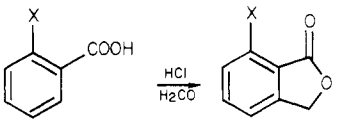
entry	arene	product	% yield[a]
1			55
2			42[b]
3			62
4			80[c]

[a] GLC yield based on 1 mmol of arene. Thallations performed according to procedures in ref 4. Carbonylation conditions: 0.1 mmol of $PdCl_2$, 2 mmol of LiCl, 1 mmol of MgO, 10 mL of CH_3OH at room temperature for 24 h. [b] Thallated for 48 h. [c] Carbonylated for 96 h.

Our results in these preliminary investigations demonstrate that the transmetalation of arylthallium compounds by palladium salts and subsequent catalytic carbonylation is potentially a very useful reaction sequence. Encouraged by the early results, we have chosen to examine the thallation–carbonylation of heteroatom-containing arenes where thallation is known to lead almost exclusively to ortho-substituted arylthallium compounds which might then be carbonylated to afford a variety of interesting cyclic carbonyl compounds. Our initial efforts focused on the synthesis of phthalides.

Phthalides. The aromatic lactones called phthalides (3*H*-isobenzofuran-1-ones) have been isolated from a variety of plants. They reportedly possess fungicidal,[14,15] bacteriocidal,[15] herbicidal,[15] and analgesic activity[16] and have proven useful in the treatment of circulatory and heart diseases.[17]

Until recently, almost all synthetic routes to phthalides started with the carboxylic acid corresponding to the lactone carbonyl group and introduced an ortho benzylic alcohol group which rapidly lactonizes (eq 7).[16] This approach suffers the disadvantage

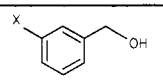
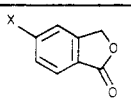
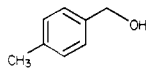
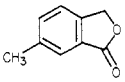
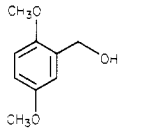
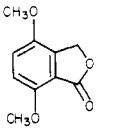
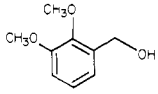
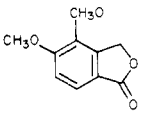


(7)

of requiring electrophilic aromatic substitution on a deactivated aromatic ring. As a consequence one often observes substitution

(14) Aoki, K.; Furusho, T.; Kimura, T.; Satake, K.; Funayama S. Japanese Patent 73 24724, 1973; *Chem. Abstr.* **1974**, *80*, 129246r.
(15) Lacova, M. *Chem. Zvesti* **1973**, *27*, 525; *Chem. Abstr.* **1974**, *80*, 59757g.
(16) Elderfield, R. C. "Heterocyclic Compounds"; J. Wiley: New York, 1951; Vol. 2, Chapter 2.
(17) Bellasio, E. German Patent 2422193, 1974; *Chem. Abstr.* **1975**, *83*, 9788j.

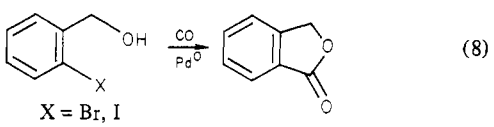
Table IV. Synthesis of Phthalides from Benzylic Alcohols

	alcohol	thallation conditions	product	% yield[a]	mp, °C (lit. mp, °C)
1					
	a, X = H	TFA, 0 °C, 1 day		33 (18)	68 (73[b])
	b, X = CH_3O	5:1 THF/TFA, 25 °C, 15 min		89 (47)	116-118 (118[c])
	c, X = HO	10:1 THF/TFA, 25 °C, 19 h		(95)	223-224 (222,[d] 223[e])
	d, X = Cl	TFA, reflux, 3 h		45	154-155 (154[f])
2		5:1 THF/TFA, 25 °C, 2 days		23 (22)	88
3		5:1 THF/TFA, 25 °C, 16 h		(32)	162-165 (168-170[g])
4		5:1 THF/TFA, 25 °C, 18 h		64 (54)	122-123 (123-124[h])

[a] GLC analysis with an internal standard (isolated, purified yield). [b] See ref 27. [c] See ref 28. [d] See ref 29. [e] See ref 30. [f] See ref 31. [g] See ref 32. [h] See ref 33.

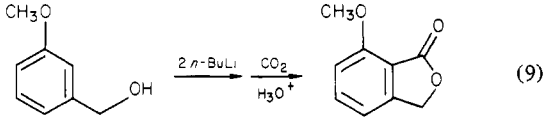
in positions other than the desired ortho position. More recently, the reduction of phthalic anhydrides has been developed as a useful approach to phthalides, although the regioselectivity of reduction is often a problem.[16,18]

A number of papers have appeared in the past few years which attack the regioselectivity problem by directed metalations of appropriately substituted arenes. One approach generates ortho-metalated aromatic compounds from ortho haloaromatics as in the facile palladium-catalyzed carbonylation of ortho halobenzyl alcohols recently reported by Mori[19] and by Stille[20] (eq 8) Unfortunately, in order to obtain substituted phthalides, one first must prepare specific ortho haloaromatic compounds, not always an easy task. Another approach involves the directed lithiation of



(8)

benzamides.[21-24] Recently, the lithiation of benzylic alcohols and subsequent treatment with carbon dioxide has provided a useful approach to phthalides (eq 9).[25,26] As will be seen, this procedure nicely complements our own thallation–carbonylation approach from benzylic alcohols to phthalides.



(9)

Benzyl alcohol is reported by Taylor and McKillop to undergo thallation exclusively (>99%) in the ortho position due to intramolecular delivery of the thallium electrophile by the alcohol oxygen.[5] No yield of arylthallium compound is reported however.

We have examined the direct thallation–carbonylation of benzyl alcohol under a wide variety of reaction conditions. The best conditions [TTFA and benzyl alcohol in TFA (1:1) at 0 °C for 1 day and carbonylation in methanol with 1 equiv of magnesium oxide] gave only a disappointing 33% yield (entry 1a, Table IV). One problem was incomplete thallation. GLC traces of all reaction mixtures showed 25–35% unreacted benzyl alcohol still present. Longer thallation times or excess TTFA only gave lower yields of phthalide. It appears that benzyl trifluoroacetate is also formed under the strongly acidic thallation conditions.

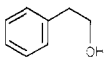
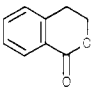
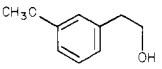
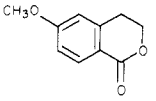
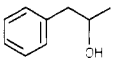
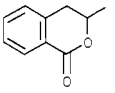
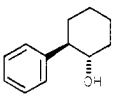
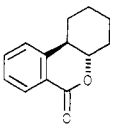
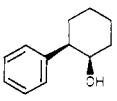
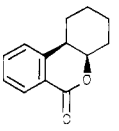
The thallation–carbonylation of a series of substituted benzylic alcohols was studied next. Since there were no reports in the literature concerning thallation of substituted benzyl alcohols, our major task became one of determining the best thallation conditions for these substrates. The best thallation conditions and yields of phthalides are reported in Table IV. Best results with activated aromatics were usually obtained by diluting the TFA with THF. As with benzyl alcohol considerable amounts of unreacted starting alcohol were sometimes observed. This was especially true with *m*-chloro- and *p*-methylbenzyl alcohols. Longer thallation times failed to remedy this situation or improve the yields of phthalides.

The regioselectivity of the thallation–carbonylation sequence is excellent. The meta-substituted benzyl alcohols (entries 1b, 1c, and 1d in Table IV) all gave exclusively the 5-substituted phthalides indicated. No 7-substituted products were observed. Evidently the 2 position (between substituents) is simply too crowded for attack by the large thallium electrophile. Our results with *m*-methoxybenzyl alcohol nicely complement those of Uemura et al.,[25] in which the same starting material is lithiated in the 2 position, eventually affording 7-methoxyphthalide (see eq 9). The importance of steric hindrance helps explain the low yield of 4,7-dimethoxyphthalide (entry 3, Table IV), since the 6 position of 2,5-dimethoxybenzyl alcohol is also crowded.

Application of our reaction sequence to 2,3-dimethoxybenzyl alcohol (entry 4, Table IV) gave a 64% yield of 4,5-dimethoxyphthalide, also called pseudomeconin. Our method affords a much higher overall yield of pseudomeconin in far fewer steps than the classical synthesis reported over 5 decades ago[34] or several more

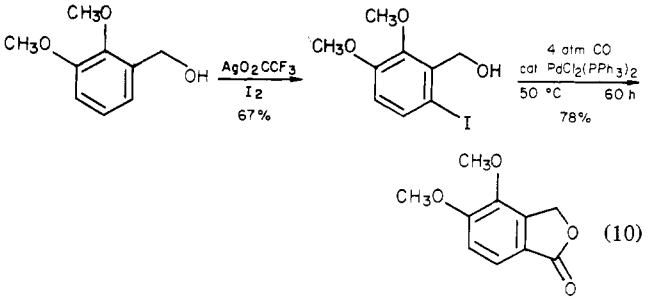
(18) McAlles, A. J.; McCrindle, R.; Sneddon, D. W. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2030–6, 2037–8.
(19) Mori, M.; Chiba, K.; Inotsume, N.; Ban, Y. *Heterocycles* **1979**, *12*, 921–4.
(20) Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193–8.
(21) Puterbaugh, W. H.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 853–6.
(22) Narasimhan, N. S.; Bhide, B. H. *Tetrahedron* **1971**, *27*, 6171–6.
(23) de Silva, S. O.; Reed, J. N.; Snieckus, V. *Tetrahedron Lett.* **1978**, 5099–5102.
(24) Watanabe M.; Snieckus, V. *J. Am. Chem. Soc.* **1980**, *102*, 1457–60.
(25) Uemura, M.; Tokuyama, S.; Sakan, T. *Chem. Lett.* **1975**, 1195–8.
(26) Meyer, N.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 521–2.
(27) Hessert, J. *Chem. Ber.* **1877**, *10*, 1445–50.
(28) Vĕne, J.; Tirouflet, J. *C. R. Hebd. Seances Acad. Sci.* **1951**, *232*, 2328–9.
(29) Rĕe, A. *Justus Liebigs Ann. Chem.* **1886**, *233*, 216–40.
(30) Levy, L. F.; Stephen, H. *J. Chem. Soc.* **1931**, 867–71.
(31) Tirouflet, J. *Bull. Soc. Sci. Bretagne* **1951**, *Spec. No. 26*, 7–122; *Chem. Abstr.* **1953**, *47*, 8692g.

Table V. Synthesis of 3,4-Dihydroisocoumarins from β-Phenethyl Alcohols

entry	alcohol	thallation conditions	product	% yield[a]	mp, °C (lit. mp, °C)
1		TFA, 25 °C, 1 day		51	oil
2		5:1 THF/TFA, 25 °C, 1 day		58 (45)	60–62 (68,[b] 71–72[c])
3		TFA, 25 °C, 1 day		75 (58)	25–28 (30,[d] 53[e])
4		TFA, 25 °C, 16 h		77 (48)	91.5–93
5		TFA, 25 °C, 16 h		88	93

[a] GLC analysis with an internal standard (isolated, purified yield). [b] See ref 22 and 43. [c] See ref 44. [d] See ref 45. [e] See ref 46.

recent syntheses.[35-37] Recently Stille has developed an approach very similar to ours which affords pseudomeconin in two steps from 2,3-dimethoxybenzyl alcohol, in 52% overall yield (eq 10).[20]

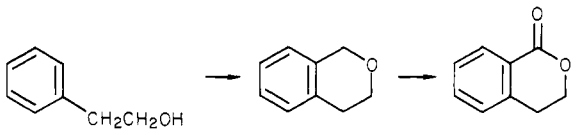


(10)

The thallation–carbonylation of several substrates failed. 4-Nitrobenzyl alcohol could not be thallated even by refluxing with TTFA in TFA for 1 day. 2-Naphthalenemethanol gave only a 4% yield of 6,7-benzophthalide (substitution in the 1 position). The low yield may be due to thallium-promoted biaryl formation.[38] 4-Methoxybenzyl alcohol in which the substituent directive effects are in opposition gave as the only recognizable products starting alcohol (10%) and *p*-anisaldehyde (12%). No simple carbonylation products were observed. Thin layer chromatography and GC–mass spectrometry indicated the presence of a number of high molecular weight compounds. α-Phenethyl alcohol gave none of the desired 3-methylphthalide. Considerable starting alcohol and at least two other products were observed. One of the latter compounds appeared to be a dicarbomethoxystyrene.

3,4-Dihydroisocoumarins. 3,4-Dihydroisocoumarins are another important class of aryl lactones which occur in a number of plants.[39,40] Several 3-alkyl-3-aryl-3,4-dihydroisocoumarins have demonstrated diuretic and hypotensive–antihypertensive activity.[41] The most widely studied 3,4-dihydroisocoumarins are the microbial toxins called ochratoxin A and B.[40]

A variety of methods exist for the synthesis of 3,4-dihydroisocoumarins, consisting mostly of condensation, cyclization, and oxidation reactions.[39] However, few of these procedures start with readily available materials and allow the introduction of a large variety of substituents. One method of some importance utilizes the chloromethylation–cyclization of readily available β-phenethyl alcohols to give isochromans, which are subsequently oxidized to 3,4-dihydroisocoumarins (eq 11). This approach suffers from

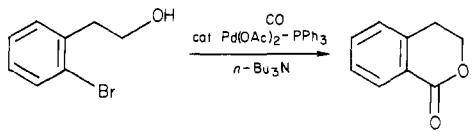


(11)

the inability of the side chain to direct attack exclusively to the ortho position. Thus, isomeric chloromethylated compounds are common side products. The oxidizing conditions also prevent the application of this sequence to phenolic substrates. The direct lithiation of aromatic substrates, which has shown such promise in phthalide syntheses, has been used only rarely for 3,4-dihydroisocoumarins.[21,22] However, the conversion of 2-halobenzoic acids to 2-allylbenzoic acids and subsequent palladium-promoted cyclization and hydrogenation afford an interesting new route to the 3,4-dihydroisocoumarin skeleton.[42] Finally, Mori and Ban

(32) Groves, W. G.; Loev, B.; Perchonock, C. D. U.S. Patent 4 032 656, 1977; *Chem. Abstr.* **1977**, *87*, P117685q.
(33) Salomon, O. *Chem. Ber.* **1887**, *20*, 883–9.
(34) Edwards, G. A.; Perkin, W. H., Jr.; Stoyle, F. W. *J. Chem. Soc.* **1925**, *127*, 195–9.
(35) Wood, J. H.; Perry, M. A.; Tung, C. C. *J. Am. Chem. Soc.* **1950**, *72*, 2989–91.
(36) Etogo Nzue, S.; Bodo, B.; Molho, D. *Bull. Mus. Natl. Hist. Nat., Sci. Phys.-Chim.* **1977**, *14*, 65–75; *Chem. Abstr.* **1978**, *89*, 128822z.
(37) Popoff, T.; Theander, O. *Acta Chem. Scand., Ser. B.* **1976**, *30*, 397–402.
(38) McKillop, A.; Turnell, A. G.; Young, D. W.; Taylor, E. C. *J. Am. Chem. Soc.* **1980**, *102*, 6504–12.
(39) Barry, R. D. *Chem. Rev.* **1964**, *64*, 229–60.
(40) Steyn, P. S. "Microbial Toxins", Ciegler, A.; Kadis, S.; Ajl, S. J., Eds.; Academic Press: New York, 1971; Vol. 6, Chapter 2.
(41) Houlihan, W. J.; Nadelson, J. British Patent 1 374 337, 1974; *Chem. Abstr.* **1975**, *83*, 43196z.
(42) Korte, D. E.; Hegedus, L. S.; Wirth, R. K. *J. Org. Chem.* **1977**, *42*, 1329–36.
(43) Mukhopadhyay, D.; Chaudhury, D. N. *J. Indian Chem. Soc.* **1963**, *40*, 433–6.
(44) Bose, N. K.; Chaudhury, D. N. *J. Indian Chem. Soc.* **1969**, *46*, 854.
(45) Tirodkar, R. B.; Usgaonkar, R. N. *J. Indian Chem. Soc.* **1969**, *46*, 935–44.
(46) Colonge, J.; Boisde, P. *Bull. Soc. Chim. Fr.* **1956**, 1337–44.
(47) Wislicenus, W. *Justus Liebigs Ann. Chem.* **1886**, *233*, 101–16.
(48) Dieckmann, W. *Chem. Ber.* **1914**, *47*, 1428–34.
(49) Davies, W.; Poole, H. G. *J. Chem. Soc.* **1928**, 1616–20.
(50) Erdmann, H. *Chem. Ber.* **1899**, *32*, 3570–3.
(51) Bogert, M. T.; Scatchard, G. *J. Am. Chem. Soc.* **1919**, *41*, 2052–68.

have reported the palladium-catalyzed carbonylation of *o*-bromo-β-phenethyl alcohol (eq 12).[19] All of these methods have their limitations.



(12)

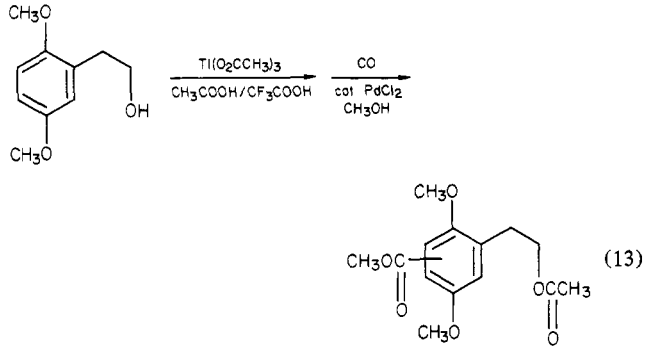
Our success with the thallation–carbonylation of benzylic alcohols prompted an analogous study on β-phenethyl alcohols as a potentially valuable new route to 3,4-dihydroisocoumarins. Our results are summarized in Table V. Preparation of the parent compound in this series (entry 1, Table V) was more successful than in the case of phthalide. However, yields were very sensitive to reaction conditions. The best thallation conditions involved thallation of β-phenethyl alcohol for 1 day, followed by carbonylation in methanol with 1 or 2 equiv of magnesium oxide added. This afforded a 51% yield of the desired lactone. Changing the carbonylation solvent from methanol to THF drastically reduced the yield (14%). A close examination of the reaction mixture indicated that starting β-phenethyl alcohol and its trifluoroacetate ester were also present in addition to methyl *p*-(2-hydroxyethyl)benzoate. This latter product no doubt results from thallation in the para position followed by carbonylation. Taylor and McKillop report that β-phenethyl alcohol gives an ortho:meta:para isomer distribution of 83:6:11.[5] We observed no meta substitution product.

Several substituted β-phenethyl alcohols were subsequently studied. 3-Methoxy-β-phenethyl alcohol (entry 2, Table V) gave best results when thallated in the diluted solvent system developed for activated benzyl alcohols. The presence of an activating group on the ring did not result in a dramatic improvement in yields as in the benzyl alcohol series and significant amounts of the starting alcohol (3%) and the corresponding trifluoroacetate ester (18%) were observed. Thallating the starting alcohol for longer periods of time had very little effect. Yields of product were higher when THF (58%) rather than methanol (41%) was used as the carbonylation solvent.

β-Phenethyl alcohols with alkyl substituents on the side chain gave good results (entries 3, 4, and 5, Table V). Unlike α-phenethyl alcohol, in which the secondary benzylic alcohol apparently underwent elimination, 1-phenyl-2-propanol gave 3-methyl-3,4-dihydroisocoumarin in good yield (entry 3). The improved yield may be due to the nonbenzylic nature of the alcohol group or to the fact that the side-chain methyl group is not α to the ring in this substrate, thus reducing steric interference at the thallation site. Yields were optimized by adjusting certain reaction conditions. Changing the temperature or the duration of the thallation reaction appeared to have little effect. Addition of bases to the carbonylation mixture had a more noticeable impact, with magnesium oxide or lithium carbonate giving significantly improved yields. Methanol and THF appeared to be equally good carbonylation solvents. In all cases, less than 10% of the starting alcohol was observed.

Both *trans*- and *cis*-2-phenyl-1-cyclohexanol (entries 4 and 5, Table V), in which the thallation sites are more sterically hindered than in 1-phenyl-2-propanol, gave high yields of the corresponding lactones. The high yields of lactones may be due in part to the somewhat rigid conformation of the alcohol. There is some precedent in the literature for this in the ortho lithiation of benzylic alcohols.[25] The only side products seen in GLC traces of these reactions were about 5% unreacted starting alcohol and about 10% of the trifluoroacetate ester of the starting alcohol. In these reactions the trans alcohol gave exclusively the trans fused lactone, whereas the cis alcohol gave only the cis lactone. The diastereomers were easily identified by NMR analysis of the different chemical shifts and coupling constants for the proton on the carbon adjacent to the lactone oxygen. These syntheses of 3-substituted and polycyclic 3,4-dihydroisocoumarins are very encouraging, since a number of naturally occurring 3,4-dihydroisocoumarins and isocoumarins are structurally similar.

Two other β-phenethyl alcohols failed to give 3,4-dihydroisocoumarins under our reaction conditions. Thallation–carbonylation of 2-naphthaleneethanol gave a mixture of unreacted starting material and tars. No lactone was observed. The thallation of 2,5-dimethoxy-β-phenethyl alcohol with TTFA gave only starting alcohol or tars. Thallation–carbonylation with thallic acetate in acetic acid/TFA produced several compounds, none of which appeared to be the desired 5,8-dimethoxy-3,4-dihydroisocoumarin. The major component of this mixture was isolated and identified as a carbomethoxy-β-phenethyl acetate (eq 13).



(13)

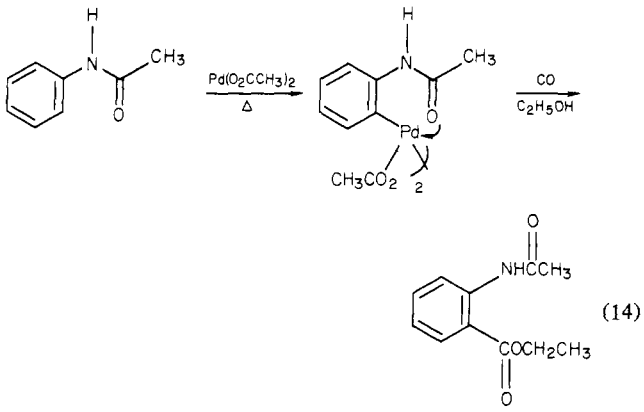
Other Carbonyl Compounds. The thallation of arenes bearing a variety of heteroatom-containing groups other than alcohols is known to proceed with a high degree of ortho selectivity.[5] For example, acids, esters, and ethers can be thallated quite selectively in the ortho position. It appeared to us that thallation–carbonylation of such substrates could greatly expand the synthetic utility of our procedure. Indeed, the thallation–carbonylation of aromatic carboxylic acids, amides, and ketones affords anhydrides, imides, and ortho-substituted methyl esters (Table VI).

The aromatic carboxylic acids, benzoic acid and phenylacetic acid, were examined first. Even though an acid group is normally a deactivating, meta-directing group in electrophilic substitution, benzoic acid is reported to give an isomer distribution of 95:5:0 for ortho:meta:para thallated material in 76% overall yield (yield of aryl iodide).[4,5] Upon thallation in refluxing TFA overnight and subsequent carbonylation in THF, we observed a 44% GLC yield of phthalic anhydride. No further attempts were made to optimize the yield. For phenylacetic acid, the reported isomer distribution ratios are 92:3:5 for ortho:meta:para thallation, in overall yields up to 72%.[5] GLC yields of homophthalic anhydride could not be determined due to the thermal instability of this compound,[47,53] so the product was isolated after carbonylating in THF. Recrystallization from benzene afforded a 46% yield of pure homophthalic anhydride. No optimization of yield was attempted.

Amides also undergo thallation–carbonylation. Benzamide (entry 3, Table VI) gave an 83% GLC yield of phthalimide. The thallation–carbonylation sequence was next applied to acetanilide (entry 4, Table VI). The anticipated acetylanthranil proved too sensitive to moisture to isolate in decent yield, so the carbonylation reaction was run in methanol in order to isolate the corresponding methyl ester. This approach afforded a 37% yield of pure methyl *N*-acetylanthranilate. Residual starting material (~25%) was also recovered from the final carbonylation mixture. No further efforts were made to optimize yields. During the course of our work the direct palladation–carbonylation of acetanilide was reported to afford the corresponding ethyl ester in 42–55% overall yield (eq 14).[54] However, this procedure requires a stoichiometric amount of palladium acetate, while ours is catalytic. We have also examined the thallation–carbonylation of phenylurea. Due to the very low solubility of 2,4-(1*H*,3*H*)-quinazolinedione in most common organic solvents, we attempted the carbonylation in methanol and isolated a 17% yield of pure recrystallized methyl

(52) McMullen, T. C. *J. Am. Chem. Soc.* **1916**, *38*, 1228–30.

(53) Graebe, C.; Trümpy, F. *Chem. Ber.* **1898**, *31*, 375–7.
(54) Horino, H.; Inoue, N. *Tetrahedron Lett.* **1979**, 2403–6.



(14)

2-ureidobenzoate (entry 5, Table VI).

Finally, benzophenone (entry 6, Table VI) was thallated and then carbonylated in methanol to give a 63% yield of methyl 2-benzoylbenzoate. Such compounds are of interest because of the ease with which they can be cyclized to the very valuable anthraquinone ring system. Approximately 11% of unreacted starting material was also observed.

Conclusions

A variety of substituted benzylic and β-phenethyl alcohols, benzoic and phenylacetic acids, benzamide, acetanilide, phenylurea, and benzophenone have been thallated in the ortho position. The resulting arylthallium compounds are readily carbonylated under mild conditions by stirring with a catalytic amount of palladium chloride and 2 equiv of lithium chloride under 1 atm of carbon monoxide at room temperature in methanol or THF. The addition of 2 equiv of magnesium oxide usually increases the yields of carbonylation products. The reaction sequence is highly regiospecific, especially in the case of 3-substituted benzyl alcohols, giving nearly exclusively the 5-substituted phthalides. In the thallation of alcohols, interfering side reactions include the formation of trifluoroacetate esters, oxidation to aldehydes, or elimination of secondary benzylic alcohols to give styrenes. Thallation in positions other than the ortho position and biaryl formation are other potential problems. Thallation is also very sensitive to steric hindrance, and α-substitution in benzylic alcohols or 2,5-disubstitution in benzylic or β-phenethyl alcohols substantially decreases the amount of ortho thallation. Nevertheless, the thallation–carbonylation sequence provides a new, general route to phthalides, 3,4-dihydroisocoumarins, anhydrides, imides, and other carbonyl compounds. It should prove useful in natural products synthesis.

Experimental Section

Reagents. A word of caution is appropriate here. **Caution**: Thallium compounds are extremely toxic! They must be handled with great care at all times.

All chemicals were used directly as obtained commercially unless otherwise indicated. Benzyl alcohol, benzoic acid, benzene, and acetanilide were purchased from Fisher; β-phenethyl alcohol came from Matheson Coleman and Bell; benzophenone and anisole came from J. T. Baker; and 3-hydroxybenzyl alcohol came from Sigma. Reagents purchased from Aldrich include fluorobenzene, *tert*-butylbenzene, 1-phenyl-2-propanol, α-phenethyl alcohol, 2,3-dimethoxybenzyl alcohol, 2-naphthaleneethanol, 2-naphthalenemethanol, 3-chlorobenzyl alcohol, 4-methoxybenzyl alcohol, 3-methoxybenzyl alcohol, 3-methoxy-β-phenethyl alcohol, 2,5-dimethoxybenzyl alcohol, 4-methylbenzyl alcohol, *trans*-2-phenyl-1-cyclohexanol, 4-nitrobenzyl alcohol, phenylacetic acid, phenylurea, and benzamide. Reduction of 2-phenylcyclohexanone (Aldrich) with L-Selectride[55] gave *cis*-2-phenyl-1-cyclohexanol, and lithium aluminum hydride reduction of 2,5-dimethoxyphenylacetic acid (ICN Pharmaceuticals, Inc.) afforded 2,5-dimethoxy-β-phenethyl alcohol. THF was distilled from calcium hydride before use, while TFA was used directly as obtained from Aldrich. Methanol from Fisher was either stored over molecular sieves or used as is. Carbon monoxide was purchased from Matheson Gas Products. The palladium chloride was generously supplied by Johnson Matthey, Inc. and Engelhard Industries. Thallic oxide was obtained from Asarco (American Smelting and Refining Co.).

Equipment. The infrared and NMR spectra were recorded on a Beckman IR-4250 infrared spectrophotometer and a Varian Associates A-60 NMR or a Hitachi Perkin-Elmer R-20B NMR spectrometer, respectively. The mass spectra were obtained on an AEI MS-902 high-resolution mass spectrometer, while the GC–mass spectra were recorded on a Finnegan 4023 GC-MS data system. GLC analyses were performed with a Varian Aerograph Model 920 gas chromatograph or a Varian 3700 gas chromatograph with an attached Varian CDS-111 chromatography data system. Thin-layer chromatography was performed on Merck 60F 254 silica gel plates from Scientific Products. Silica gel for column chromatography (60–200 mesh) was purchased from Davison Chemical, and fractions were collected automatically by a Model FC-100 Micro Fractionator from Gilson Medical Electronics.

Preparation and Use of Thallium(III) Trifluoroacetate. Our difficulties in obtaining commercial consistently high-quality TTFA led us to prepare our own by modifying slightly the procedure given by McKillop et al.[4] Usually, thallium(III) oxide (25 g) was weighed into a 250-mL round-bottom flask. TFA (100 mL) was added and the mixture was stirred vigorously. Water (12 mL) was then added. The flask was wrapped with aluminum foil and the mixture was refluxed overnight (12–19 h). Filtration of the hot reaction mixture provided a colorless solution which was evaporated to dryness under vacuum. Yields ranged from 95 to 99%. The reagent was stored in the freezer wrapped in aluminum foil. Exposure to warm, moist air caused the white solid to become brown and sticky. The reagent was weighed out (as quickly as possible, to avoid exposure to moisture) and dissolved in the appropriate amount of TFA prior to each experiment.

Thallation of Arenes. For the most part, thallations were carried out using literature procedures, which entailed stirring the substrates in a 1 *M* solution of TTFA in TFA for a certain time period at a certain temperature, depending on the substrate.[4,5] Best results were obtained when 1.0–1.2 equiv of TTFA were used per equiv of substrate. As in the literature,[5] alcohols were cooled to 0 °C and then the freshly prepared TTFA solution was added. The resulting yellow, green, or brown mixture, protected from light, was stirred at 0 °C for 3 h and then allowed to warm up to room temperature and stirred overnight. Excess TFA was coevaporated with 1,2-dichloroethane. However, this procedure did not work for aryl alcohols with one or more activating groups (methoxy, hydroxy) on the ring, as these tended to polymerize under these conditions. Diluting the solution with THF solved the problem.

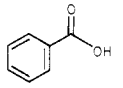
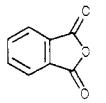
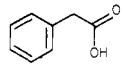
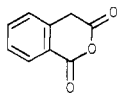
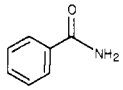
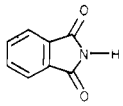
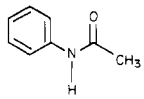
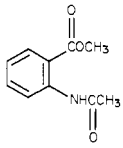
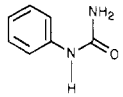
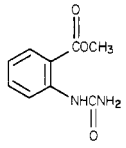
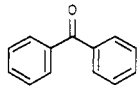
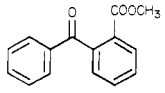
The thallation of 2,3-dimethoxybenzyl alcohol is representative of the technique used. One millimole of the alcohol was weighed into a 50-mL round-bottom flask. One millimole of TFFA was dissolved in 1 mL of TFA and then 5 mL of THF was added to this solution. This mixture was added to the alcohol slowly with stirring, producing a light yellow solution. The flask was then stoppered and wrapped with aluminum foil and the solution was stirred overnight at room temperature. Solvents were removed on a rotary evaporator, and the residue was coevaporated with 1,2-dichloroethane. The flask was evacuated at 1–3 mm Hg on a vacuum pump for 5–10 min to remove as much TFA as possible and then the material was carbonylated immediately without further purification. The best thallation conditions observed are reported in the various tables.

Carbonylation Model Studies. The following procedure is representative of that used to study the effect of added salts and various reaction temperatures on the carbonylation of phenylthalliumbis(trifluoroacetate). Palladium chloride (0.1 mmol, 0.0178 g), 2 mmol of anhydrous lithium chloride (0.0844 g), 1 mmol of magnesium oxide (0.0402 g), and 5 mL of methanol were placed in a 50-mL round-bottom flask with a septum inlet. The system was flushed with carbon monoxide. Phenylthallium bis(trifluoroacetate)[4] (1 mmol, 0.507 g) was dissolved in 5 mL of methanol and added to the salts against a carbon monoxide backflush. The system was again flushed with carbon monoxide and a balloon filled with carbon monoxide was connected to a gas inlet adapter seated in the top of the flask. The reaction was then stirred at room temperature overnight. The effects of varying the relative amounts of the inorganic salts and the temperature of carbonylation are shown in Table I. Table II shows the effect of stoichiometry on the thallation reaction. In these "direct" carbonylation reactions, the phenylthalliumbis(trifluoroacetate) was not purified prior to carbonylation. Rather, the crude thallation mixture was coevaporated with 1,2-dichloroethane and evacuated to dryness on a vacuum pump. This mixture, when run on a 1 mmol scale, was then dissolved in 5 mL of methanol and added to the inorganic salts as described above. The aryl esters shown in Table III were prepared by this same "direct" carbonylation procedure.

Carbonylation of Arylthallium Intermediates. Phthalides, 3,4-dihydroisocoumarins, and methyl esters of substituted benzoic acids were

(55) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159–61.

Table VI. Thallation–Carbonylation of Aromatic Carboxylic Acids, Amides, and Ketones

entry	starting material	thallation conditions	product	% yield[a]	mp, °C (lit. mp, °C)
1		TFA, reflux, 16 h		44	
2		TFA, 25 °C, 2 days		(46)	137–139 (140.5–141,[b] 141–142[c])
3		TFA, reflux, 16 h		83	
4		TFA, 25 °C, 16 h		(39)	98 (100–101[d])
5		TFA, 25 °C, 15 h		(17)	175–176 (177–177.5[e])
6		TFA, 25 °C, 4 days		(63)	48–50 (52[f])

[a] GLC yield with an internal standard (isolated, purified yield). [b] See ref 47. [c] See ref 48 and 49. [d] See ref 50. [e] See ref 51. [f] See ref 52.

prepared according to the following representative procedure. One millimole of appropriately substituted arene was thallated as described above and was used without further purification. Palladium chloride (0.1 mmol, 0.0178 g), 2 mmol of anhydrous lithium chloride (0.0844 g), and either 2 mmol of magnesium oxide (0.0804 g) or 1 mmol of lithium carbonate (0.0739 g) (β-phenethyl alcohol only) and 5 mL of methanol were placed in a round-bottom flask with a septum inlet. The system was flushed with carbon monoxide. The flask containing the arylthallium intermediate was removed from the vacuum pump and the thallated substrate was dissolved in 5 mL of methanol and added to the salts while backflushing with carbon monoxide. The system was again flushed with carbon monoxide and a balloon filled with carbon monoxide was connected to the top of the flask. The reaction was then stirred at room temperature overnight. Anhydrides and phthalimide (from aryl acids and benzamide, respectively) were prepared in nearly identical fashion, except that no inorganic base was used, and THF was employed as the solvent. All yields determined by GLC analysis were run this way, with an appropriate internal standard added before analysis. Yields were calculated by using internal standard correction factors determined by using authentic product samples, either purchased or synthesized.

Isolated yields were determined by using the above procedure on either a 5-mmol or a 10-mmol scale. A typical workup of a 5-mmol scale carbonylation reaction, run in 50 mL of methanol, was performed as follows. The reaction mixture (usually black) was diluted with 100 mL of ether to precipitate as many inorganic salts as possible and then vacuum filtered through Celite filter aid. The filtrate was concentrated on a rotary evaporator and the residue was suspended in 150 mL of fresh ether. This was washed with three 100-mL portions of saturated aqueous ammonium chloride solution and one 100-mL portion of saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The crude product was either recrystallized or purified by column chromatography. The water-sensitive homophthalic anhydride was isolated by diluting the carbonylation solvent (THF) with chloroform, filtering the solution, and evaporating the solvents. The residue was extracted repeatedly with chloroform. The combined extracts were again concentrated and the solid residue was recrystallized from benzene.

The compounds purified by silica gel column chromatography follow. Phthalide: R_f 0.42; ether:hexane (1:1) as eluent. 3,4-Dihydroisocoumarin: R_f 0.41, ethyl acetate:hexane (1:1), and then R_f 0.60, chloroform. Reaction mixture from 4-methoxybenzyl alcohol:ether. 6-Methoxy-3,4-dihydroisocoumarin: R_f 0.45, ether. Methyl *N*-acetylanthranilate: R_f 0.68, ether as eluent, followed by recrystallization from ethanol. Methyl 2-benzoylbenzoate: R_f 0.38, ether:hexane (1:1).

The following new compounds were prepared and characterized. 6-Methylphthalide: ^{1}H NMR ($CDCl_3$) δ 2.47 (3 H, s, CH_3), 5.28 (2 H, s, $-CH_2-$), 7.20–7.75 (3 H, m, aromatic); IR (max) ($CHCl_3$) 1765 (C=O), 1120–1160 (C–O) cm^{-1}; *m/e* 148.05241 (calcd for $C_9H_8O_2$, 148.05243). Anal. Calcd for $C_9H_8O_2$: C, 72.96; H, 5.44. Found: C, 72.87; H, 5.50. *trans*-1,2,3,4,4a,10b-Hexahydro-6*H*-dibenzo[*b,d*]pyran-6-one: ^{1}H NMR ($CDCl_3$) δ 1.2–2.7 [8 H, m, $(-CH_2-)_4$], 2.7–3.0 (1 H, m, methine), 3.9–4.3 (1 H, d of t, J_{ax-ax} = 10 Hz, J_{ax-eq} = 4 Hz, methine), 7.2–8.2 (4 H, m, aromatic); IR (max) ($CHCl_3$) 1720 (C=O), 1280 (C–O), 1160 (C–O) cm^{-1}; *m/e* 202.09854 (calcd for $C_{13}H_{14}O_2$, 202.09938). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.07; H, 7.09. *cis*-1,2,3,4,4a,10b-Hexahydro-6*H*-dibenzo[*b,d*]pyran-6-one: ^{1}H NMR ($CDCl_3$) δ 1.3–2.3 [8 H, m, $(-CH_2)_4$], 2.6–3.0 (1 H, br s, methine), 4.6–4.8 (1 H, br s, methine), 7.2–8.3 (4 H, m aromatic); IR (max) ($CHCl_3$) 1710 (C=O), 1280 (C–O) cm^{-1}; *m/e* 202.10007 (calcd for $C_{13}H_{14}O_2$, 202.09938). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20: H, 6.98. Found: C, 77.27; H, 7.07.

Spectral data not previously reported for known compounds are as follows. 5-Methoxyphthalide: ^{1}H NMR ($CDCl_3$) δ 3.87 (3 H, s, CH_3O), 5.1 (2 H, br s, CH_2), 6.85–7.1 (2 H, m, aromatic), 7.7–7.9 (1 H, d, *J* = 8 Hz, aromatic next to carbonyl); IR (max) ($CHCl_3$) 1750 (C=O), 1602 (C=C), 1260–1190 (C–O) cm^{-1}; *m/e* (rel intensity) 164 (parent, 32), 163 (16), 146 (46), 135 (69), 134 (14), 119 (18), 118 (base peak, 100), 106 (18), 105 (26), 92 (21), 91 (10), 90 (15), 78 (26), 77 (56), 76 (23), 75 (11), 65 (12), 64 (11), 63 (25), 62 (10), 51 (45). 4,5-Dimethoxyphthalide: ^{1}H NMR ($CDCl_3$) δ 3.95 (6 H, s, CH_3O), 5.30 (2 H, s, CH_2), 7.05 (1 H, d, *J* = 8 Hz, aromatic), 7.60 (1 H, d, *J* = 8 Hz, aromatic next to carbonyl); IR (max) ($CHCl_3$) 1760 (C=O), 1475 (CH_2O), 1270–1180 (C–O), 2940, 2815 (d, CH_3, CH_2), 1585, 1615 (d, C=C) cm^{-1}; *m/e* 194 (parent and base peak, 100%). 4,7-Dimethoxyphthalide: ^{1}H NMR ($CDCl_3$) δ 3.8 (3 H, s, CH_3O), 3.9 (3 H, s, CH_3O), 5.17 (2 H, s, CH_2), 6.85 (1 H, d, *J* = 9 Hz, aromatic), 7.08 (1 H, d, *J* = 8 Hz, aromatic next to carbonyl); IR (max) ($CHCl_3$) 1750 (C=O), 2950, 2860 (d, CH_3, CH_2), 1470–1410 (CH_2–O), 1270–1150 (C–O), 1600 (C=C) cm^{-1}; *m/e* (rel intensity) 194 (parent, 83), 193 (30), 180 (14), 176 (13), 166 (14), 165 (59), 151 (25), 150 (11), 149 (20), 148 (50), 135 (15), 123 (12), 122 (15), 121 (24), 120 (19), 188 (base peak, 100), 107 (16), 93 (11), 79 (13), 77 (18), 75 (10), 65 (12), 63 (14), 53 (14), 51 (15). 5-Hydroxyphthalide: ^{1}H NMR (Me_2SO-d_6) δ 3.75 (1 H, s, OH), 5.29 (2 H, s, CH_2), 6.9–7.1 (2 H, m, aromatic), 7.6–7.75 (1 H,

d, J = 9 Hz, aromatic next to carbonyl); IR (max) (KBr) 1715 (C=O), 3260 (O–H), 1270 (C–O), 1463 (CH_2–O), 1600, 1615 (d, C=C) cm^{-1}; m/e (rel intensity) 150 (parent, 34), 149 (13), 121 (base peak, 100), 93 (21), 92 (14), 77 (12), 65 (43), 63 (28), 55 (19), 51 (17), 44 (43), 43 (22), 41 (25). Homophthalic anhydride: ^{1}H NMR ($CDCl_3$) δ 4.12 (2 H, s, CH_2), 7.25–7.85 (3 H, m, aromatic), 8.10–8.25 (1 H, d with fine structure, J = 8 Hz, aromatic next to carbonyl); IR (max) ($CHCl_3$) 1803, 1754 (d, C=O), 1605 (C=C), 1280 (C–O) cm^{-1}; m/e 162.03168 (calcd for $C_9H_6O_3$, 162.03170). Methyl N-acetylanthranilate: ^{1}H NMR ($CDCl_3$) δ 2.01 (3 H, s, CH_3CO), 3.80 (3 H, s, CH_3O–), 6.85–8.02 (3 H, m, aromatic), 8.55–8.70 (1 H, d with fine structure, J = 14 Hz, aromatic next to carbonyl), 11.95 (1 H, br s, N–H); IR (max) ($CHCl_3$) 1705, 1685 (d, C=O), 1610, 1590 (d, C=C), 1265 (C–O), 3320 (N–H) cm^{-1}; m/e 193.07491 (calcd for $C_{10}H_{11}NO_3$, 193.07390). Methyl 2-ureidobenzoate: ^{1}H NMR ($CDCl_3$ + Me_2SO-d_6) δ 2.88 (2 H, s, NH_2), 3.90 (3 H, s, CH_3), 5.75 (1 H, br s, N–H), 6.95–8.05 (3 H, m, aromatic), 8.40–8.54 (1 H, d with fine structure, J = 8 Hz, aromatic next to carbonyl); IR (max) (KBr) 1600, 1575 (d, C=C), 1260 (C–O), 3410 (N–H), 3270, 3210 (d, N–H) cm^{-1}; m/e 194.06912 (calcd for $C_9H_{10}N_2O_3$, 194.06915).

Acknowledgment. The authors gratefully acknowledge the assistance of Drs. Bernhard Riefling and Hans-Hermann Lau and the generous support of the National Institutes of Health (GM24254). We also wish to recognize the National Science Foundation (CHE 76-80362) for funds used in the purchase of the Finnegan 4023 GC–mass spectrometer used in this work. Special thanks go to Johnson Matthey Inc. and Engelhard Industries for generous loans of palladium chloride used in this work.

Registry No. Benzene, 71-43-2; fluorobenzene, 462-06-6; methoxybenzene, 100-66-3; (1,1-dimethylethyl)benzene, 98-06-6; benzoic acid methyl ester, 93-58-3; 4-fluorobenzoic acid methyl ester, 403-33-8; 4-methoxybenzoic acid methyl ester, 121-98-2; 4-(1,1-dimethylethyl)-benzoic acid methyl ester, 26537-19-9; benzenemethanol, 100-51-6; 3-methoxybenzenemethanol, 6971-51-3; 3-hydroxybenzenemethanol, 620-24-6; 3-chlorobenzenemethanol, 873-63-2; 4-methylbenzenemethanol, 589-18-4; 2,5-dimethoxybenzenemethanol, 33524-31-1; 2,3-dimethoxybenzenemethanol, 5653-67-8; 1(3*H*)-isobenzofuranone, 87-41-2; 5-methoxy-1(3*H*)-isobenzofuranone, 4741-62-2; 5-hydroxy-1(3*H*)-isobenzofuranone, 55104-35-3; 5-chloro-1(3*H*)-isobenzofuranone, 54109-03-4; 6-methyl-1(3*H*)-isobenzofuranone, 72985-23-0; 4,7-dimethoxy-1-(3*H*)-isobenzofuranone, 64019-78-9; 4,5-dimethoxy-1(3*H*)-isobenzofuranone, 4741-58-6; benzeneethanol, 60-12-8; 3-methoxybenzeneethanol, 5020-41-7; α-methylbenzeneethanol, 698-87-3; *trans*-2-phenylcyclohexanol, 2362-61-0; *cis*-2-phenylcyclohexanol, 16201-63-1; 1*H*-2-benzopyran-1-one, 491-31-6; 6-methoxy-1*H*-2-benzopyran-1-one, 20678-26-6; 3-methyl-1*H*-2-benzopyran-1-one, 29539-21-7; *trans*-1,2,3,4,4a,10b-hexahydro-6*H*-dibenzo[*b*,*d*]pyran-6-one, 72331-11-4; *cis*-1,2,3,4,4a,10b-hexahydro-6*H*-dibenzo[*b*,*d*]pyran-6-one, 72331-10-3; benzoic acid, 65-85-0; benzeneacetic acid, 103-82-2; benzenamide, 55-21-0; *N*-phenylacetamide, 103-84-4; phenylurea, 64-10-8; benzophenone, 119-61-9; 1,3-isobenzofurandione, 85-44-9; 1*H*-2-benzopyran-1,3(4*H*)-dione, 703-59-3; 1*H*-isoindole-1,3(2*H*)-dione, 85-41-6; 4-acetylaminobenzoic acid methyl ester, 17012-22-5; *N*-(2-methoxycarbonylphenyl)-urea, 2242-77-5; 2-benzoylbenzoic acid, 606-28-0; thallium(III) trifluoroacetate, 23586-53-0.

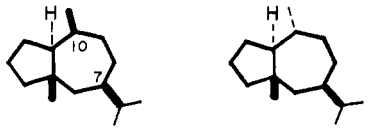
Synthesis of Sesquiterpene Antitumor Lactones. 9.[1] The Hydronaphthalene Route to Pseudoguaianes. Total Synthesis of (±)-Confertin[†]

Clayton H. Heathcock,* Eric G. DelMar, and Samuel Lindsay Graham

Contribution from the Department of Chemistry, University of California, Berkeley, California 94720. *Received August 10, 1981*

Abstract: The feasibility of using hydronaphthalene precursors for the synthesis of pseudoguaianes has been examined. The dimethyldecalyl tosylate **13** was prepared as shown in Scheme II. Its solvolysis was studied in methanol and in buffered acetic acid. In methanol, **13** gives keto ether **14**, enone **15**, and cyclopropyl ketone **16**. In acetic acid, the products are **15** and **16**. In neither solvent is any hydroazulenone produced. The desoxy analogue **28** was prepared as shown in Scheme IV and solvolyzed in buffered acetic acid. The only products obtained are octalins **25** and **29**. The solvolytic behavior of tosylates **13** and **28** is compared with that of the related tosylates **17** and **21**, which had been studied earlier, and a mechanistic rationale is advanced to explain the divergent behavior. Vicinal diol monotosylate **34** has been prepared and solvolyzed in basic *tert*-butyl alcohol. The rearrangement of **34** can be made to give keto ester **35** by using lithium hydroxide or keto alcohols **36** and **37** by the use of potassium hydroxide. This novel difference in reaction course results from the fact that potassium hydroxide saponifies the transannular acetate group prior to solvolysis. The resulting diol tosylate adopts a different reacting conformation, leading to the production of **36** (Scheme VII). Keto ketal **39** is converted into enone **43** by a novel new reaction involving treatment of **39** sequentially with trimethylaluminum and methyllithium. Lithium/ammonia reduction of **43** gives hydroxy ketone **50**, which has been converted into (±)-helenalin. Catalytic hydrogenation of **43** gives **51**, which is converted via enol lactone **56** into acetoxy lactone **58**. This intermediate is converted by Danishefsky's procedure into (±)-confertin (**1**).

The pseudoguaianolides are a group of more than 100 sesquiterpenes having the general skeleton shown in **i** and **ii**. The family is subdivided into a more abundant group in which the C_{10}-methyl occupies the β-position on the *trans*-hydroazulene nucleus (the ambrosanolides, **i**) and a less abundant 10α-configured group (the helenanolides, **ii**). Both subgroups have the β configuration at C_7. Interest in the pseudoguaianolides has been strongly stimulated by the discovery that many members of the family have cytotoxic and antitumor properties[2] and chemists have reported total syntheses of 18 pseudoguaianolides since 1975.[3]



i *ii*

[†] Dedicated to Professor Gilbert Stork on the occasion of his 60th birthday.

(1) For part 8 see C. M. Tice and C. H. Heathcock, *J. Org. Chem.*, **46**, 9 (1981).

(2) S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971).

(3) For a complete survey of the activity in this field see C. H. Heathcock, S. L. Graham, M. C. Pirrung, F. Plavac, and C. T. White in "The Total Synthesis of Natural Products", Vol. 5, J. W. ApSimon, Ed., Wiley, New York, 1982.

0002-7863/82/1504-1907$01.25/0